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Brainwaves beyond diagnosis: Wider applications of EEG in idiopathic generalized epilepsy.

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ABSTRACT

EEG has long been used as a versatile and non-invasive diagnostic tool in epilepsy. With the advent of digital EEG, more advanced applications of EEG have emerged. Compared with technologically advanced practice in focal epilepsies, the utilization of EEG in idiopathic generalized epilepsy has been lagging, often restricted to a simple diagnostic tool. In this narrative review, we provide an overview of broader applications of EEG beyond this narrow scope, discussing how the current clinical and research applications of EEG may potentially be extended to idiopathic generalized epilepsy. The current literature, though limited, suggests that EEG can be used in syndromic classification, guiding antiseizure medication therapy, predicting prognosis, unravelling biorhythms, and investigating functional brain connectivity of idiopathic generalized epilepsy. We emphasize the need for longer recordings, particularly 24-hr ambulatory EEG, to capture discharges reflecting circadian and sleep-wake cycle associated variations for wider EEG applications in IGE. Finally, we highlight the challenges and limitations of the current body of literature and suggest future directions to encourage and enhance more extensive applications of this potent tool.

Keywords: syndrome, treatment, prognosis, graph theory, biorhythm, connectivity

KEY POINTS

- EEG is mostly used to diagnose idiopathic generalized epilepsy, but there are other useful clinical and research applications
- Characteristics of epileptiform discharges and spike densities can aid syndromic classification
- Epileptiform discharges are valuable in guiding antiseizure medication therapy
- Characteristics of epileptiform discharges, duration of spike-wave paroxysms, and spike densities are useful markers for predicting prognosis

- Mapping functional brain connectivity and exploring rhythmic cycles are emerging applications of EEG

INTRODUCTION

Despite the advent of many technologically advanced investigations, electroencephalography (EEG) remains one of the most widely used tools playing a critical role in the diagnosis of epilepsy. In particular, EEG abnormalities are vital in the classification of epilepsies into focal and generalized subgroups.

Given typically normal structural neuroimaging, EEG is particularly valuable in establishing the diagnosis of idiopathic generalized epilepsy (IGE) which accounts for 15-20% of all epilepsies across all age groups.[1] The generalized spike-wave complex, first described by Gibbs in 1935, is the electrographic signature of IGE.[2] Generalized polyspikes, polyspike-wave discharges, paroxysmal fast rhythm, photoparoxysmal response, eye-closure sensitivity, fixation-off sensitivity, epileptiform K-complexes, and occipital intermittent rhythmic delta activity are other EEG abnormalities described in IGE.[3, 4] Furthermore, these changes typically emerge from a normal background.

With advances in epilepsy surgery, EEG has wide applications beyond establishing the diagnosis of focal epilepsy. Both surface and intracranial EEGs are indispensable for the

localization of the epileptogenic zone in the presurgical workup. EEG source localization is a technique for epileptogenic zone localization non-invasively.[5] Similarly, EEG-correlated functional MRI (EEG-fMRI) is another non-invasive tool incorporating EEG for source localization.[6] The application of EEG in seizure prediction and unravelling underlying biorhythms is evolving.[7-9] EEG is also used as a prognostic tool and the appearance of interictal epileptiform discharges after anterior temporal lobectomy predicts a higher risk of seizure recurrence.[10]

The application of EEG in IGE is mostly restricted to confirming the diagnosis and remains underutilized compared with focal epilepsies. This narrative review focuses on broader uses of EEG in IGE with applications in clinical and research fronts involving classification of syndromes, guiding treatment, predicting prognosis, studying biorhythms, and exploring epileptic networks.

METHODS

We conducted an electronic search using the PubMed database from its inception to May 2021. The search terms included idiopathic generalized epilepsy, genetic generalized epilepsy, epilepsy syndrome, EEG, antiseizure medication, prognosis, circadian rhythm, sleep-wake cycle, high-density EEG, EEG-fMRI, TMS-EEG, graph theory, and synonyms as well as relevant medical subject headings (Epilepsies, Generalized; Generalized Epilepsies; Generalized Seizure Disorder). The search terms were combined with Boolean operators. We only included the literature published in the English language. Reviews were perused for additional information and references.

CLASSIFICATION OF SYNDROMES

Idiopathic generalized epilepsy is classified into four main syndromes: childhood absence epilepsy (CAE), juvenile absence epilepsy (JAE), juvenile myoclonic epilepsy (JME), and generalized epilepsy with tonic-clonic seizures alone (GTCA).[11] Though key electrographic features of IGE are seen across all four syndromes, some qualitative and quantitative differences do exist helping the clinician differentiate and classify.[12]

Childhood absence epilepsy

Interictal

Fragments of epileptiform discharges are seen during drowsiness and sleep in over 90% of cases.[13] Polyspikes and polyspike-wave discharges are usually seen in sleep.[13, 14] However, a study based on 24-hour ambulatory EEG in an adult cohort reported polyspikes and polyspike-wave discharges in wakefulness as well.[12] This discrepancy may be due to differences in cohorts (adult vs children), disease severity, and the length of EEG recording. The photoparoxysmal response is evident in one-fifth of patients.[13, 15] Approximately 20-30% of children demonstrate occipital intermittent rhythmic delta activity (OIRDA).[16, 17] However, it should be noted that OIRDA is not specific for CAE and it can be seen in focal epilepsies as well as rarely in encephalopathies.[18, 19] The density of epileptiform discharges, including polyspikes and polyspike-wave discharges, is significantly lower compared with JAE and JME. Atypical epileptiform abnormalities such as focal discharges, focal onset and offset of paroxysms, amplitude asymmetry, and atypical morphology are well recognized in IGE. Around 50% of CAE patients demonstrate such atypical abnormalities and focal discharges are less frequent than in other syndromes.[20] Epileptiform K-complexes in sleep are least common (53.3%) in CAE compared with other syndromes (Figure 1).[21]

Ictal

During an absence seizure, the frequency of spike-wave discharges tends to be slightly faster in the first second and slightly slower in the terminal phase.[22] In the mid-phase, the frequency ranges from 2.7 to 3.3 Hz with a mean of 3 Hz.[22] Though the mean spike-wave frequency is slightly slower than in JME, there is no statistically significant difference among syndromes.[12] Absence seizures of CAE are significantly shorter than JAE and disorganized discharges are least common in CAE compared with JAE and JME (Figure 2).[13, 22] Generalized spike-wave paroxysms are considered disorganized when (1) the entire paroxysm is irregular and arrhythmic, or (2) regular and rhythmic (organized) discharges are interrupted by ‘complexes of different frequencies and morphologies’.[13] It is not unusual to find polyspikes and polyspike-wave discharges admixed in a generalized spike and wave paroxysm. The ‘pure’ generalized spike-wave paroxysms (without polyspikes or polyspike-wave intrusions) are more likely to occur in CAE (Figure 3).[12] Hyperventilation induces absence seizures in 87% of untreated children with CAE.[23] This phenomenon is less common (4.1%) in adult cohorts of CAE, probably reflecting the impact of antiseizure medications (ASM) and perhaps brain maturation.[24]

