PAPER

Persistent abnormality detected in the non-ictal electroencephalogram in primary generalised epilepsy

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Objectives: Gamma oscillations (30–100 Hz gamma electroencephalographic (EEG) activity) correlate with high frequency synchronous rhythmic bursting in assemblies of cerebral neurons participating in aspects of consciousness. Previous studies in a kainic acid animal model of epilepsy revealed increased intensity of gamma rhythms in background EEG preceding epileptiform discharges, leading the authors to test for intensified gamma EEG in humans with epilepsy.

Methods: 64 channel cortical EEG were recorded from 10 people with primary generalised epilepsy, 11 with partial epilepsy, and 20 controls during a quiescent mental state. Using standard methods of EEG analysis the strength of EEG rhythms (fast Fourier transformation) was quantified and the strengths of rhythms in the patient groups compared with with controls by unpaired *t* test at 1 Hz intervals from 1 Hz to 100 Hz.

Results: In patients with generalised epilepsy, there was a threefold to sevenfold increase in power of gamma EEG between 30 Hz and 100 Hz ($p<0.01$). Analysis of three unmedicated patients with primary generalised epilepsies revealed an additional 10-fold narrow band increase of power around 35 Hz–40 Hz ($p<0.0001$). There were no corresponding changes in patients with partial epilepsy.

Conclusions: Increased gamma EEG is probably a marker of the underlying ion channel or neurotransmitter receptor dysfunction in primary generalised epilepsies and may also be a pathophysiological prerequisite for the development of seizures. The finding provides a new diagnostic approach and also links the pathophysiology of generalised epilepsies to emerging concepts of neuronal correlates of consciousness.

Epilepsies collectively constitute common disorders of humans (0.4% lifetime prevalence[1]) and are characterised by unpredictable brief seizure episodes of electroencephalographic (EEG) discharges often accompanied by disturbances in behaviour or cognitive impairment. One important class of human epilepsies, the primary generalised epilepsies (PGE), are characterised by large convulsive seizures sometimes associated with myoclonic jerks and absences, but lack a defined pathophysiology despite the recent identification of some of the causative ion channel or neurotransmitter receptor channel mutations.[2 3] Oocyte expression of these mutated channels shows alterations in function,[2] but the links between changes in channel function and seizure occurrence remain unknown. We have previously modelled in rats epilepsies induced by excessive excitability and diminished inhibitory activity using intravenous infusions of the glutamate-kainate/AMPA receptor agonist kainic acid[4] and the $GABA_A$ receptor-chloride channel blocking agent picrotoxin,[5] respectively. In the kainic acid treated rat we found that EEG rhythms in the gamma frequency range (30 Hz–100 Hz, especially 30 Hz–50 Hz), exhibited increased power preceding epileptiform discharges.[6 7]

Gamma oscillations are 30 Hz–100 Hz rhythms in the EEG and they are of low voltage compared with slower rhythms. Gamma EEG correlates with high frequency synchronous rhythmic bursting in assemblies of neurons participating in the formation of percepts,[8] working memory,[9] selecting objects for attention,[10] and in sensory motor processing,[11] all components of cerebral activity underlying consciousness. Because they are difficult to quantify in paper recordings gamma frequencies have rarely been studied in clinical EEG settings and their role in central nervous system disorders is unknown.

Our findings with kainic acid treated rats were consistent with gamma oscillations having a pathophysiological role in epileptogenesis.[6 7] We therefore recorded EEG in groups of patients and controls and used standard methods of EEG analysis, specifically measuring the power of EEG frequencies. Here we show that in the inter-ictal EEG of a group of patients with PGE, there is a persistent increase in gamma EEG in the absence of active epileptiform discharges.

METHODS

Subjects

With approval of the Flinders Clinical Research Ethics Committee, adults with a persistent seizure tendency (seizure within three months of study with no change in medication) were identified from patients of the Flinders Medical Centre. Persistence of seizures was related either to the patient's choice to remain unmedicated or to refractoriness to treatment. Patients were then studied who had specific epilepsy diagnoses based on the International League Against Epilepsy Classification (1989)[12] using available clinical, EEG, and magnetic resonance imaging (MRI) information. There were 11 patients with partial epilepsy (presumptively attributable to a focal brain lesion, categories 1.2 and 1.3), described in tables 1 and 2. Ten patients had primary generalised epilepsy (category 2.1) (tables 1 and 3). All patients with partial epilepsy had simple or complex partial seizures, while six also had secondary generalised seizures. Six patients with partial epilepsy had structural lesions on brain MRI and two had

