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SPECTRAL EEG ANALYSIS IN REFRACTORY JUVENILE MYOCLONIC EPILEPSY: A NEW BIOMARKER IN EPILEPSY

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INTRODUCTION

Epilepsy

The difference between seizures and epilepsy is commonly confused. The two are not the same. Epilepsy is defined by a state of recurrent, spontaneous seizures. If one seizure occurs in an individual, it may not necessarily mean that they have epilepsy because the seizure may have been provoked and that individual may never have a seizure again.

The concept of epileptogenesis refers to the development of the state of epilepsy. It refers to the sequence of events that converts the normal brain into one that can support a seizure. It is assumed that groups of neurons become hyperexcitable, poised to abnormally discharge.

Much of what we know about epilepsy emerged in the 1800s with the first evaluation of autopsy specimens from individuals with epilepsy. The seminal work of Bouchet and Cazauvieilh in 1825, followed by Sommer and other scientists decades later suggested profound structural changes to the brain in patients with epilepsy. A new era in epileptology began with neurologists such as Hughlings Jackson in the late 1800s providing suggestions for the ways seizures might occur. In the 1900s, the most important advances were the development of the electroencephalogram (EEG) and the first recordings of the EEG in patients with epilepsy by Gibbs, Jasper, and Penfield. In parallel, the breakthroughs in understanding the essential aspects of nerve cell function, from Hodgkin and Huxley to others, shaped a growing appreciation that epilepsy was a complex disorder that could best be understood through diverse approaches.

Neurobiology of the epilepsy

The ionic basis of the *action potential* is a fundamental aspect of neurobiology that can suggest potential mechanisms of seizures. Neurons are designed to discharge because of an elegant orchestration of sodium and potassium channels that rely on chemical and ionic gradients across the cell membrane. Normally a high concentration of potassium exists inside a neuron and there is a high extracellular sodium concentration, as well as additional ions, leading to a net transmembrane potential of -70 mV. If the balance is perturbed (e.g., if potassium is elevated in the extracellular space), this can lead to depolarization that promotes abnormal activity in many ways: terminals may depolarize, leading to transmitter release, and neurons may depolarize, leading to action potential

discharge. Pumps are present in the plasma membrane to maintain the chemical and electrical gradients, such as the sodium-potassium ATPase, raising the possibility that an abnormality in these pumps could facilitate seizures. In addition to pumps, glia also provide important controls on extracellular ion concentration, which has led many to believe that glia are just as important as neurons in the regulation of seizure activity. Thus, the control of the ionic environment provides many potential targets for novel anticonvulsants.

Voltage-gated sodium channels (VGSCs) are integral membrane proteins (Figure 1). They are essential for normal neurologic function and are, currently, the most common recognized cause of genetic epilepsy. The most important sodium channel subunit of relevance to epilepsy is SCN1A, in which over 650 genetic variants have been discovered. SCN1A mutations are associated with a variety of epilepsy syndromes; the more severe syndromes are associated with truncation or complete loss of function of the protein. SCN2A is another important subtype associated with epilepsy syndromes, across a range of severe and less severe epilepsies. This subtype is localized primarily to excitatory neurons, and mutations have a range of functional effects on the channel. SCN8A is the other main adult subtype found in the brain and has recently emerged as an epilepsy gene, with the first human mutation discovered in a severe epilepsy syndrome.

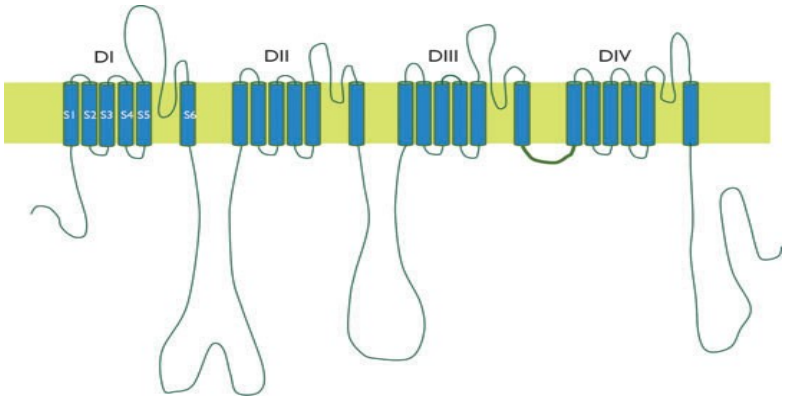

Figure 1. The structure of the VGSC

Research into seizures has gravitated to mechanisms associated with *synaptic transmission* because of its critical role in maintaining the balance between excitation and inhibition. As more research has identified the molecular mechanisms of synaptic transmission, it has become appreciated that defects in almost every step can lead to seizures. Glutamatergic and γ-aminobutyric acid (GABA)-ergic transmission, as the major excitatory and inhibitory transmitters of the nervous system, respectively, have been examined in great detail. It is important to point out, however, that both glutamate and GABA may not have a simple, direct relationship to seizures. GABA-ergic transmission can lead to depolarization rather than hyperpolarization if the gradients responsible for

ion flow through GABA receptors are altered. The relationship of glutamate to excitation may not always be simple either. One reason is that glutamatergic synapses innervate both glutamatergic neurons and GABA-ergic neurons in many neuronal systems. Exposure to glutamate could have little net effect as a result, or glutamate may paradoxically increase inhibition of principal cells because the GABA-ergic neurons typically require less depolarization by glutamate to reach threshold. It is surprisingly difficult to predict how glutamatergic or GABA-ergic modulation will influence seizure generation in vivo, given these basic characteristics of glutamatergic and GABA-ergic transmission. In 1964, Matsumoto and Ajmone-Marsan found that the electrographic events recorded at the cortical surface during seizures corresponded to paroxysmal depolarization shifts (PDS) of cortical pyramidal cells occurring synchronously.