Juvenile absence epilepsy

Interictal

Fragmented discharges, polyspike, and polyspike-wave discharges are seen in sleep similar to CAE.[23] However, prolonged (24-hr) ambulatory EEG reveals those abnormalities in wakefulness as well and all types of epileptiform discharge densities are the highest in JAE among all syndromes.[12] Atypical epileptiform EEG abnormalities, including focal discharges, are seen in 82% of patients.[20] The photoparoxysmal response is elicited in 25% of untreated children with JAE.[23] Among the syndromes, epileptiform K-complexes are most frequently seen in JAE (70.6%).[21]

Ictal

The mean spike-wave frequency is 3.2 Hz.[12, 23] Absence seizures of JAE are significantly longer than in other syndromes (Figure 4).[12, 22] 'Pure' generalized spike-wave paroxysms and fragments are as common as in CAE,[12] whereas disorganized discharges during an absence seizure are eight times more likely to occur compared with CAE.[23] Similar to CAE, 87% of untreated children demonstrate hyperventilation-induced absence seizures.[23] However, it is less frequently observed in adult cohorts (5.2%) on ASM therapy.[24]

Juvenile myoclonic epilepsy

Interictal

Disorganized generalized polyspikes and polyspike-wave discharges occurring in the form of both fragments and paroxysms in all states of vigilance predominate the EEG (Figure 5).[13] The photoparoxysmal response is significantly more frequent (83%) among untreated patients.[13] The total epileptiform discharge density is much higher than CAE and GTCA, but on par with JAE.[12] 68% of patients demonstrate atypical epileptiform EEG abnormalities on the EEG.[12] Focal epileptiform discharges are evident in 18% of patients.[20] 'Pure' generalized spike-wave activity, both in fragments and paroxysms, is least likely to occur in JME compared with CAE and JAE.[12]

Ictal

The mean spike-wave frequency of absence seizures is around 3.5 to 3.8 Hz.[12, 23] The average duration of an absence seizure is around 7 seconds with a range of 3-18 seconds.[22] The paroxysms usually consist of a mix of spike-wave activity, polyspikes, and polyspike-wave

discharges while disorganized discharges are 110 times more likely in JME than CAE.[13] Hyperventilation induced absence seizures are least common in JME with studies reporting 33% among untreated patients and rarely seen (1%) in subjects on ASM.[13, 24]

The ictal rhythm of generalized tonic-clonic seizures does not differ among syndromes. However, in JME, myoclonic jerks electrographically characterized by a burst of high-amplitude generalized polyspike-wave activity may precede the generalized tonic-clonic seizure.

Generalized epilepsy with tonic-clonic seizures alone

Interictal

We found only four studies, with three based on the same cohort of patients, systematically investigating EEG abnormalities in GTCA. In addition to generalized spike-wave activity, polyspikes and polyspike-wave discharges are seen during both sleep and wakefulness.[12, 25] The mean frequency of generalized spike-wave discharges is 3.5 Hz.[12] The majority of discharge paroxysms (defined as generalized discharges lasting >2 seconds) consist of a mix of spike-wave discharges, polyspikes, and polyspike-wave discharges.[12] Based on 24-hour ambulatory EEGs, paroxysms of GTCA are briefer than in other syndromes with means of 2.5 seconds (all paroxysms) and the longest duration of 2.8 seconds.[12] Epileptiform discharge densities are similar to CAE and significantly lower than JAE and JME.[12] Atypical epileptiform discharges are evident in 54% of patients whilst 14% demonstrate focal discharges.[20] Hyperventilation induced generalized epileptiform discharges in 2% of patients on treatment whereas photoparoxysmal response was elicited in 5% of subjects in the same cohort.[24] Another study reported photoparoxysmal response in 27.8%. However, this study was based on a mixed adult and paediatric cohort in which some patients were not on ASM therapy which may explain the higher rate of photosensitivity.[25]

Ictal

Our literature search did not reveal any primary research studies describing ictal EEG changes in GTCA. According to an expert review, the EEG seizure is characterized by a low-voltage generalized fast rhythm which may be preceded by brief lead-in generalized spike-wave or polyspike-wave discharges.[26]

Challenges in interpretation

Heterogeneity among studies poses a major challenge in interpreting the results. Many variables such as the state of vigilance, antiseizure medications (ASM), age, activation methods such as photic stimulation and hyperventilation, length of the EEG, and technical aspects of EEG recording influence the outcome of EEG abnormalities captured. For example, photoparoxysmal response decreases with age and ASM therapy,[27, 28] whilst sleep EEG significantly increases the yield of epileptiform discharges.[29, 30] Only a small number of studies have investigated EEG differences among IGE syndromes in a systematic manner. Table 1 is an attempt to summarize the main EEG differences among syndromes as a practical guide for clinical practice. Table 2 summarizes results and factors influencing the yield from key studies on EEG differences among IGE syndromes.

GUIDING ANTISEIZURE MEDICATION THERAPY

Commencing treatment after the first unprovoked seizure

Commencing ASM therapy in epilepsy is essentially a clinical decision based on multiple factors. This decision can be particularly difficult in patients who have experienced their first unprovoked seizure. The estimated risk of seizure recurrence plays a major role in this decision-making process.[31] Epileptiform abnormalities, compared with normal EEG, after the first unprovoked seizure are associated with twice the relative risk of recurrence at two years.[32] Approximately 15% of patients in this population demonstrate epileptiform abnormalities in their EEGs.[33] It is possible to diagnose epilepsy after the first unprovoked seizure according to the ILAE criteria.[34] Hence, the detection of generalized epileptiform discharges in this population plays an important role in guiding ASM therapy. Furthermore, prolonged ambulatory EEG is very useful to capture absence seizures missed by patients and family members to initiate treatment.

Monitoring response to treatment

Having commenced ASM therapy, the response to treatment is usually measured on clinical grounds based on the degree of seizure control reported by patients and family members. However, studies have demonstrated that patients tend to under-report their seizures and clinicians need more reliable tools to monitor treatment response.[35] This is particularly relevant for absence seizures. Epileptiform discharge burden captured on EEG is a potential

surrogate marker of seizure control.[36] Several studies have demonstrated decreases in epileptiform discharge density, frequency, cumulative duration, and burst duration with ASM therapy in IGE.[37-41]A systematic review has revealed that ASM-induced reduction in epileptiform discharge burden, captured on prolonged EEG recordings (≥24 hours), in IGE is accompanied by improved seizure control.[42] However, there was only one randomized controlled trial among the publications analyzed in that systematic review.[42] Well-designed prospective studies are needed to evaluate the applicability of interictal epileptiform discharge measurements to monitor response to ASM therapy in clinical practice.