Abbreviations: EEG, electroencephalography; PGE, primary generalised epilepsies

Table 1 Summary of patient characteristics

	M:F	Age (y) mean (SD)	Duration of condition (y) mean (SD)	Medicated (n)
Primary generalised epilepsy (10)	2:8	41 (4)	18 (4)	7
Focal (partial) epilepsy (11)	6:5	38 (5)	15 (3)	8

Table 2 Clinical features of 11 patients with partial epilepsy

Sex, age (duration (y))	EEG	Seizures*	Pathology	Localisation
F 45 (26)	Bilateral temporal sharp waves	CPS	Hippocampal cysts	Temporal
F 26 (6)	R frontotemporal theta	CPS, SGS	R frontal porencephalic cyst	Frontal
M 47 (13)	R frontal spikes	SPS, CPS, SGS	Post-encephalitis	Frontal
M 28 (18)	Bilateral 3 Hz sharp-wave slow-wave with R frontal spikes	SPS, CPS	R frontal tumour (benign)	Frontal
F 29 (1)	Normal	SPS, SGS	Unknown	Unknown
M 52 (34)	L and R spikes, sensory cortex (corticography)	CPS	Unknown	Parietal
M 68 (9)	Not diagnostic	CPS	L temporal tumour	Temporal
F 30 (20)	Not diagnostic	SPS, CPS, SGS	L mesial temporal sclerosis	Temporal
M 54 (20)	L temporal and bilateral sharp waves	SPS	Post-cardiac bypass	Temporal
M 29 (5)	L frontotemporal theta and sharp waves	CPS, SGS	Left temporal lobectomy (oligo)	Temporal
F 26 (13)	L and R temporal sharp waves	SPS, SGS	Unknown	Temporal

*SPS = simple partial seizures; CPS = complex partial seizures; SGS = secondary generalised seizures.

Table 3 Clinical features of 10 patients with generalised epilepsy

Sex, age (duration (y))	EEG	Convulsive seizures	Absences	Myoclonic jerks	Classification*
F 46 (32)	Not diagnostic	+		+	JME
F 23 (13)	4 Hz spike and wave	+	+++		CAE
F 27 (0.7)	3 Hz spike and wave, poorly formed	+			IGE
F 37 (27)	3 Hz spike and wave	+	+	+++	JME
F 72 (40)	Not diagnostic (photic not tested)	+ photosensitive		+++ photosensitive	Photosensitive epilepsy
M 62 (36)	Normal	++		+	JME
M 24 (8)	3 Hz spike and wave, poorly formed	+			IGE
F 19 (5)	Not diagnostic	+		+	JME
F 30 (15)	Spike and wave, with myoclonus	+	+++	++	JAE
F 21 (17)	Bilateral polyspike and 3 Hz spike and wave	+	+++ with blinking		CAE

*JME = juvenile myoclonic epilepsy; CAE = childhood absence epilepsy; JAE = juvenile absence epilepsy; IGE = idiopathic generalised epilepsy.

other disorders on the basis of a known aetiology (table 2). Diagnoses in the groups with PGE were: juvenile myoclonic epilepsy (4), idiopathic generalised epilepsy (2), childhood absence epilepsy (2), juvenile absence epilepsy (1), and photosensitive epilepsy (1). Age, sex, and education matched controls were recruited from the friends of patients or from Flinders Medical Centre staff.

EEG

EEG was recorded digitally (bilateral ear reference electrodes, 512 sample per second digitisation rate, 107 Hz low pass filter, 16 bit precision) using a 64 channel EEG system (Compumedics, Victoria, Australia) and the data were processed offline using programs written within Matlab (The Mathworks, MA, USA). Recordings were made with the eyes open while subjects performed a control task (looking at a blank computer screen) and eight other active tasks (to be reported elsewhere).

EEG analysis

The strength of EEG rhythms of different frequencies was determined by standard methods of power spectral analysis of EEG signals using fast Fourier transformation with a Hanning window. Power was determined at 1 Hz intervals from 1 Hz to 100 Hz, averaging estimates from one second lengths of EEG calculated from the maximum amount of good quality EEG available from each subject, usually around 20 seconds per subject. Kolmogorov-Smirnov testing indicated that the distribution of power estimates was not always normally distributed, but that the log transformed power estimates were normally distributed. We therefore tested the significance of differences in power in different groups by using unpaired *t* tests of log transformed data at every 1 Hz interval from 1 Hz to 100 Hz. Contamination of recordings by 50 Hz power supply frequency and 60 Hz computer monitor refresh rate prevented analysis of power at 50±1, 60±1, 99, and 100 Hz and values for these frequencies were removed from the spectra.