Thalamocortical circuits have an intrinsic capacity to generate state-dependent oscillations of different frequency and degrees of synchrony. This modulation may have implications for a better understanding of the descending control of thalamic nuclei by the cortex, and the genesis of pathological rhythmical activity, such as absence seizures (Bal 2000).Authors suggest that differential activation of thalamic $GABA_A$ and $GABA_B$ receptors in response to varying corticothalamic input patterns may be critical in setting the oscillation frequency of thalamocortical network interactions (Blumenfeld 2003). Enhanced cortical output, as might occur for example during cortical disinhibition, appears to be able to transform normal thalamic rhythmic activity into pathophysiologcial hypersynchronous discharge. This suggests that either cortical or thalamic mechanisms can lead to degeneration of an absence discharge. These results are important because they show additional mechanisms in which the thalamic portion of the circuit can be recruited to produce a generalized seizure.

Thalamocortical signaling is primarily excitatory, causing the activation of corresponding areas of the cortex, but is mainly regulated by inhibitory mechanisms. The specific excitatory signaling is based upon glutamatergic signaling, and is dependent on the nature of the sensory information being processed. Computational neuroscientists are particularly interested in thalamocortical loops because they represent a structure that is disproportionally larger and more complex in humans than other mammals which may contribute to humans' special cognitive abilities.

Thalamocortical radiations have been researched extensively in the past due to their relationship with attention, wakefulness, and arousal. Past research has shown how an increase in spike-and-wave activity within the thalamocortical network can disrupt normal rhythms involved with the sleep-wakefulness cycle, ultimately causing seizures. Burst firing within a part of the thalamocortical network stimulates GABA receptors within the thalamus causing moments of increased inhibition, leading to frequency spikes, which offset oscillation patterns (Figure 2).

Previous neurophysiological studies demonstrates frontal involvement in the generation of GSW discharges in patients with IGE (Santiago-Rodriguez 2002). The pathophysiology underlying the initiation of GSW discharges is believed to involve an extensive network encompassing the thalamus and cortex circuitry.

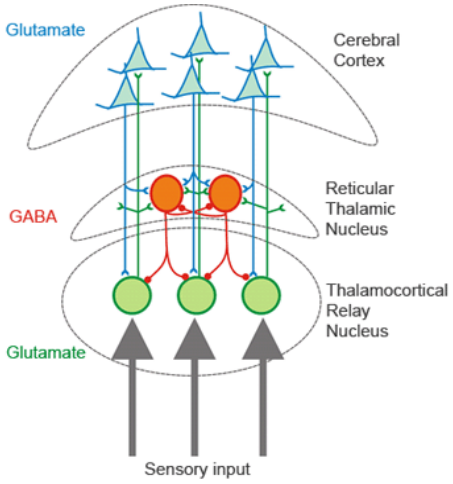

Figure 2. Thalamocortical circuit

Quantitative electroencephalogram analysis

The aim of *functional neuroimaging* is to understand the functional organization of the brain. This aim incorporates several aspects of functional neuroanatomy: the location of processing area, the time course or dynamics of their activities, and the nature of their interactions. Changes in neuronal activity induce variations in cerebral metabolism, blood flow, blood volume and blood oxygenation and electromagnetic fields. Changes in these haemodynamic and electromagnetic signals can be measured by several noninvasive techniques, such as positron emission tomography (PET), functional magnetic resonance imaging (fMRI), electroencephalography (EEG) and magnetoencephalography (MEG).

The brain consists of two hemispheres separated by the longitudinal fissure. The hemispheres are further divided into lobes by two deep fissures: the Rolandic fissure cuts vertically the outer part of both hemispheres and the Sylvian fissure is almost horizontal. There are four lobes in each half of the cortex: frontal, parietal, temporal and occipital (Figure 3). Each lobe assumes specific functions.

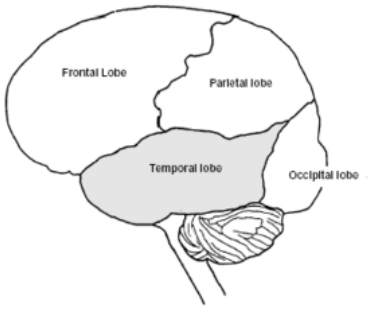

Figure 3. Anatomy of the brain

The total surface of the cortex is about 1600 cm^2, highly folded to fit in the skull compartment. The neurons and the glia cells are the principal "building blocks" of the brain. There are about 1010-1011 neurones in the brain, and they are vastly outnumbered by the glial cells. The glial cells ensure the psysical structure of the brain, the proper concentration of ions and the transport of the nutrients between blood vessels and brain tissue. Neurons are the information-processing units of the brain. The cell bodies and dentrites of the neurons are found in the grey matter, which constitutes the thin outer layer of the cortex and the subcortical structures like the thalamus. The interior of the brian is largely occupied by nerve fibres, called white matter because of the mylenated appearance of the axons that constitute it. These axons connect different cortical areas, possibly in different hemispheres, and between the cortex and the subcortical structures.

Quantitative EEG (qEEG) is a computer analysis of the EEG data obtained using Fast Fourier Transform (Welch 1967). qEEG plays a significant role in basic research and clinical studies of brain injury, neurological disorders, epilepsy, sleep studies and consciousness and brain function. It tipically uses 19 or more channels of simultaneous EEG recording under specific recording conditions. This EEG data are usually compared against a reference databases of other people's EEGs. The analysis identifies and highlights variations from the norm. There was a great of effort to create these averages, also called "normal databases". It involves careful screening to exclude people with a history of problems like depression, anxiety, learning and attention problems, etc (Thatcher 2003).

qEEG can indicate brain areas where there's too much or too little EEG activity compared to the normal database. It could also show which areas may not be communicating well with other areas. Excessive EEG activity or poor communication tend to correlate with less brain efficiency.

To improve the spatial resolution, qEEG analysis has also combined with medical imaging technology as CT, MR, PET, etc. (Nitish 2004).

