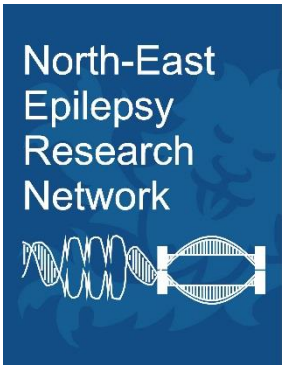
Friday 9th October 2015
Beamish Hall Hotel

North East Epilepsy Research Network Meeting



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Programme

08.30-09.15	Registration and coffee
09.15-09.30	Introduction – Drs Baker/Cunningham/Hart/Taggart/Trevelyan

Session 1: Festschrift for Dr Margie Jackson
Chair –Professor Doug Turnbull

09.30-09.40	Professor Doug Turnbull (Newcastle University) *Opening remarks*
09.40-10.20	Dr Yvonne Langan (Trinity College Dublin / St James Hospital) *SUDEP in Ireland*
10.20-11.00	Professor Tony Marson (Walton Centre & University of Liverpool) *Identifying and delivering clinical and cost effective treatments for epilepsy in the NHS*
11.00-11.30	Tea/Coffee View Exhibition/Posters

Session 2: Festschrift for Dr Margie Jackson
Chair – Dr Mark Cunningham

11.30-12.10	Professor David Chadwick (University of Liverpool) *The tyranny of evidence based medicine: valproate syndrome as an exemplar*
12.10-12.50	Dr Susan Duncan (Western General Hospital, Edinburgh) *JME and Cognition*
12.50-14.00	Lunch View Exhibition/Posters

Session 3: Epilepsy and depression
Chair – Dr Yvonne Hart

14.00-14.30	Dr Niruj Agrawal (South West London & St George's Mental Health Trust) *Epilepsy and Depression*
14.30-15.00	Dr Jasvinder Singh (Northumberland Tyne & Wear NHS Foundation Trust) *Epilepsy and Psychosis*
15.00-15.30	Tea/Coffee View Exhibition/Posters

Programme (continued)

Session 4: **Ketogenic diet and epilepsy**
Chair – Dr Ming Lai

15.30-16.00	Dr Anita Devlin (Newcastle Upon Tyne Hospitals NHS Foundation Trust) *Evidence for Ketogenic Diet in Epilepsy: Is It effective in all age groups?*

Session 5: **Basic science and epilepsy**
Chair – Dr Andrew Trevelyan

16.00-16.15	Dr Anupam Hazra (Newcastle University) *Contribution of corticothalamic dysfunction to epilepsy and cognitive deficits in Alzheimer's disease mice*
16.15-16.30	Dr Ryley Parrish (Newcastle University) *Differential gene and protein expression changes induced by disparate patterns of epileptiform activity*

Session 6: ***Festschrift for Dr Margie Jackson***
Chair – Dr Simon Taggart

16.30-17.10	Professor John Duncan (University College London / National Hospital for Neurology and Neurosurgery) *Impact of 3D multimodal imaging on epilepsy surgery*
17.10-17.20	Dr Margie Jackson *Closing remarks*
17.20-17.30	Presentation of poster prize and concluding remarks (Dr Hart and Dr Jackson)
17.30-	Drinks and dinner (*Stables*)

SUDEP in Ireland

Dr Yvonne Langan
Trinity College Dublin &
St James's Hospital

Identifying and delivering clinical and cost effective treatments for epilepsy in the NHS

Professor Tony Marson
The Walton Centre NHS Foundation Trust &
University of Liverpool

The tyranny of evidence based medicine: valproate syndrome as an exemplar

Professor David Chadwick
University of Liverpool

JME and Cognition

Dr Susan Duncan
Western General Hospital, Edinburgh,
NHS Lothian

Epilepsy and Depression

Dr Niruj Agrawal
South West London & St George's
Mental Health Trust

Epilepsy and Psychosis

Dr Jasvinder Singh
Northumberland Tyne and Wear
NHS Foundation Trust

Evidence for Ketogenic Diet in Epilepsy: Is It effective in all age groups?