To facilitate presentation, the mean EEG power in the each group is displayed relative to the mean power of all controls (n=20), there being no significant difference between the two groups of controls. The relative power increase is displayed from 1 Hz to 100 Hz in spectra for each electrode in the montage. Similarly, the statistical evaluation of each frequency from 1 Hz to 100 Hz is presented in spectra corresponding to each electrode in the montage.

RESULTS

No epileptiform activity was recorded during the studies. Artefact free and EMG free EEG was recorded from most of the scalp. EMG potentials were sometimes present in several anterior and lateral leads, resulting in high variances of mean EEG power from those sites.

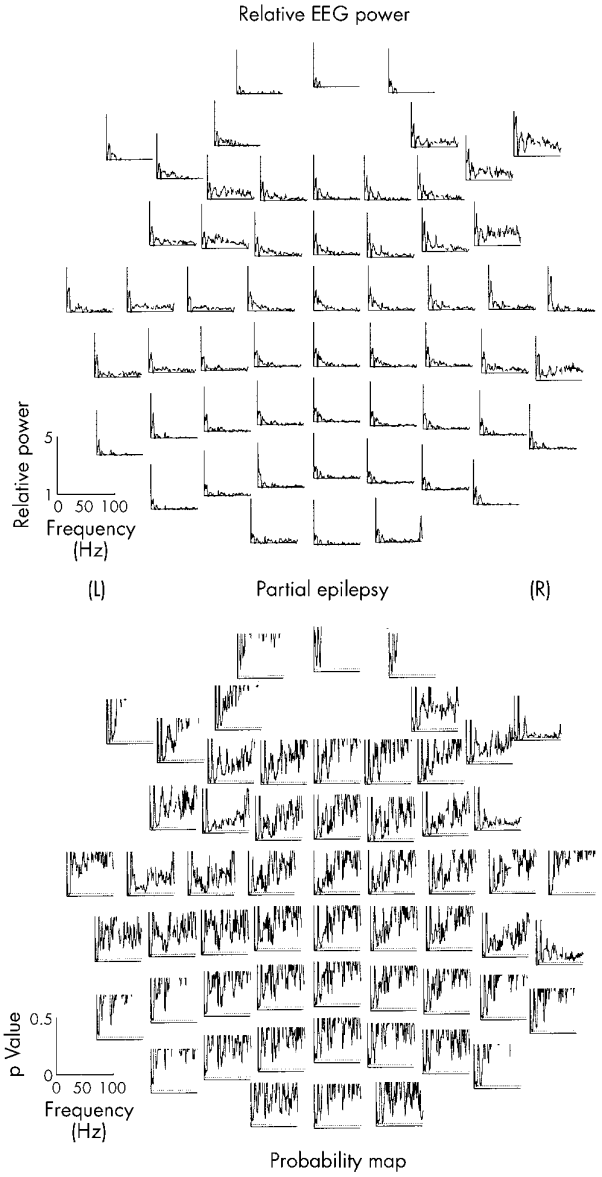

Figure 1 (Top) Montage display of mean EEG power increases in 11 patients with partial epilepsy compared with 20 normal subjects (ordinate scale from onefold to fivefold) between 0 Hz and 100 Hz (abscissa) recorded over the scalp; (below) probability map (scale p=0 to 0.5) for power increases, unpaired *t* test (horizontal dotted line, p=0.05). Increases above controls were not significant except at low frequencies. Muscle artefact increased the variance in some anterior and lateral leads. (L) = left, (R) = right.