Quantitative EEG techniques include frequency analysis (spectral analysis), significance probability

mapping, and other analytic technique. Each can be done on spontaneous EEG in various states or in conjunction with sensory stimulation (Lehmann 1987). Several types of displays are available, including topographic mapping of scalp electrical activity. Assessment of normality in these records must take into account age, gender, state of alertness, medications and other factors (Nuwer 1998).
Apart from standard i.e. visual analysis of EEG, analyses in the frequency domain i.e. quantitative analyses are powerful methods to evaluate frequency composition of ongoing EEG activity.
In cerebrovascular disease, this method can confirm the existence of lesions that are too mild to show up on routine EEG or too early to show up on computed tomography. The results correlate well with cerebral blood flow studies.
In epilepsy, qEEG technique have found subtle degrees of background EEG changes near epileptic foci. Other methods can quantify epileptic spikes in useful ways and can indicate which region is driving other regions during seizures.
Quantification is also useful for measuring drug effects when drugs (such as thiopental) are given deliberately to provoke acute EEG changes.
In patients with mass lesions and metabolic encephalopathies, quantitative EEG changes do occur, and some of these correlate with the clinical state.
For dementia and neurodegenerative diseases, quantitative EEG techniques are being developed. Some of these tests are accurate in moderately or severely demented patients, but there is still poor accuracy for early or borderline cases.
For dyslexia, schizophrenia and depression, there is a considerable volume of research reports, but still no consensus about how to use quantitative EEG tests for care of individual patients.
These tests require substantial user expertise in EEG. At present, these tests should be viewed as adjunctive to traditional EEG testing: such routine EEG testing should serve as the foundation for any clinical use of qEEG tools.

Juvenile Myoclonic Epilepsy (JME)

JME is one of the Genetic Generalised Epilepsy (GGE) syndromes, which were previously referred to as the Idiopathic generalised epilepsy (IGE). Other recognised syndromes include childhood absence epilepsy, juvenile absences and grand mal seizures on awakening. GGE is a group of epilepsy syndromes with a no focal mechanism of onset and no identifiable cause other than a genetic predisposition (Panayiotopoulos 2005).
The worldwide prevalence of epilepsy is approximately 1%, with idiopathic generalized epilepsy (IGE) diagnoses accounting for 20-40% of all cases. An interictal EEG with typical generalized

spike-and-wave (GSW) discharges in the context of a normal background is supportive of an GGE diagnosis (ILAE 1989; Panayiotopoulos 2002).

JME is a type of epilepsy that typically begins around puberty. It is characterized by myoclonic jerks mostly in the morning and tonic-clonic seizures (TCS) and around one third of people will also have absence seizures (Janz 1998). About 30% of people with JME continue to have seizures despite treatment with antiepileptic drugs (refractory JME). JME is believed to be a genetic condition although, for most people with JME, the genes responsible have not yet been identified. Compared to focal epilepsies, there have been fewer treatment advances for JME or other GGE's.

Typical EEG features of JME consist of generalized discharges of single or multiple spike and slow-wave of frequency of 3-5 Hz, often with frontal-central accentuation, with normal background activity, although occasional complexes as slow as 2 Hz or as fast as 7 Hz may be evident. In addition, a detailed study of EEGs of patients with an unequivocal diagnosis of JME showed a high prevalence of focal EEG abnormalities. Localization–related EEG anomalies are evident in 15-40% of the patients such as focal slow waves, spikes and sharp waves and focal onset of the generalised discharge (Aliberti 1994).

Visual assessment of structural magnetic resonance imaging (MRI) is normal in patients with JME, however recent quantitative MRI studies have shown structural abnormalities in cortical and thalamic grey matter, especially in the frontal lobe, in patients with JME (Kim 2007).

The results of many studies using quantitative EEG (qEEG) technique in clinical settings have been published. In epilepsy qEEG studies have focused on assessing background EEG changes near epileptic foci (Miyauchi 1991), spike quantification on order to identify which region drives other regions during seizures and assessing drug effects when drugs are given deliberately to provoke acute EEG changes (Nuwer 1998).

Most studies using qEEG in GGE have compared inter-ictal background quantitative EEG measures in generalized epilepsies with normal controls, but have not specifically studies patients with JME as a separate group (Clemens 2011). Previous authors hypothesise that these IGE frequency profiles reflect widespread cortical dysfunction essentially common to all the investigated IGE syndromes (Clemens 2000). In some cases, visual analysis of background EEG activity has been described as normal, except for some degrees of intermittent theta activity in patients with poor seizure control or in cases with polytherapy antiepileptic drugs (Clemens 2007). One study attemps to study inter-ictal backgroung qEEG measures between patients diagnosed exclusively JME and healthy controls and its relation with various and standard EEG abnormalities (Tikka 2013). Another recent study analysed background qEEG activity of patients with JME with and without antiepileptic drugs (Santiago-Rodríguez 2008).

Cognitively, frontal dysexecutive, verbal and attentional neuropsychological impairments have been reported in JME. Neuropsychological and anatomical studies have indicated frontal lobe dysfunction in the disease. However, in addition to direct cortical effect, such frontal executive changes can also occur as a function of subcortical damage, via the disruption of striato-thalamo-frontal circuits (Krause 2012). Subcortical structural alterations have been reported in idiopathic generalized epilepsies and JME specifically (Keller 2011). Thus, although frontal cognitive dysfunction is commonly linked to subtle focal cortical abnormalities (Kim 2007), epilepsy is a pathology of functional networks and subcortical integrity is critical for normal cortical network function. The pathogenesis of idiopathic generalized epilepsy is unclear, but the characteristic generalized spike and wave discharges implicate thalamocortical interactions (Blumenfeld 2003). Clinical studies indicate that patients diagnosed with GGE exhibit focal electroencephalographic abnormalities, which involve the talamocortical circuitry. This circuitry is a key network that has been still implicated in the initiation of generalized discharges and may contribute to the pathophysiology of GSW discharges. No studies on refractory JME has been found. In this study we wished to characterise qEEG characteristics of patients with refractory JME.

OBJECTIVE OF THIS STUDY

The objective of this paper was to investigate spectral analysis of background EEG activity, correlating clinical and standard EEG abnormalities with spectral EEG findings of patients with refractory Juvenile Myoclonic Epilepsy (rJME).