Antiseizure medication withdrawal

The value of epileptiform discharges in the EEG as a predictor of seizure recurrence has been debated for decades. One review found that out of 37 studies, 21 had reported abnormal EEG as a predictor of seizure recurrence and six studies drew this conclusion based on multivariable analysis.[43] A meta-analysis on this topic found eight independent predictors of seizure recurrence: epileptiform EEG abnormalities before ASM withdrawal, developmental delay, epilepsy syndromes that are not self-limiting, seizure-free interval, duration of epilepsy, number of seizures before remission, epilepsy onset age, and history of febrile convulsions.[44] However, conclusions from these reviews and metanalyses are based on mixed cohorts of IGE and focal epilepsies.

Only a handful of studies have investigated the use of EEG as a predictor of seizure recurrence following ASM withdrawal in IGE. A retrospective study based on 31 adults with JME followed up for a minimum of 25 years (mean 39.1 y) found the presence of photoparoxysmal response (PPR) predicted seizure recurrence following ASM withdrawal (positive predictive value=90.9%).[45] Another retrospective analysis of 59 adults and children with IGE reported worsening of epileptiform EEG abnormalities during or after ASM withdrawal as a significant predictor of seizure relapse (hazard ratio=4.67 with 95% confidence interval 1.08-12.01).[46] Similar results were observed in a prospective study of 63 patients (both adults and children) diagnosed with IGE.[47] Another prospective study randomized 154 children with epilepsy (IGE 53, focal 86, undetermined 15) for ASM withdrawal after 1 or 3 years of treatment who achieved >6 months of seizure freedom. The presence of irregular spike-wave discharges in the pre-ASM withdrawal EEG was associated with a higher rate of seizure recurrence (67%) compared with normal EEGs (33%) and other types of epileptiform discharges (33%).[48] However, the syndromic breakdown of this

outcome is not provided in the publication. A more recent study took a step further to investigate different qualities of epileptiform discharges associated with seizure relapse following ASM withdrawal.[49] The authors retrospectively analyzed 32 prolonged (22-hr) ambulatory EEG recordings from 26 adults with JME to evaluate the predictive value of the total number, frequency, spike density, and mean/maximum duration of epileptiform discharges. In the multivariable analysis, the maximum length of epileptiform discharge paroxysm emerged as the only significant marker with ≥2.68 duration predicting seizure recurrence (specificity 100%, sensitivity 93%).[49]

Challenges in interpretation

However, results from these studies should be interpreted with caution. Most studies are retrospective with relatively small sample sizes. EEG recordings were not uniform, ranging from short outpatient EEGs to prolonged ambulatory recordings. Yet, epileptiform abnormalities in the pre-ASM withdrawal EEG emerge as a potential signal. It is likely EEG abnormalities are in the mix of several other predictors including epilepsy syndrome, seizure type, and seizure-free duration as seen in epilepsies in general. Prospective multicentre studies using prolonged EEGs are warranted to solve this question.

PREDICTING PROGNOSIS

Remission versus refractoriness

There are variable EEG predictors reported in the literature in association with seizure remission and refractoriness as summarized in table 3. The presence of atypical epileptiform abnormalities such as focal and asymmetric generalized discharges are reported as predictors against remission in at least two studies.[50, 51] Photosensitivity is rarely reported as a predictor of poor prognosis,[52] whereas other studies report that the presence of epileptiform discharges predicts against achieving remission.[53, 54] Only one study found background EEG slowing to be a poor prognostic factor.[55] More recently, a study found a significant association of generalized polyspike train during sleep with drug-resistant IGE (odds ratio=4, p=0.012).[56] Similarly, higher epileptiform discharge densities and longer generalized spike-wave paroxysms have been found to be significantly associated with shorter durations of seizure freedom.[57] However, several studies did not find any association between EEG abnormalities and seizure remission.[58-66]

Response to antiseizure medications

Polyspikes and polyspike-wave discharges during sleep were found to be associated with poor response to ASM therapy in CAE.[14] Generalized spike-wave frequency of <3.2 Hz in the pre-treatment EEG predicted poor response to therapy in a mixed IGE cohort.[67] In JME, focal discharges, lack of photosensitivity, and epileptiform discharges on neuropsychological activation were associated with poor treatment response in a retrospective study.[68] A randomized clinical trial investigated the duration of the longest absence seizure paroxysm captured on pre-treatment 1-hour video-EEG in CAE. Shorter absence seizures were found to be significantly associated with better treatment success in CAE (Table 3).[16]

Cognitive and behavioural outcomes

A meta-analysis reported significantly reduced cognitive functions across all domains except visuospatial abilities in IGE.[69] However, only a small number of studies have investigated the EEG predictors of cognitive and behavioural outcomes. A study based on 24-hr ambulatory EEG data demonstrated that reduced cognitive and memory functions were associated with higher cumulative duration of epileptiform discharges in IGE.[70] Similarly, cumulative duration of generalized epileptiform discharges captured on pre-treatment 24-hr video-EEG demonstrated a negative correlation with visual memory task scores among a cohort of children with CAE and JAE.[71] Absence seizures lasting ≥20 seconds in the pre-treatment video-EEG predicted worse performances on baseline measures of attention in CAE.[16]

Challenges in interpretation

The interpretation of data from multiple studies is difficult due to heterogeneity among studies. The results from these studies depend on many factors: study design (prospective vs retrospective), cohort (incident vs prevalent, and age group), setting (community vs tertiary center), duration of follow-up, number lost to follow-up, diagnostic accuracy, definitions used (e.g. ILAE criteria), and technical aspects of EEG recording.[72] Despite these limitations, a common pattern emerges which shows prolonged epileptiform discharges and cumulative discharge burden have a negative impact on outcomes.

UNRAVELLING BIORHYTHMS

Focal seizures and interictal EDs demonstrate ultradian, circadian, and infradian rhythmicity.[7, 8] Rhythmicity of generalized EDs has been investigated rarely. One of the early studies based on two patients with ‘petit mal’ seizures detected ultradian cycles of higher

spike rate every 90-100 minutes.[73] A study based on 24-hour ambulatory data found two peaks of ED density (11 pm to 7 am and 12 noon to 4 pm) and two troughs (9 am to 11 am and 6 pm to 8 pm).[30] Using a strict forced desynchrony protocol to eliminate external influences on the intrinsic circadian rhythm, researchers were able to find two peaks of ED occurrence; 7 am to 11 am and 10.10 pm to 02.10 am in two patients diagnosed with IGE.[29] These studies suggest time-dependent circadian rhythmicity of ED generation in IGE.

The EDs in IGE also demonstrate rhythmicity in relation to the sleep-wake cycle. Across the 24-hour sleep-wake cycle, 67% of EDs emerge from non-rapid eye movement (NREM) sleep.[30] Epileptiform discharges tend to be significantly less frequent and longer in duration during wakefulness compared with NREM sleep.[30, 73] Another study based on a mixed IGE cohort found a significant and sudden increase in ED rate in the first hour after sleep onset ('sleep surge') and a significant decrease in the second hour after awakening.[74]

These studies show the value of prolonged EEG to unravel underlying biorhythms in ED generation. These findings have considerable clinical implications. For example, diagnostic EEGs are more likely to be successful if NREM sleep is captured, and therapy can be targeted to match the disease activity when at its maximum. Given the variability of ED rate throughout the day, a brief EEG recording is less useful for diagnosis and other broader applications in IGE. Ambulatory EEG is particularly valuable to capture natural sleep in subjects' own environment and ED spread across the day.