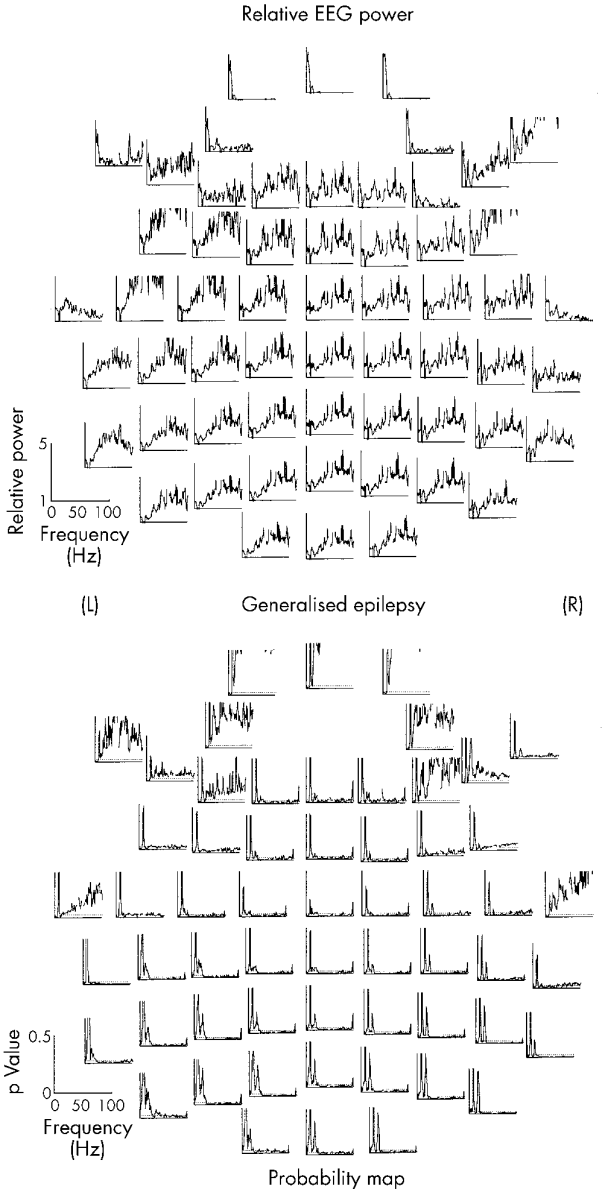

Figure 2 (Top) Montage display of mean EEG power increases in 10 patients with generalised epilepsy compared with 20 normal subjects (ordinate scale: from onefold to fivefold) between 0 Hz and 100 Hz (abscissa) recorded over the scalp; (below): probability map (scale p=0 to 0.5) for power increases, unpaired *t* test (horizontal dotted line, p=0.05). Increases above controls were significant, especially for frequencies above 25 Hz. Muscle artefact increased the variance in some anterior and lateral leads. (L) = left, (R) = right.

A medication effect was tested for by comparing all treated (n=15) with all untreated patients (n=6). There were small increases in power at 2 Hz–4 Hz, albeit barely significant, and at 7 Hz–8 Hz because of a slowed dominant alpha frequency from 12 Hz to 8 Hz, data not shown. These effects of medication are known.[13 14] There were no effects of medication on EEG in the gamma frequency range.

In patients with partial epilepsy, there were significant changes in the power spectrum at 3 Hz–7 Hz centrally, and at 15 Hz–17 Hz anteriorly, both more to the right (fig 1). There were no significant changes at gamma frequencies. By contrast, in patients with PGE, there were significant increases in power above 25 Hz in all leads (fig 2). In addition there were the same changes in the power spectrum at 3 Hz–7 Hz and 15 Hz–17 Hz as seen in patients with partial epilepsy. Above 30 Hz, spectra exhibited considerable variation, but average increases were around threefold, with some peaks of power reaching sevenfold or more and with p values across the gamma range often less than 0.01. Because the power spectra between 1 Hz to 30 Hz in partial and generalised epilepsies were not different from each other (unpaired *t* tests), the spectra were combined and the topographical distributions of significant increases in power at 3 Hz–7 Hz and 15 Hz–17 Hz are shown in fig 3(A) and 3(B). The topographical distribution of the significant increase in gamma frequencies in patients with generalised epilepsies is shown in fig 4.

Separate analysis of unmedicated patients revealed a borderline increase in gamma EEG frontally in patients with partial epilepsy (n=3), not shown. In contrast, a remarkable increase in gamma EEG was seen in the three unmedicated patients with PGE who had a 10-fold increase in mean power

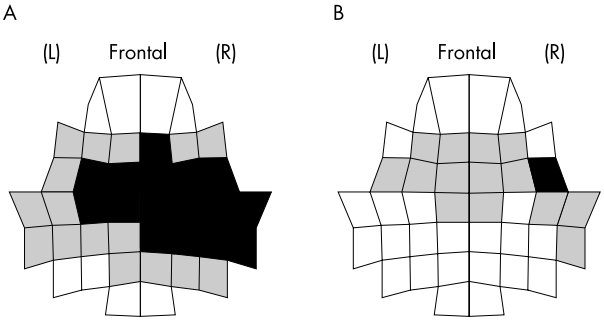

Figure 3 Statistical topographical maps showing increases in power for 3 Hz–7 Hz and 15 Hz–17 Hz in combined partial and generalised epilepsies (n=21) compared with controls (n=20). There is a widespread increase in 3 Hz–7 Hz activity (A), and a frontal and right sided increase in 15 Hz–17 Hz EEG activity (B) in patients with epilepsy. Shaded: p=0.05; black: p=0.01.