Furthermore, was studied whether background activity exhibit frontal lobe disfunction in the disease. Given its presumed thalamocortical basis, was still investigated thalamocortical structural connectivity, as measured by quantitative analysis in patients with rJME.

METHODS

Patient population

This study included data from 19 patients that participated in Refractory Juvenile Myoclonic Epilepsy Cohort (ReJuMec) that was funded by the Medical Research Council in the UK. The main ReJuMec Study objectives were: to characterise the partecipants using EEG and neuropsychology testing; to obtain DNA samples for use in research investigating the genetics of epilepsy and its response to treatment. Patients were recruited to ReJuMec if they had a clinical diagnosis of JME including: 1. generalised seizures with myoclonic jerks with or without absence seizures and TCS; 2. no evidence of focal neurological or intellectual deficit; 3. were refractory to treatment (failed treatment with sodium valproate at a dose of 1000 mg/die over a minimum period of 3 months).
Inclusion criteria in ReJuMec were: all the participant had JME (Commission on Classification and Terminology of the ILAE); the partecipants had aged between 14 and 65 years (adults); the partecipants failed to achieve seizure control with sodium valproate at a dose of 1000 mg/day over a minimum period of 3 months; the partecipants had an average of 4 days with myoclonic seizures per month over the past 3 months; the participant had an average of 4 days with absence seizures per month over the past 3 months.
Following informed consent a detailed clinical and family history was taken, a DNA sample was taken and a 48 hour EEG and neuropsyhometric testing were undertaken.

This study cohort consisted of 6 females and 13 males, all Caucasian, with a mean age of 29.8 years, and with an age range between 16 and 60 years. All patients presented myoclonic seizures, 16 patients had absences and 16 tonic-clonic seizures (TCS). All patients were under standard antiepileptic drug treatment. Of these, 5 patients on monotherapy and 14 patients on polytherapy.
All patients underwent ambulatory EEG recording over 24-48 hours using the Xltek System. Amplifier characteristics were: 10,000 dB gain, low frequency filters at 0.5 Hz and high pass filters at 70 Hz.
The recording was bipolar consisting of 19 electrodes in the standard International 10/20 System (Figure 4). The impedance was under 5 KΩ in all electrodes. The sampling frequency was 256 Hz.

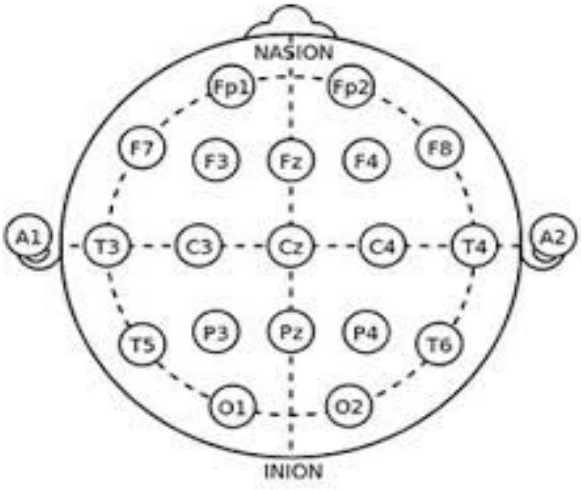

Figure 4. Standard International 10/20 System

Spectral EEG analysis

The following criteria for the selection of EEG sample: from 2 to 5 minutes of artefact-free background EEG data were visually selected from each recording.

Only EEG segments in which the patient was awake and with closed eyes were analysed. Two samples were selected per patient, morning and evening sample. Morning sample (MS) was defined as a 20-60 second, eyes closed sample recorded at least 2 hours after patient awoke from sleep; evening sample (ES) was defined as a 20-60 second, eyes closed sample recorded 8 hours after waking up. Each sample was subjected to visual/qualitative analysis by a neurophysiologist who was blinded to patient selection.

Continuous EEG samples ranging between 20 to 60 seconds of recording, free from artefact and epileptiform discharges were selected. Artefact such as muscle/movement artefact, sweat artefact, drowsiness (identified by lateral eye movements or vertex sharp waves) and electrical interference were excluded. The sample were converted to EDF and exported to the qEEG software.

The analysis of background EEG activity was carried out with the fast Fourier transform (FFT). Selected EEG epochs were re-computed against common average reference. Spectral power, expressed in μV, were calculated using Welch's averaged periodogram method (Welch 1967). Frequencies between 0.5 and 100 Hz analysed, divided into delta (0.5-4 Hz), theta (4-7 Hz), alpha (8-12 Hz), and beta (13-30 Hz) bands with a resolution of 0.25 Hz (Michel 1992). Spectral power was averaged region-wise (right and left frontal, parietal, temporal and occipital, and central).

NeuroGuide Software was used for spectral EEG analysis.

The following parameters were assessed for spectral/quantitative analysis for each sample:

1. Dominant rhythm in standard EEG (sEEG) was compared to dominant rhythm in quantitative EEG (qEEG).
2. The global absolute power was calculated for each frequency for each sample.
3. These parameters were also compared with Z scores, available on the software. These Z-values for each variable and band were obtained by comparison with population (American population) parameters based on the age-dependent regression function. Values outside the interval -1.96 to 1.96 were considered abnormal.
4. Each frequency in both the groups was calculated and then compared to the global mean absolute power.
5. Mean absolute power Z scores per frequency per each lead were also calculated in both groups.
6. Theta/alpha index for each sample was calculated and then compared between the two groups. The cut off for the T/A index was considered 1.50; values greater than 1.50 were considered abnormal. In addition, theta/alpha index was compared to Cognitive Scores (WAIS-III test). We had considered as IQ results: ≥ 130 Very Superior; 120-129 Superior; 110-119 High Average, 90-109 Average, 80-89 Low Average; 70-79 Borderline; ≤ 69 Extremely Low.

The statistical analysis of differences between the two groups was carried out by Student's t-test for indipendent samples. Pearson's Linear Regression Analysis was conducted in our study. The data was tested or normal distribution using the Kolmogorov-Smirnov test and transformed when not normally distributed using log10.