EXPLORING FUNCTIONAL CONNECTIVITY AND EPILEPTIC NETWORKS

High-density EEG

Providing a much higher spatial resolution than conventional 10-20 system, high-density EEG is a valuable tool for electrical source imaging of seizure foci for source localization in epilepsy surgery workup. In a surgical series, high-density EEG had a sensitivity of 84% and a specificity of 88% in localizing seizure foci.[75] Furthermore, high-density EEG provides an opening to study the network properties in epilepsy.[76] Only a handful of studies have applied this technique in IGE. One such study was able to demonstrate the propagation pattern of absence seizure from the onset in the orbitofrontal and dorsolateral frontal regions.[77] A similar analysis has revealed the involvement of the ventromedial frontal network in the propagation of spikes during absence seizures.[78] In JME, restricted cortical networks in the mesial orbitofrontal as well as anterior and basal medial temporal lobe are involved during

discharges.[79] These studies are in favour of 'cortical focus theory' of absence seizures demonstrated in animal models in which generalized spike-wave activity originates in the somatosensory cortex followed by rapid propagation through the cortico-thalamic network.[80]

Simultaneous EEG and functional MRI

One major drawback of standard scalp EEG is poor spatial resolution despite the high temporal resolution. On the contrary, fMRI has an excellent spatial resolution. Simultaneous recording of the EEG and functional MRI (EEG-fMRI) provides an opening to study brain metabolic changes accompanied by ED by measuring blood oxygenation level-dependent (BOLD) signal changes. The EEG-fMRI is a valuable non-invasive tool to study functional connectivity and epileptic networks associated with EEG activity.[81] In focal epilepsies, EEG-fMRI helps localize seizure foci during the pre-surgical planning.[82] EEG-fMRI technique has been applied in investigating photoparoxysmal response, ASM responsiveness, and functional networks in IGE.

As summarized in a previous review,[83] three key findings emerge from EEG-fMRI studies in relation to IGE networks: evidence of thalamic activation in the vast majority of studies, cortical (particularly fontal) activation preceding the thalamic peak in some studies,[84, 85] and deactivation of default mode network regions.[86] Though there is an inter-individual variation in the pattern of cortical activation, highly consistent changes are observed within individuals during absence seizures.[84] Early activation of the frontal cortical region in the epileptic network reinforces evidence supporting the 'cortical focus theory'.[84]

Several fMRI studies have investigated network correlates of treatment responsiveness in IGE. An EEG-fMRI study found evidence of different spike-wave generators among valproate-resistant IGE patients with more prominent cortical involvement compared with valproate-responsive patients.[87] The same group found significantly reduced default mode network connectivity and cerebellar resting-state functional connectivity among patients with valproate-resistant IGE.[88, 89] Hippocampal functional connectivity was found to be impaired and negatively correlated with epilepsy duration in drug-resistant GTCS in IGE whilst drug-responsive patients demonstrated compensatory improvement in hippocampal functional connectivity on follow-up.[90] However, a recent study using the graph theory on resting state fMRI data did not find significant differences in network topology between drug-resistant and responsive IGE.[91]

EEG-fMRI studies have also provided useful insights into the network involvement in photoparoxysmal response and photosensitivity in IGE. Activation of premotor and parietal cortices was found three seconds before the onset PPR and before activation of the visual cortex.[92] A study involving JME patients with PPR detected early involvement of putamen and sensorimotor cortex.[93] Abnormal connectivity between the visual thalamus and several cortical regions (occipital, sensory-motor, supplementary motor, anterior cingulum) was demonstrated among IGE patients with PPR in another study.[94] These studies point to a cortical-subcortical network in association with PPR.

Transcranial magnetic stimulation combined with EEG

Transcranial magnetic stimulation (TMS) is a non-invasive technique to stimulate the brain using an external magnetic field. Combining TMS and EEG provides an opportunity to study the signal propagation within functionally connected brain regions or brain networks.[95] Other applications of TMS-EEG in epilepsy include localization of epileptogenic zone, mapping of eloquent cortex, and measurement of cortical excitability.[96] There have been only a few studies describing TMS-EEG applications in IGE. A TMS-EEG study involving 10 JME patients demonstrated significantly increased cortical excitability in the frontal region following sleep deprivation.[97] Among patients with IGE, the TMS evoked potential analysis revealed significantly increased N100 component compared with healthy subjects.[98] Another study involving 25 patients diagnosed with GGE reported similar results in addition to TMS-induced ED in two subjects.[99] We did not find any studies describing connectomes in IGE using this technique.

Single pulse TMS can be used to induce epileptiform discharges from the epileptogenic cortex in focal epilepsy.[100] Using the paired-pulse TMS paradigm, researchers have demonstrated induction of generalized epileptiform discharges among some patients with IGE.[101] These studies suggest that TMS-induced epileptiform discharges may be a biomarker of cortical hyperexcitability during the interictal state.

With TMS-EMG methodology, researchers have demonstrated that, in IGE, cortical hyperexcitability is associated with attention dysfunction and mood disturbances.[102, 103] TMS-

EEG has the potential to be used as a noninvasive tool to evaluate cognition and mood in IGE. At present, TMS-EEG remains an underutilized tool in IGE.

EEG and graph theory

Epilepsy is conceptualized as a disorder of brain networks. Brain regions represented by 'nodes' and connections among the nodes represented by 'edges' constitute a network. Graph theory provides a mathematical conceptual structure to study such networks and it can be applied to data derived from neuroimaging and electrophysiology including EEG.[104]
Our search yielded five studies on IGE cohorts with applications of graph theory based on EEG data. One study compared network topology among IGE patients, their unaffected first-degree relatives, and healthy controls. The network topology was different between patients and controls, but some similarities were found between patients and unaffected relatives suggesting network topology in IGE is an inherited endophenotype.[105] Two studies on drug naïve JME demonstrated differences in functional connectivity between patients and controls,[106, 107] while one study found increased functional connectivity in the preictal state compared with the interictal state.[106] When the four main IGE syndromes (CAE, JAE, JME, GTCA) were compared, differences in functional connectivity measures were detected among those groups.[108] Another study comparing groups of well-controlled IGE, drug-resistant IGE, and healthy controls found differences in network topology in the alpha band (10-12 Hz) between well-controlled IGE and controls.[109] These studies suggest that the graph theory approach can be used to investigate a wide range of clinical and research questions in our understanding of networks in IGE.

CLINICAL VERSUS RESEARCH APPLICATIONS

Not all EEG applications discussed above have direct relevance for clinical practice. The use of EEG in the classification of IGE syndromes, guiding ASM therapy, and predicting prognosis are examples of clinical applications of EEG to help the clinician make critical decisions in routine practice. Unravelling biorhythmicity and exploring functional connectivity are predominantly research applications though with some clinical relevance. For example, the knowledge of circadian rhythmicity can help select the appropriate type of EEG recording whereas functional connectivity studies may shed some light on drug resistance.