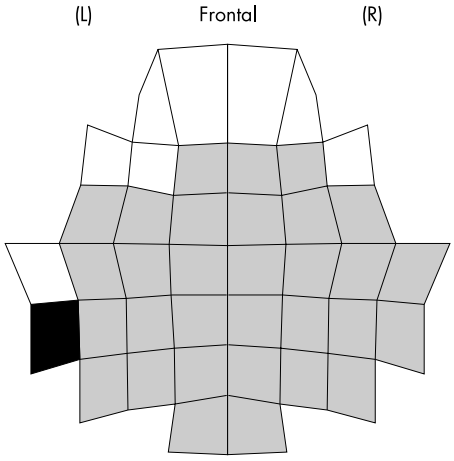

Figure 4 Statistical topographical map of increases in power for 30 Hz–98 Hz in generalised epilepsies (n=10) compared with controls (n=20). There is a wide distribution of increased gamma EEG in generalised epilepsy. Shaded: p=0.05; black: p=0.01.

at 34 Hz–38 Hz (fig 5). These patients had peak power increases of threefold, sixfold, and 25-fold.

DISCUSSION

The key new finding of this study is that there is a persistent abnormality in the resting, non-ictal EEG of people with PGE. The abnormality is an enhancement in power of high frequency rhythms in the gamma EEG range (30 Hz–100 Hz). Additionally, in a non-medicated subgroup, larger increases were seen in narrow band EEG between 34 Hz and 38 Hz. These findings closely reflect EEG changes seen in an animal model of acute epileptogenesis, the kainic acid treated rat. In this model, gamma EEG of hippocampal and neo-cortical origin precedes epileptiform discharges.[6 7] Kainic acid is neuroexcitatory by opening a mixed cation (sodium and calcium) channel.[15] A mutation in a sodium channel underlies epileptogenesis in one human primary generalised epilepsy GEFS+.[2] In our mixed PGE group, although there were no examples of GEFS+, it is probable that ion channel or neurotransmitter receptor pathophysiology is causative in PGE.[3 16] Our evidence indicates there are similar actions on resting EEG of the pharmacological agent kainic acid and genetic mutations leading to PGE. This study, therefore provides a possible link between the basic pathophysiology of generalised epilepsy and seizure tendency.

Gamma EEG activity correlates with high frequency synchronous rhythmic bursting in assemblies of neurons participating in many cerebrocortical processes underlying

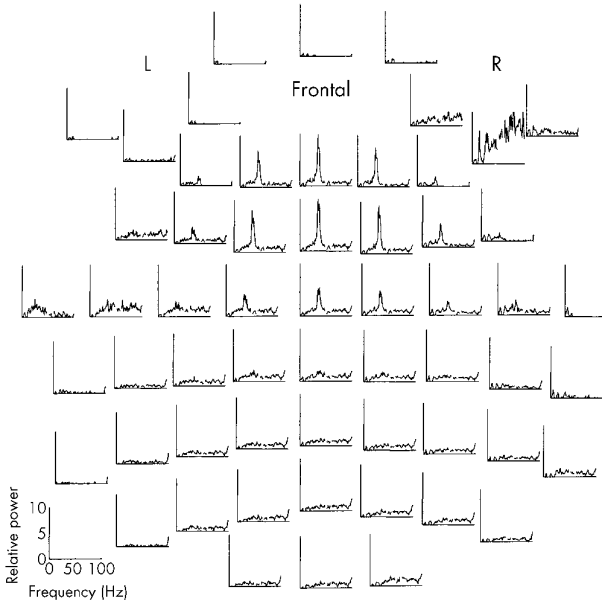

Figure 5 Montage map of mean EEG power increases in individual electrodes in three unmedicated patients with PGE compared with 20 normal subjects showing striking increase in mean power from 34 Hz to 38 Hz in frontocentral leads ($p<0.0001$). Increases are significant ($p<0.05$) for many frequencies above 30 Hz in these and other leads (probability map not shown). L = left; R = right.