RESULTS

Summary of patient population

Were selected 38 samples, 19 morning sample (MS) and 19 evening sample (ES) from ReJuMec study. This cohort consisted of 6 females and 13 males, all Caucasian, with a mean age of 29.8 years, and with an age range between 16 and 60 years. The mean age of onset of epilepsy was 12.8 years with a mean of epilepsy duration of 17.4 years. All patients presented myoclonic seizures, 16 patients had absences and 16 tonic-clonic seizures (TCS). Myoclonic seizures were always present in the first hour after awakening. The patients had normal neurological examinations and characteristic paroxysmal generalized activity with polyspike-wave complexes PSWC in EEG recordings. All patients were under standard antiepileptic drug treatment. Specifically, 6 patients were under treatment with lamotrigine (LTG), 9 with topiramate (TPM), 7 with valproate (VPA), 9 with levetiracetam (LEV), 3 with zonisamide (ZNS) and 5 with clobazam (CLB). Of these, 5 patients on monotherapy and 14 patients on polytherapy (see table 1).

Spectral EEG analysis

Spectral EEG analysis showed the following interesting results:

1. When I compared dominant rhythm in standard EEG to dominant rhythm in qEEG (ie. highest global power frequency in AP) I found correlation in 8 samples. This indicates a 42% agreement between MS and ES group (see table 2).In MS group there was a 42% agreement between visual analysis and quantitative analysis which is considered to be a fair agreement using Cohen's Kappa coefficient (=0.261); 4.1 % agreement occurred by chance. In ES group there was a 42% agreement between visual analysis and quantitative analysis which is again considered to be a fair agreement using Cohen's Kappa coefficient (=0.226); 4.8 % agreement occurred by chance.

2. The mean global absolute power of each frequency band was calculated and compared between morning and evening sample. The difference was considered significant if p-Value < 0.05 or if t-Value > 2.09. Mean global power for each frequency was not significantly different ($p > 0.05$) in the MS group when compared to ES group. Statistical analysis shows a positive correlation for theta and beta bands between MS and ES groups; R-Squared value for theta of 55.5% and R-Squared value for beta of 42.6%.

3. AP for each lead were obtained and compared with those of a normal population of the same age to yield Z scores in MS group and in ES group (see table 3); the difference was considered significant if p-Value < 0.05 or if t-Value > 2.09. The Z scores global power for each frequency was not significant different (p > 0.05) in the MS group when compared to ES group. The results of the statistical analysis of differences between the two groups are shown in the table 4.

4. I have reported in the table 5 global mean AP that revealed the highest value in delta and beta band in both groups with clearly more delta and theta in MS group.

5. Table 6 shows mean AP Z scores per frequency per each lead in both groups. In the MS group, the AP delta, theta and beta bands revealed the highest power frequency in left frontal leads. In this group the AP alpha band was normal. In the ES group, the AP theta and beta band showed the highest power frequency in left frontal lead. In this group, the AP delta and alpha bands were normal.

6. Global theta/alpha index was calculated and then compared between two groups for all the samples (see table 7). As shown in the scatter plot diagram (figure 5) a positive correlation was seen between theta-alpha index in MS and ES with R-squared value of 32.3%. This is influenced by the increased theta power in the samples.
In addition, I have compared global theta/alpha index to cognitive IQ score for 12 participants, who underwent to neuropsychological testing (WAIS-III test) during ReJuMec study, as shown in the same table 7. High IQ scores is associated with small theta-alpha index and low IQ scores is associated with high theta-alpha index. In the MS group the scatter plot diagrams (figures 6) shows a negative correlation between IQ scores and theta-alpha index with R-squared value of 58.7%. The scatter plot diagrams (figure 7) shows a weak correlation in ES group between IQ scores and theta-alpha index with R-squared value of 12%.

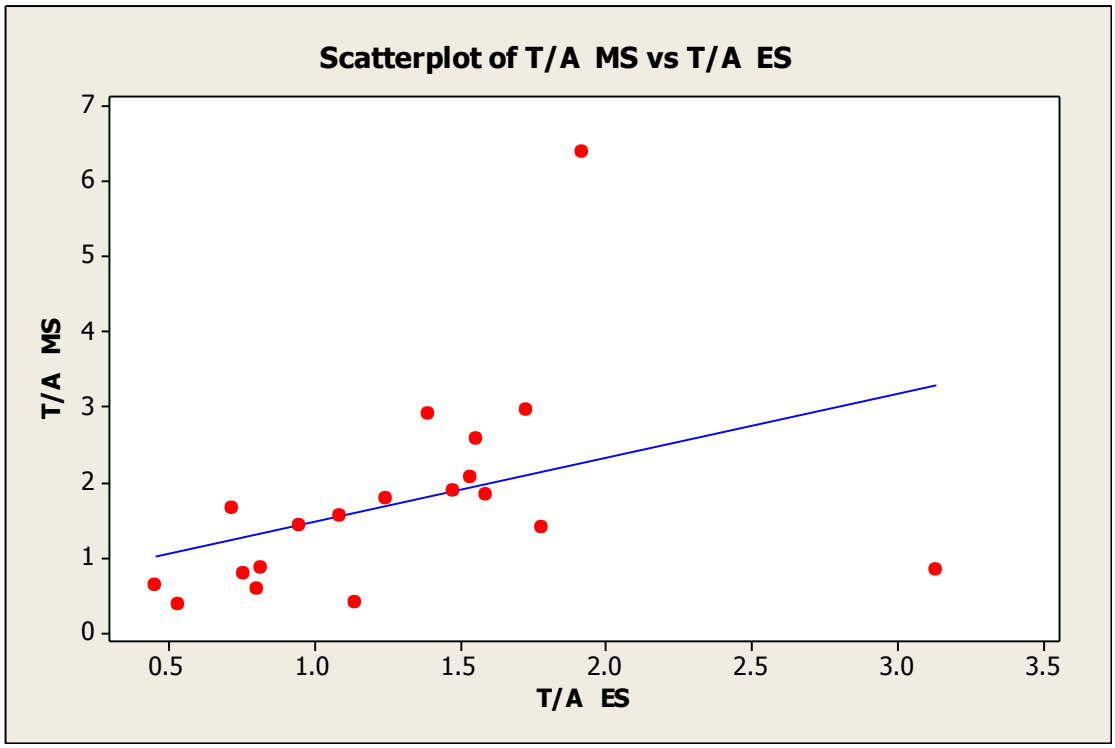

Figure 5. Theta/Alpha index in morning sample (MS) and evening sample (ES)
R-Sq = 32.3%