THE CHOICE OF EEG TEST TYPE

The EEG can be recorded in several ways ranging from outpatient routine EEGs to inpatient video-EEG monitoring (VEM) with outpatient routine recordings being the cheapest option. More recently, prolonged outpatient ambulatory EEG has emerged as a more cost-effective alternative for VEM.[110] Studies have demonstrated a significantly higher yield of both the ictal and interictal epileptiform abnormalities in prolonged ambulatory EEG compared with the routine EEG.[111] The capture of natural sleep-associated epileptiform discharges is a major reason for the higher yield in prolonged ambulatory EEG.[30, 74]

Which type of EEG is the best in option IGE? This decision depends on the indication, availability, and cost. For diagnostic purposes, it is reasonable to request a routine outpatient EEG first as it is a readily available and relatively inexpensive option while bearing in mind the yield is low, around 6%.[112] If the routine EEG is normal, one should consider a sleep-deprived outpatient EEG as the next step. However, if the resources are available, 24-hr ambulatory EEG is a much better test with a higher diagnostic yield. Data gathered from a short outpatient EEG recording is often inadequate for syndromic classification, predicting prognosis, and guiding ASM therapy. We recommend outpatient short-term VEM for 3-4 hours (with sleep) as the minimum requirement, however, 24-hr ambulatory EEG is the preferred option for these purposes. The technology has evolved enabling outpatient ambulatory video-EEG recordings for 7-10 days. Such prolonged recordings are useful to study ultradian and circadian rhythms in IGE. Prolonged EEG recordings extending for months are required to study longer epileptiform cycles in IGE and the recent invention of a sub-scalp long-term EEG monitoring system is a potential tool for this purpose.[113] In functional connectivity studies, the length of EEG recording is driven by the relevant test paradigm of the specific investigation.

LIMITATIONS AND FUTURE DIRECTIONS

Specific limitations of the literature have been discussed under relevant sections. In general, these emerge at four levels: study design, cohort, eligibility criteria, and EEG outcome. Retrospective studies were more common among the reviewed literature, but prospective studies are likely to yield more robust data. Patients seen in the pediatric and adult cohort may have different disease trajectories. Similarly, subjects recruited from tertiary centers are likely to be more severe cases and investigated thoroughly compared with those seen in the primary care setting. Drug naïve versus treated patients diagnosed with the same IGE

syndrome may have different EEG outcomes (e.g. photoparoxysmal response). Eligibility and diagnostic criteria of recruitment may differ among studies, particularly depending on when the study was conducted. What we capture on the EEG depends on multiple factors ranging from the length of the recording to activation procedures. The vast majority of publications were based on a qualitative assessment of EEG, simply answering the question of whether a particular EEG abnormality is present or not. Only a few studies provided quantitative data such as ED density and paroxysm duration. Furthermore, there is a bias towards JME and CAE whilst GTCA is underrepresented amongst published literature.

High-frequency oscillations (HFO), captured on both intracranial and scalp EEG, are recognized as a biomarker of epilepsy.[114] Growing evidence supports the notion that HFOs mark the seizure-onset zone and resection of the region generating HFOs is associated with better surgical outcomes in drug-resistant focal epilepsy.[115] Furthermore, physiological HFOs may be useful in functional mapping of the eloquent cortex.[116] The applications of HFOs have been rarely studied in IGE. High-frequency oscillations captured on magnetoencephalography (MEG) recordings have been demonstrated to be valuable in studying networks associated with absence seizures.[117] Another study based on MEG found an association between the severity of absence seizures in CAE and HFOs.[118]

To circumvent these limitations, prospective studies using stringent eligibility criteria are encouraged. Ambulatory EEG recording for at least 24 hours is preferred over brief outpatient EEGs because of its higher yield, ability to capture circadian variations, and greater ability to discriminate among syndromes. Serial EEGs, starting from the pre-treatment stage, would be useful to evaluate syndromic differences and prognosis. Quantitative evaluation of EEG abnormalities is likely to yield more robust results. Reading and quantifying the EEG changes manually by human raters is tedious and of variable interrater agreement. The feasibility of automated computer-assisted techniques has been described which should pave way for future research and clinical applications in this field.[119, 120] There is scope for EEG-HFO research in IGE to investigate applications in diagnosis, network mapping, and prognosis.

Personalized medicine (precision medicine) refers to targeted therapy based on individual genetic, environmental, and lifestyle characteristics riding on the assumption that phenotype is determined by specific genetic abnormalities.[121] This is an evolving field and personalized

medicine is currently available for a small number of monogenic epilepsies. Ketogenic diet in GLUT1-deficiency syndrome and sodium channel blockers in *PRRT2*-related epilepsy are classical examples of precision medicine.[121] Certain rare single gene mutations such as *GABRG2, GABRA1,* and *SLC2A1* are associated with genetic generalized epilepsies.[122] Though there is no current evidence, we can speculate that detailed EEG signal analysis might reveal a correlation with the genotype, thus serving as a potential biomarker for personalized medicine in the future.

CONCLUSION

EEG is a powerful non-invasive tool. Compared with extensive and advanced techniques of applications in focal epilepsies, EEG utilization in IGE often remains restricted to a diagnostic tool. In this review, we have highlighted many clinical and research applications of EEG in IGE beyond confirming the diagnosis. The current literature, albeit limited, suggests the feasibility of more advanced applications of EEG to enhance our understanding of underpinning pathophysiologic processes and improve the overall management of IGE.

ETHICAL PUBLICATION STATEMENT

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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Figure 1: An epileptiform K-complex

Figure 2: EEG characteristics of 'organized' versus 'disorganized' absence seizures.

A. Regular and rhythmic 3 Hz generalized spike-wave discharges of an absence seizure in childhood absence epilepsy.
B. The disorganized ictal rhythm of an absence seizure in juvenile myoclonic epilepsy. Note the irregular mix of generalized spike-wave and polyspike-wave discharges.

Figure 3: 'Pure' versus 'mixed' generalized epileptiform paroxysms in idiopathic generalized epilepsy.

A. A ‘pure’ generalized epileptiform paroxysms containing regular spike-wave discharges in childhood absence epilepsy.
B. A ‘mixed’ paroxysm in juvenile absence epilepsy. Note the irregular mix of spike-wave and polyspike-wave discharges.

Figure 4: The EEG characteristics of an absence seizure in juvenile absence epilepsy. The salient features to be noted are (a) long paroxysm-only 10 seconds of the 26-second-long paroxysm is shown here, (b) predominant polyspike-wave discharges with occasional spike-wave intrusions, and (c) disorganization of the ictal rhythm due to spike-wave discharge intrusions.

Figure 5: ‘Pure’ versus ‘mixed’ generalized epileptiform fragments in idiopathic generalized epilepsy.

A. A ‘pure’ generalized epileptiform fragment containing spike-wave discharges in childhood absence epilepsy.
B. A ‘mixed’ fragment in juvenile absence epilepsy. Note the mix of spike-wave and polyspike-wave discharges.