consciousness.[8–11] Our evidence is that broad band background gamma as well as possibly synchronous narrow band "binding gamma" is markedly increased in people with PGE. The presence of intensified gamma EEG in patients with epilepsy provides a new and natural model for examining behavioural correlates of gamma oscillations. It is yet to be determined if increased strength of gamma oscillations correlates with any change in intellectual processing. We hypothesise that people with epilepsy, by having increased gamma EEG at rest, either have a lower signal to noise ratio in neuronal rhythms, related to increased broad band gamma activity, or have over-processing of some aspects of information related to increased broad band or narrow band gamma activity, or both. The presence of narrow band gamma in unmedicated patients is consistent with suppression of this form of gamma by antiepileptic drugs in medicated patients, while its distribution is consistent with the evidence pointing to frontal mechanisms in epilepsy pathophysiology.[6 17 18] Cognitive processes are known to induce epileptiform activity in some patients with PGE,[19] so that augmented resting gamma activity in patients with PGE in combination with a cognitive load, further augmenting gamma activity, may play a part in seizures induced by intellectual activity.

The EEG provides a measure of summed electrical fields produced by post-synaptic potentials in populations of neurons and so is an indirect measure of the activity of input neurons. Increased gamma rhythms therefore reflect increased post-synaptic activity of local neurons. In terms of its relevance to epileptogenesis, increased neuronal activity changes the ionic environment of neurons[20] that can lead to increased burst firing of neurons[21] as well as intensified slow rhythms,[22] both of which contribute to the genesis of seizures in different circumstances.[23 24] Intensified gamma rhythms involving widespread assemblies of cortical neurons may also contribute to the widely distributed nature of the generalised epileptic disturbance characteristic of PGE; it is also consistent with an increased level of excitation between cortical neurons, an underlying assumption in the thalamocortical hypothesis of absence epilepsy.[25 26] Evidence of an increased excitability of

cortex in PGE has also been obtained from transcranial magnetic stimulation studies.[27]

Several differences in approach account for the major differences in findings between this study and earlier studies of generalised epilepsies. Firstly, we recorded EEG activity to 100 Hz in contrast with only examining frequencies below 30 Hz.[13] Secondly, we used an "eyes open" mind wandering condition while subjects looked at a blank computer screen, in contrast with an "eyes closed" condition typically used in clinical studies. Eye opening has been avoided in clinical studies because it produces an alerting appearance of the EEG and eye movements contaminate low frequencies in the EEG signal.

Although not the primary intent of our study, by averaging over frequency ranges similar to Miyauchi *et al*[13] who studied 128 subjects, we found support for some of their findings in the frequency range 2 Hz –30 Hz in our 20 subjects. For example, in patients with partial and generalised epilepsies we found significant increases in delta-theta (3 Hz–7 Hz) with a widespread distribution (fig 3(A)), similar to changes revealed by Miyauchi and colleagues for 2 Hz–4 Hz and 4 Hz–8 Hz. We also found significant increases at 15 Hz–17 Hz in generalised and partial epilepsies although the distribution was more symmetrical (fig 3(B)) than was shown by Miyauchi and colleagues for 13 Hz–20 Hz. Like Miyauchi and colleagues, we found no significant differences between the generalised and partial epilepsies in frequencies below 30 Hz. In our own groups, significant and consistent differences between these groups were only present above 25 Hz–30 Hz, just at and above the limit of the frequency range examined by Miyauchi *et al*.[13] Thus there are changes in the background EEG power range especially in the delta-theta and low beta ranges in patients with epilepsy that are common to both partial and generalised subtypes. The mechanism of these changes remains unknown. However, we have now demonstrated unique changes in the high frequency EEG in patients with generalised epilepsies.

Not only does this study extrapolate findings in an animal model to the clinical setting but it also presents the first evidence of pathophysiological significance linking gamma oscillations to a disease process. Specifically, intensified gamma EEG links seizure tendency with its basic genetic cause. These findings have important clinical potential. Substantiation of a high sensitivity and specificity of our finding will open up new diagnostic approaches for epilepsy. If increases in gamma EEG are confirmed as inversely related to seizure control, our finding may also result in a useful measure of the therapeutic efficacy of antiepileptic drugs.

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