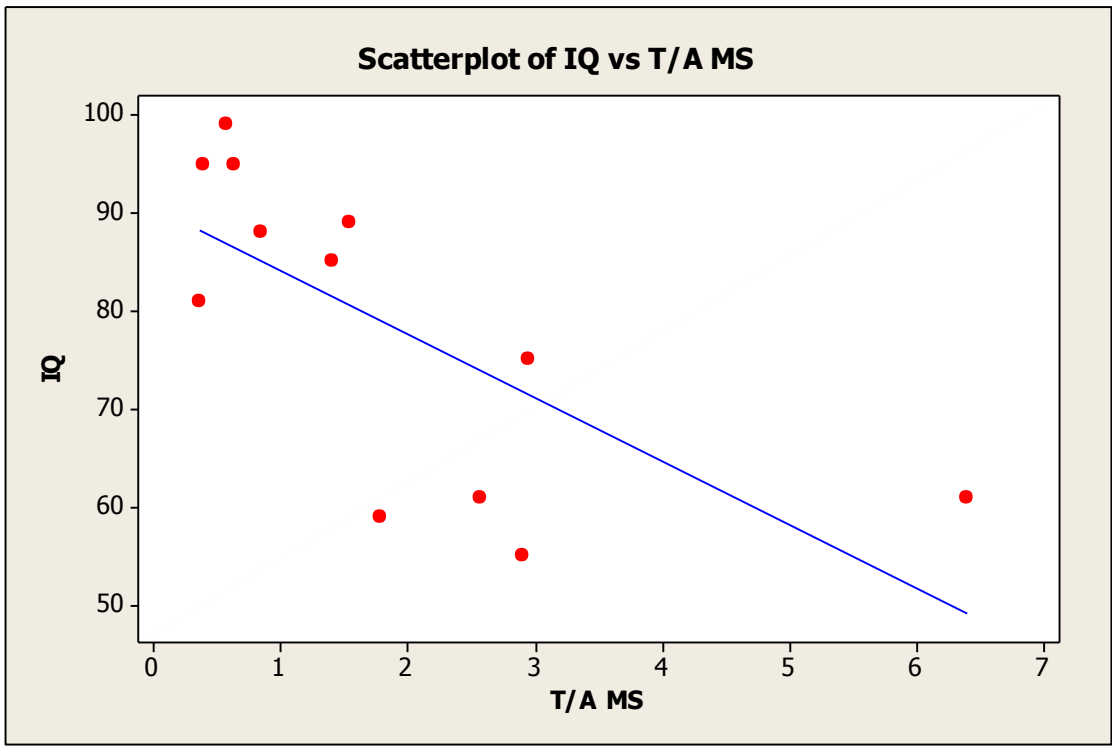

Figure 6. Theta-Alpha index in morning sample (MS) and cognitive IQ scores
R-Sq = 58.7 %

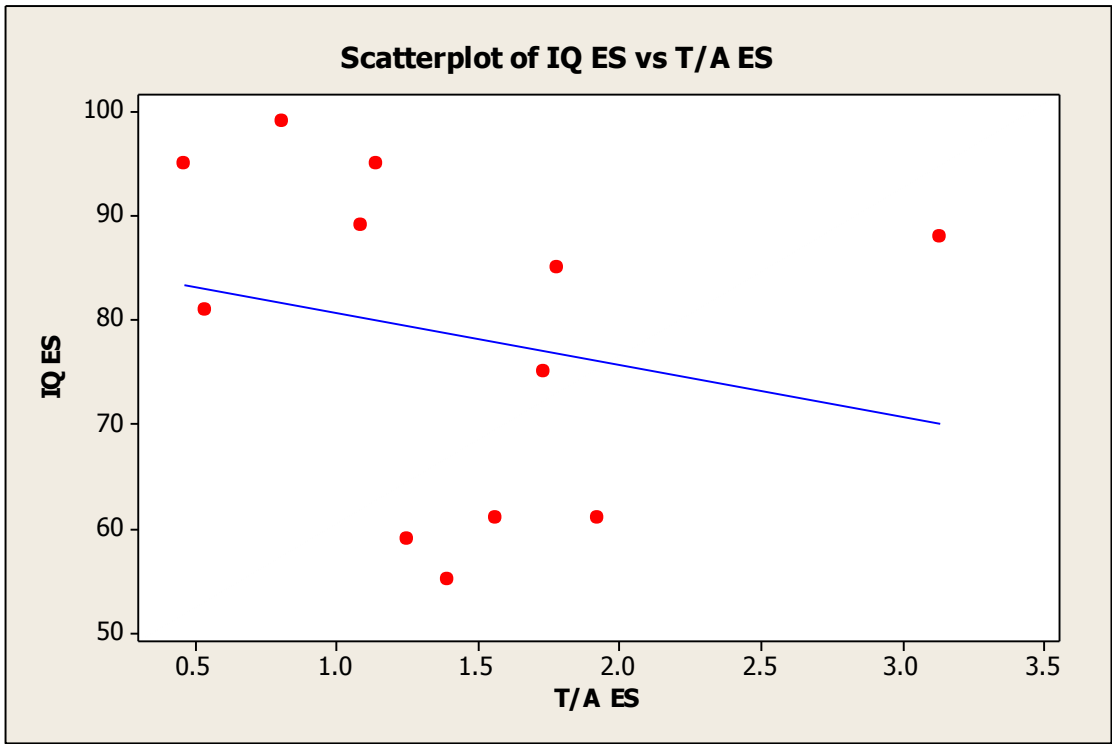

Figure 7. Theta-Alpha index in evening sample (ES) and cognitive IQ scores
R-Sq = 12 %

Table 1. Clinical characteristics of all the samples.