Table 1: Comparison of EEG characteristics among the four main syndromes of idiopathic generalized epilepsy.

EEG feature	CAE	JAE	JME	GTCA
PS & PSW during wakefulness	+	++	++	+
PS & PSW density	+	+++	++	+
Total ED density	+	+++	+++	+
Atypical ED	+	++	++	+
OIRDA	+	—	—	—
Photoparoxysmal response	+	+	+++	+
'Pure' generalized discharges	++	++	+	+

Disorganized generalized paroxysms	+	++	+++	+
Duration of generalized paroxysms	++	+++	++	+
Absence seizures during hyperventilation	+++	+++	+	─
Duration of absence seizures	++	+++	++	─

Abbreviations: +, likelihood, duration or density (+ indicates lowest and +++ indicates highest); ─ , not applicable or not found; CAE, childhood absence epilepsy; ED, epileptiform discharge; GTCA, generalized epilepsy with tonic-clonic seizures alone; JAE, juvenile absence epilepsy; JME, juvenile myoclonic epilepsy; OIRDA, occipital intermittent rhythmic delta activity; PS, polyspikes; PSW, polyspike-wave discharges; paroxysm is defined as generalized epileptiform discharges lasting >2 seconds.

Table 2: **EEG differences among syndromes of idiopathic generalised epilepsy**

EEG abnormality	CAE	JAE	JME	GTCA	Cohort	Design	AED	EEG recording details	References
INTERICTAL Fragments	92% (in D & S)	100% (in D &S)	100% (in A, D & S)		70 Children <18y with absence seizures	R	No	SDEEG, HV, IPS, 30 minute recording with A & S	Sadleir et al., 2009
Polyspikes	A-0, D-13%, S-40%	A-0, D-12%, S-24%	A-50%, D-50%, S-50%			R	No		Sadleir et al., 2009
		-	-	33.3% (A & S)	18 adults & children	R	Mix	SDEEG, HV, IPS	Koutroumanidis et al., 2008
Polyspike or polyspike-waves	24.2% (in S), 0% (A)	66.6% (in S), 0% (A)	-		80 children & adults with CAE, JAE	R	Yes	NS	Bartolomei et al., 1997
PPR	18%	7.5%	30.5%		103, age 10-25y	R	Mix	NS	Wolf & Goosses, 1986
	21%	25%	83%			R	No		Sadleir et al., 2009
				27.8%	18 adult & children	R	Mix	SDEEG, HV, IPS	Koutroumanidis et al., 2008
OIRDA	21%	-	-		450 children with CAE	P	No	1-hr video-EEG with HV, IPS. No S	Dlugos et al., 2013
	32%	-	-		Similar to Sadleir et al., 2009	R	No	Similar to Sadleir et al., 2009	Sadleir et al., 2006
Focal ED	13.3%	32.4%	17.9%	14.3%	107 adults	R	Mix	24-hr ambulatory EEG, HV, IPS	Seneviratne et al., 2016
Any atypical epileptiform EEG abnormality	53.3%	82.4%	67.9%	53.6%	107 adults	R	Mix	24-hr ambulatory EEG, HV, IPS	Seneviratne et al., 2016
Mean frequency of ED	3.3 Hz	3.2	3.9	3.6	105 adults	R	Mix	24-hr ambulatory EEG, HV, IPS	Seneviratne et al., 2017
Mean duration of ED paroxysms (seconds)	2.76	4.63	3.23	2.53	105 adults	R	Mix	As above	Seneviratne et al., 2017
Mean of the longest ED	7.16 (7.87)	12.54 (14.92)	7.40 (7.37)	2.9 (1.1)	105 adults	R	Mix	As above	Seneviratne et al., 2017

paroxysm & SD (sec)									
Epileptiform K-complexes and sleep spindles	53.3%	73.5%	71.4%	67.8%	107 adults	R	Mix	As above	Seneviratne et al., 2016
ICTAL (ABSENCE SEIZURE) Median frequency (during the first second)	3 Hz	3.25	3.5						Sadleir et al., 2009
Mean frequency (mid phase: 2-4 seconds)	3 (range 2.7-3.3) Hz	2.9 (range 2.5-3.2)	2.8 (range 2.2-3.5)		20 subjects, age 5-22 with AS	R	NS	3-7 hrs with HV, IPS	Panayiotopoulos et al., 1989
AS during hyperventilation	87%	87%	33%			R	No		Sadleir et al., 2009
Disorganized discharges	Least common	8 times more likely than CAE	110 times more likely than CAE			R	No		Sadleir et al., 2009
Seizure duration (seconds)	12.4±2.1	16.3±7.1	6.6±4.2		20 subjects, age 5-22 with AS	R	NS	3-7 hrs with HV, IPS	Panayiotopoulos et al., 1989

A=awake, AED= antiepileptic drugs at the time of recording, AS=absence seizures, CAE=childhood absence epilepsy, D=drowsy, ED= epileptiform discharges, GTCA=generalized epilepsy with tonic-clonic seizures alone, HV= hyperventilation done, IPS=intermittent photic stimulation done, JAE=juvenile absence epilepsy, JME= juvenile myoclonic epilepsy, OIRDA= occipital intermittent rhythmic delta activity, PPR= photoparoxysmal response, S=sleep, SD=standard deviation, SDEEG=sleep deprived EEG, P=prospective, R=retrospective, NS=not specified. (Adapted and reproduced with permission from the publisher. Seneviratne U, et al. Can EEG Differentiate Among Syndromes in Genetic Generalized Epilepsy? J Clin Neurophysiol. 2017;34:213-221. Wolters Kluwer Health Inc.)

Table 3: EEG features predictive of prognosis in idiopathic generalized epilepsy

Reference	Design	Cohort	Syndrome	N	Age onset range years (mean)	Statistics	Outcome	EEG features studied	EEG poor prognostic features
Bartolomei (1997)	R	Hospital	CAE, JAE	80	10-26 (9,14)	UV, MV	Response to ASM	FA, PS, PD, POS	POS in sleep in CAE
Baykan (2008)	R	Hospital	JME	48	(14.4±2.9)	UV	Remission	FA, PS, SWDHV, NRX	None
Benjamin (2011)	R	Hospital	CAE, JME, IGE	21	2-20	UV	Response to ASM	GSWD frequency	GSWD frequency <3.2Hz
Callenbach (2009)	P	Hospital	CAE	47	1-9.7 (5.4)	UV	Remission	BG, ED	None
Currier (1963)	R	Hospital	Petit mal	32	3-17	NS	Remission	GSWD frequency/ duration/ amplitude, EEG seizure	None
Del Felice (2010)	R	Hospital	IGE, focal, single seizure	352	3-84 (31.5)	UV, MV	Remission	ED, slow activity	Abnormal EEG (only in UV analysis)
Dlugos (2013)	P	Hospital	CAE	446	2.5-13	UV, MV	Freedom from failure and seizure free at 16-20 weeks	Duration of absence seizure	Longer seizures
Gibberd (1966)	R	Hospital	Petit mal	139	NS	NS	Remission	BG, GSWD	None
Grosso (2005)	R	Hospital	CAE	119	NS	UV, MV	Remission	Typical GSWD, atypical (PS, abnormal BG, irregular GSWD, 'lead-in', fixation-off)	Atypical EEG

Kamel (2010)	R	Hospital	IGE, focal	34	NS	UV	Remission	ED	Presence of ED
Loiseau (1983)	R	Hospital	Absence epilepsy	90	NS	UV	Remission, development of GTCS	Regularity of GSWD, PD, PS, absence seizure on EEG	PS, lack of PD
Matsuoka (1992)	R	Hospital	JME	32	NS	NS	Response to ASM	NS	Focal ED, lack of PS, ED on neuropsychological activation
Mohanraj (2007)	P	Hospital	IGE	103	5-51	UV	Remission	ED	None
Nicholson (2004)	R	Hospital	IGE	962	NS	UV	Remission	GSWD, PS, FA	None
Sato (1976)	P	Hospital	Absence epilepsy	52	5.3-24.3 (10.5)	UV, MV	Remission	BG normal or abnormal	None
Seneviratne (2017)	R	Hospital	IGE	105	13.3 (SD 5.1)	UV, MV	Duration of seizure freedom	ED density, duration of generalized paroxysms, atypical EEG abnormality	Higher ED density, longer paroxysms
Sinclair (2007)	R	Hospital	Absence epilepsy	119	NS	NS	Remission	Typical versus atypical (BG slow, FA, irregular GSWD)	None
Sun (2018)	R	Hospital	IGE	165	NS	UV, MV	Drug resistance	GPT in sleep/wakefulness, focal spikes, polyspike-wave, GPFA	GPT in sleep
Szaflarski (2010)	R	Hospital	IGE	267	NS	UV	Remission	Symmetry of GSWD, focal ED, focal slow	Focal ED, focal slow, asymmetric GSWD
Verrotti (2009)	P	Hospital	IGE	63	6.7-20.8	UV	Remission	PS	None
Wirrell (1996)	R	Population	CAE	72	1-14 (5.7)	UV, MV	Remission	GSWD, BG, PS, SWDHV	BG slowing

R, retrospective; P, prospective; CAE, childhood absence epilepsy; ED, epileptiform discharge; JAE, juvenile absence epilepsy; JME, juvenile myoclonic epilepsy; IGE, idiopathic generalized epilepsy; NS, not specified; MV, multivariate; UV, univariate; ASM, antiseizure medication; GPT, generalized polyspike train; GPFA, generalized paroxysmal fast activity; GTCS, generalized tonic-clonic seizures; FA, focal abnormalities; PS, photosensitivity; PD, posterior delta rhythm; POS, polyspikes; SD, standard deviation; SWDHV, spike-wave discharges induced by hyperventilation; NRX, normalization of EEG on treatment; GSWD, generalized spike-wave discharge; BG, background, ED,

epileptiform discharges; EEG, electroencephalogram; N, total number of subjects. (Adapted and reproduced with permission from the publisher. Seneviratne U, et al. The prognosis of idiopathic generalized epilepsy. Epilepsia. 2012;53:2079-2090. John Wiley & Sons.)

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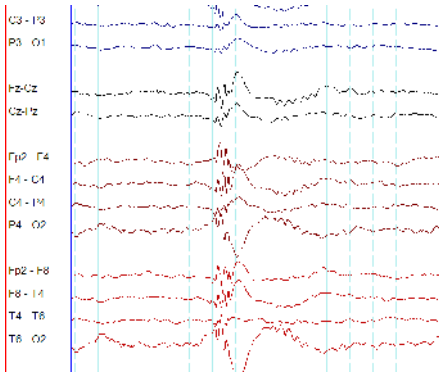

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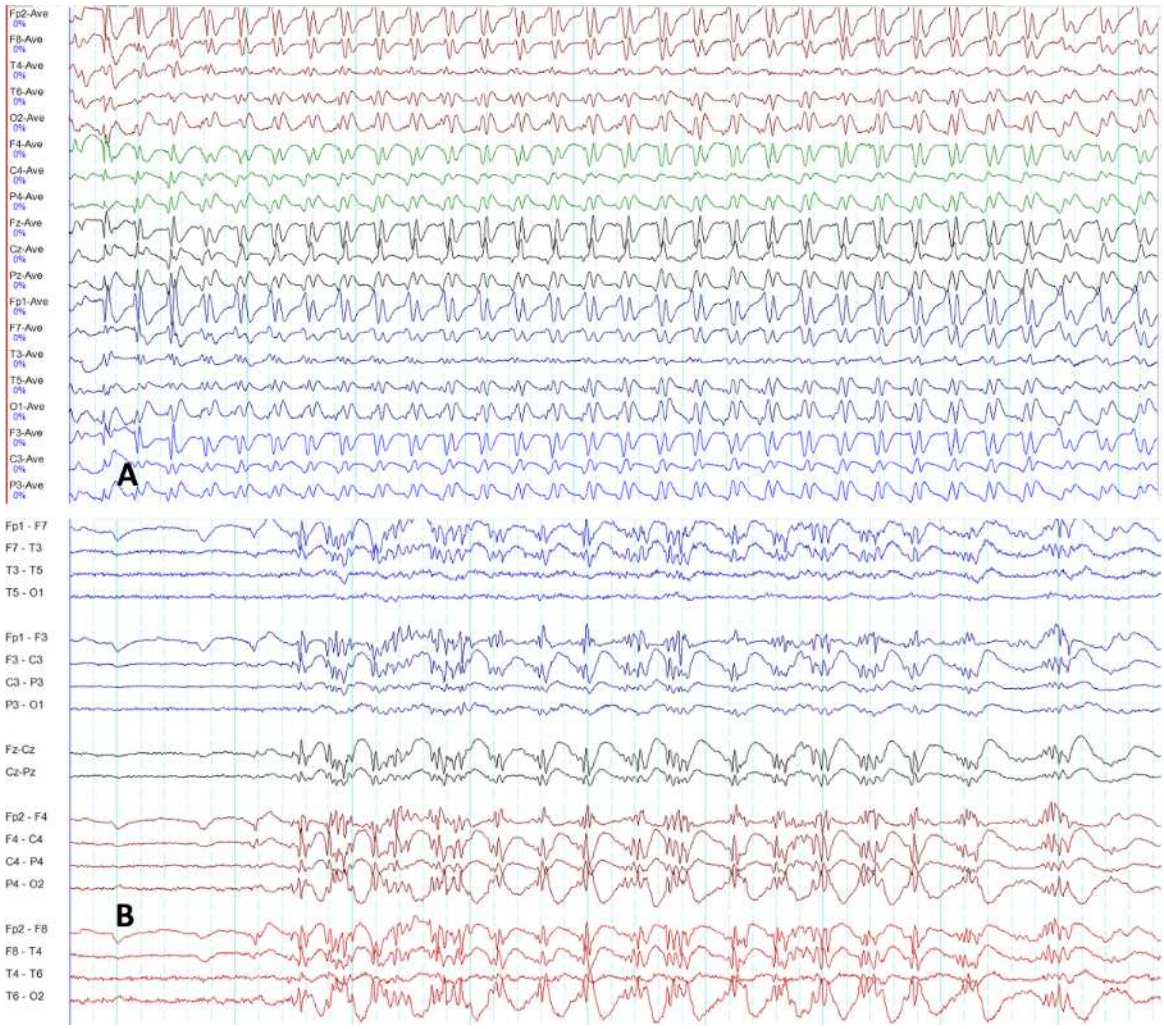