Number of partecipants	19
Gender n (%)	
Male	6 (31.6 %)
Female	13 (68.4 %)
Age (y) Mean ± SD	29.8 ± 12.6
Range	16 – 60
Onset of epilepsy (y) ± SD	12.8 ± 2.8
Years of seizure disorders ± SD	17.4 ± 13.1
Seizure types n (%)	
Myoclonic	19 (100 %)
Absence	16 (84.2 %)
TCS	16 (84.2 %)
Treatment n (%)	
Monotherapy	5 (26.3 %)
Politherapy	14 (73.7%)
AEDs (n)	
LTG	6
TPM	9
VPA	7
LEV	9
ZNS	3
CLB	5

Table 2. Comparison between dominant rhythm in standard EEG and dominant rhythm in quantitative EEG

MORNING SAMPLE		EVENING SAMPLE	
Visual Analysis Standard EEG	**Quantitative analysis qEEG**	**Visual Analysis Standard EEG**	**Quantitative analysis qEEG**
Beta	*Delta*	*Beta **	*Beta **
*Theta **	*Theta **	*Theta*	*Delta*
*Theta **	*Theta **	*Beta **	*Beta **
Theta	*Alpha*	*Beta*	*Delta*
Theta	*Delta*	*Theta*	*Delta*
*Beta **	*Beta **	*Beta **	*Beta **
Theta	*Delta*	*Beta **	*Beta **
*Beta **	*Beta **	*Beta **	*Beta **
Theta	*Delta*	*Theta **	*Theta **
*Beta **	*Beta **	*Theta*	*Beta*
*Beta **	*Beta **	*Beta **	*Beta **
Theta	*Delta*	*Theta*	*Delta*
Beta	*Delta*	*Theta*	*Delta*
Beta	*Delta*	*Theta*	*Beta*
*Beta **	*Beta **	*Theta*	*Delta*
Beta	*Delta*	*Beta*	*Delta*
*Beta **	*Beta **	*Theta*	*Delta*
Theta	*Delta*	*Beta **	*Beta **
Theta	*Delta*	*Theta*	*Delta*

Table 3. Global Absolute Power Z scores for each sample in two the groups

	Delta MS	Theta MS	Alpha MS	Beta MS		Delta ES	Theta ES	Alpha ES	Beta ES
Pt									
1	1.05	0.43	-0.46	1.11		0.75	0.18	-0.41	1.48
2	2.01	1.99	0.37	0.95		0.71	1.17	0.07	1.33
3	0.26	-0.24	-0.88	0.13		0.23	0.01	-0.86	0.67
4	0.14	1.84	0.53	-0.42		1.12	1.23	-0.37	0.88
5	1.32	0.06	0.11	1.60		0.79	0.05	0.42	1.75
6	0.38	0.46	-0.76	-0.79		0.22	0.92	-0.35	0.01
7	0.41	0.30	0.06	1.70		8.47	0.57	0.14	0.83
8	1.43	0.88	0.68	1.21		-0.27	-0.27	-0.57	1.00
9	0.73	2.46	0.47	-0.23		0.02	0.62	0.02	0.55
10	-0.68	0.14	0.37	0.64		0.94	0.37	0.25	0.41
11	0.49	1.15	0.63	1.20		0.52	1.10	0.66	1.22
12	-0.44	-0.43	-0.99	-1.18		-0.53	-0.74	-1.41	-0.72
13	1.93	1.80	-0.70	-0.34		1.94	2.40	0.35	-0.51
14	0.33	0.83	-0.87	0.54		-0.42	-0.20	-1.02	0.02
15	1.71	3.29	0.80	0.95		0.63	1.24	0.15	-0.39
16	-0.45	-0.15	0.42	1.80		0.31	-0.16	0.09	1.38
17	3.81	3.47	1.64	1.34		2.64	3.61	1.83	1.45
18	1.14	-0.08	-0.92	0.18		0.98	0.48	0.01	0.37
19	1.07	1.23	0.06	1.11		1.44	1.25	0.30	1.03

Abbreviations: Pt: patient; MS: morning sample; ES: evening sample.

Table 4. Student's t-test

Global Absolute Power

	Delta	***Theta***	***Alpha***	***Beta***
p-value	0.549	0.253	0.596	0.861
t-value	0.61	1.16	0.53	-0.18

Global Absolute Power Z scores

	Delta	***Theta***	***Alpha***	***Beta***
p-value	0.592	0.292	0.113	0.455
t-value	0.54	1.07	1.63	0.76

Table 5. Global Mean Absolute Power for each frequency in two the groups

	Morning Sample	Evening Sample
Delta	15.50	11.77
Theta	9.29	7.08
Alpha	6.77	6.12
Beta	10.54	10.33

Table 6. Mean Absolute Power Z scores per frequency per region in all the samples

	Delta		Theta		Alpha		Beta		Total	
	MS	ES	MS	ES	MS	ES	MS	ES	MS	ES
FP2-F8	1.43	1.30	1.51	1.16	0.79	0.64	1.32	1.21	5.05	4.31
F8-T4	0.48	0.46	1.01	0.57	0.11	0.05	0.80	0.73	2.40	1.81
T4-T6	0.52	0.27	0.62	0.29	-0.40	-0.47	0.32	0.44	0.59	0.53
T6-O2	0.50	0.29	0.63	0.38	-0.55	-0.55	-0.36	0.04	0.22	0.16
FP2-F4	1.23	0.94	1.22	0.81	0.47	0.35	1.45	1.38	4.37	3.48
F4-C4	1.22	0.67	1.32	0.79	0.01	-0.07	0.59	0.74	3.14	2.13
C4-P4	0.73	0.33	0.62	0.32	-0.43	-0.54	0.03	0.06	0.95	0.17
P4-O2	1.18	0.69	0.97	0.74	-0.36	-0.38	0.08	0.31	1.87	1.36
FP1-F7	**1.99**	1.82	**2.27**	**2.00**	1.35	1.22	**2.09**	**2.02**	7.70	7.06
F7-T3	0.22	0.25	0.72	0.55	0.02	0.13	0.79	0.83	1.75	1.76
T3-T5	0.49	0.43	0.68	0.48	-0.25	-0.28	0.58	0.61	1.50	1.24
T5-O1	0.46	0.29	0.68	0.42	-0.40	-0.50	-0.20	-0.15	0.54	0.06
FP1-F3	1.52	1.54	1.78	1.56	0.96	0.90	1.67	1.69	5.93	5.69
F3-C3	0.76	0.58	1.03	0.72	-0.04	-0.09	0.56	0.67	2.31	1.88
C3-P3	0.29	-0.06	0.33	0.08	-0.67	-0.67	-0.26	-0.17	-0.31	-0.82
P3-O1	1.15	0.77	0.97	0.77	-0.31	-0.33	0.21	0.29	2.02	1.50
Total	14.17	10.57	16.36	11.64	0.30	-0.59	9.00	10.70	40.03	32.32

Abbreviations: MS: morning sample; ES: evening sample.

Table 7. Theta/alpha index and cognitive IQ scores of study groups

	T/A Index MS	T/A Index ES	Cognitive IQ scores
Pt			
1	**1.54**	1.09	89
2	**1.89**	1.48	-
3	**2.06**	**1.54**	-
4	0.84	**3.13**	88
5	0.63	0.46	95
6	**1.82**	**1.59**	-
7	0.79	0.76	-
8	0.40	1.14	95
9	**2.57**	**1.56**	**61**
10	0.57	0.81	99
11	0.85	0.82	-
12	1.40	**1.78**	85
13	**6.39**	**1.92**	**61**
14	**2.95**	**1.73**	**75**
15	**2.90**	1.39	**55**
16	0.37	0.54	81
17	**1.78**	1.25	**59**
18	**1.65**	0.72	-
19	1.42	0.95	-
Mean	*1.70*	*1.20*	

Abbreviations: MS: morning sample; ES: evening sample; IQ: Intelligence Quotient; Pt: patient.

DISCUSSION AND CONCLUSIONS

The advantage of qEEG over visual analysis of EEG is evident, and this has been observed in neurological and psychiatric diseases (Samson-Dollfuss 1993). In this study a key advantage I had was prolonged ambulatory EEG data. This gave me the opportunity to compare various physiological states of the patient, in particular morning and evening.
It is documented that AP findings in qEEG were interpreted as enhanced synchronization of different neuronal population in the 0.5-12.0 Hz frequency range together with the tendency of decreasing synchrony in faster (12.5-32.0 Hz) frequencies (Muthuswamy 1998).
Neuronal network hypersynchronization is a fundamental mechanism in IGE. The delta band range lies within the same polyspike-wave complexes range characteristic of JME. In fact, the increase in AP delta is common to all IGE syndromes sharing the same psysiophatological mechanism (Gloor 1994).
In previous studies patients with JME have shown an increase in AP delta, alpha and beta bands, which is more evident in fronto-parietal regions (Santiago-Rodríguez 2008).
Neuropsychological and anatomical studies have indicated frontal lobe dysfunction in JME.
In addition, left frontal and central theta/alpha index has significant correlation with the presence of cognitive disturbance (Schmidt 2013).

In this study standard EEG visual analysis of background EEG activity revealed inter-ictal abnormalities in all patients, in the morning and evening samples. This is commonly seen in JME patients with poor seizure control especially in cases with antiepileptic polytherapy. During visual analysis the alterations found in background EEG activity in patients with JME were localized to left frontal region. When I compared dominant rhythm in standard EEG with dominant rhythm in quantitative EEG we have found that is < 50% observer agreement. Agreement occurred in samples dominated by increased amount of theta and beta in both visual and quantitative EEG.
With spectral analysis for each sample the global absolute power in all bands showed not statistical significant differences between MS and ES groups. In brief, when MS and ES groups were compared, there was no statistically significant difference of global power in all the bands; the same result was found using Z scores. A positive correlation is seen in theta and beta bands between the two groups, while alpha and delta bands showed weakly positive correlation. Theta is increased in the MS but not significantly. I think that this lack of statistical difference is due to our relatively small sample size.

In the analysis of this cohort, all the samples were characterized by increased global mean absolute power in delta and theta bands more evident in MS group and in beta band more evident in ES group. In addition, there was an increase in global absolute power in theta and beta bands when comparing morning and evening sample. Possibilities that might explain this include the patients' antiepileptic medications and their dosage and possibly fragmented sleep.
In addition, there is an increase in mean AP Z scores delta, theta and beta in MS group and theta and beta in ES group, which is more evident in left frontal region. Delta, theta and beta bands are increased and are abnormal when compared to Z scores. Alpha band was within normal limits compared to Z scores and was the same in MS and ES.
The certainty of these conclusions is probably limited by small sample size and by polytherapy and by AEDs as VPA that is known to influence EEG power.
Finally, a positive correlation is seen between theta/alpha index in MS and ES group. I have found that increase theta/alpha index > 1.50 is associated with a decrease in cognitive IQ scores. This rJME profiles reflect widespread cortical dysfunction essentially common to all the investigated IGE syndromes. The correlation between global theta/alpha index with Cognitive IQ scores is influenced by increased theta power.

Study' results suggest that is not significant difference between physiological states, morning or evening, in patients with rJME.

In addition I found clear evidence, during background activity in patients with rJME, of focal predominance in left frontal regions. The pathogenesis of JME is still unclear, but my sample exhibit focal abnormalities by spectral analysis, which provide convincing evidence for abnormalities in thalamocortical circuits.

This study confirms that *theta/alpha index* represent a good marker for cognitive deficit in all of patients with frontal lobe disfunction and that *spectral EEG analysis,* as functional neuroimaging, can be use as "biomarker of an altered neurobiological process" in epilepsy.

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