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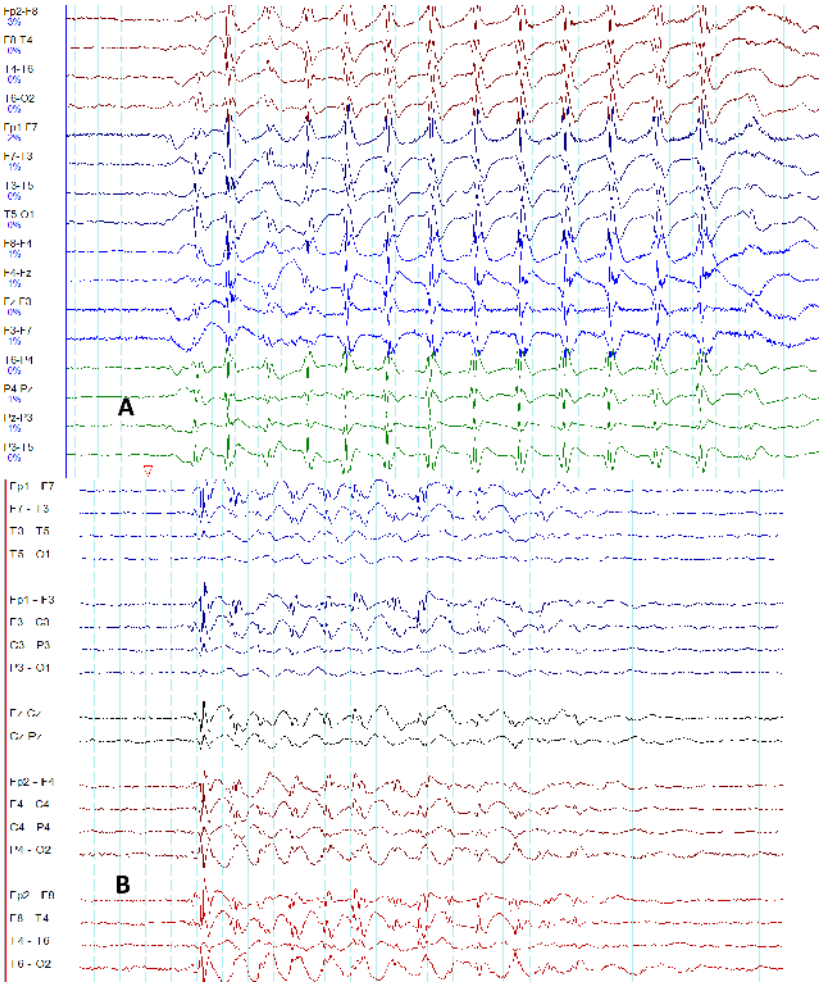

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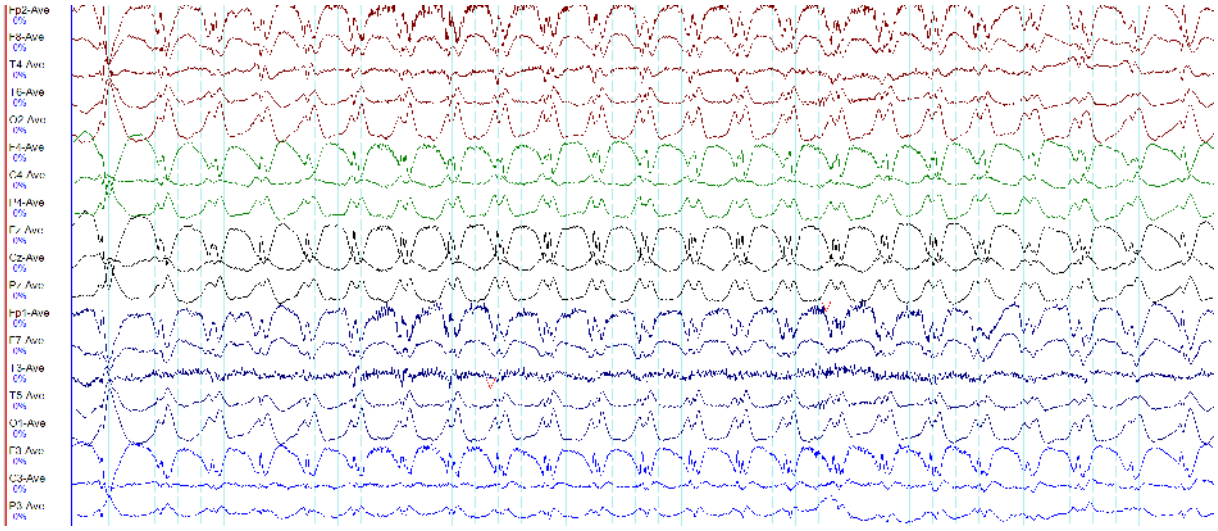

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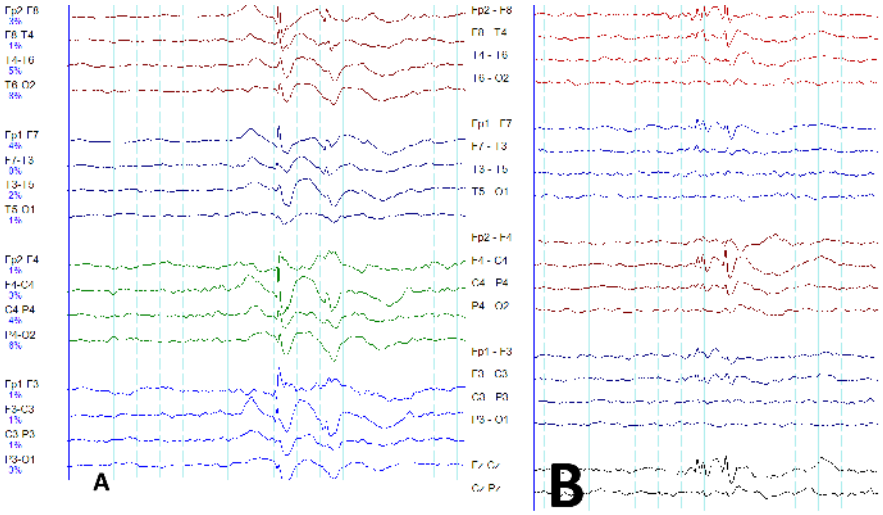

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