Dr Anita Devlin
The Newcastle Upon Tyne Hospitals
NHS Foundation Trust

Contribution of corticothalamic dysfunction to epilepsy and cognitive deficits in Alzheimer's disease mice

Dr Anupam Hazra
Institute of Neuroscience,
Newcastle University

Differential gene and protein expression changes induced by disparate patterns of epileptiform activity

Dr Ryley Parrish
Institute of Neuroscience,
Newcastle University

Impact of 3D multimodal imaging on epilepsy surgery

John Duncan
University College London /
National Hospital for Neurology and Neurosurgery

Posters

- Mr Anderson Brito Da Silva, Newcastle University
  High Frequency Oscillations in neocortical epilepsy: A case report

- Mr Neela Codadu, Newcastle University
  Characteristics of evolving epileptiform activity in different cortical areas

- Dr Ryley Parrish, Newcastle University
  Differential gene and protein expression changes induced by disparate patterns of epileptiform activity

- Dr Anupam Hazra, Newcastle University
  Reduced seizure like events in neocortical slices prepared using sucrose based artificial cerebrospinal fluid

- Ms Frances Hutchings, Newcastle University
  Predicting surgery targets for Temporal Lobe Epilepsy

- Dr Soumyasanta Laha, Newcastle University
  Proposed Closed Loop Algorithm System Implementation for controlling focal epilepsy using Optogenetics.

- Mr Christoforos A. Papasavvas, Newcastle University
  Fragile recurrent activity of local cortical networks shown by optogenetic manipulation of basket cells.

- Dr Emma Robinson, NUTH NHS Foundation Trust
  Dissociative Seizures: A Psychobiological Perspective

- Dr Hannah Steele, Newcastle University & NUTH NHS FT
  The 100,000 Genomes Project & Epilepsy

- Dr Peter Taylor, Newcastle University
  Predicting neurosurgical outcomes in focal epilepsy patients using computational modelling

- Mr Chris Thornton, Newcastle University
  Inhibitory synapse location and the propagation of seizure-like events

- Dr Yujiang Wang, Newcastle University
  Mechanisms underlying different focal seizure onset patterns

High Frequency Oscillations in neocortical epilepsy: A case report

Anderson Brito Da Silva
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Newcastle University

Introduction: Almost 30% of patients with partial epilepsy are refractory to anti-epileptic medication. Resective epilepsy surgery is a potential therapeutic option available for this group. Unfortunately, there is no current technique capable of reliably determining the Epileptogenic Zone (EgZ), i.e., the region of neocortex responsible for the generation of the epileptic seizures. From a neurosurgical perspective it is imperative that this region can be successfully identified as its total resection is necessary to achieve seizure-free outcomes. Recently, brain oscillations in frequency bands above 80 Hz, High Frequency Oscillations (HFO), have been described as potential biomarkers for regions implicated in epileptogenesis. For example, an increased incidence of HFO is seen in the epileptogenic lesion and in Seizure Onset Zone (SOZ) [1].
Aims: To investigate the potential of HFO as a biomarker for the EgZ, our epilepsy surgery service has begun to use a higher sampling frequency (2kHz) to record intracranial (iEEG) data. In this work we will present the preliminary results from our first patient recording.
Methodology: KS, a 17 year old female, presented with focal seizures and occasional bi-lateral convulsive seizures from the age of 6. Imaging showed two dysplasic lesion in left frontal lobe, one anterior assessed by a six electrode strip (S1 to S6) and other medial-posterior assessed by a ten contact deep electrode (DA1 to DA10).
In total, there were 9 days of recording, divided in 921 epochs with a duration of 15 minutes each. The HFOs was detected by Filter-Hilbert method [2] in 20 randomly selected epochs, with a band pass filter between 80-200 HZ for Ripples (Rp) and 200-600 Hz for Fast Ripples (FRp).
After the detection, clustering analysis was performed and each cluster was visually inspected to reject artifacts.
Results: In total, 130 Rp and 769 FRps were detected. The peak frequency was 91.77 ± 20.83 Hz for Rp and 274.82 ± 54.43 Hz for FRp with Rp lasting, in mean, 46 ± 15 ms, while FRp was 2 ± 9 ms.The electrode S3, S2 and S4 were the most active contacts for Rp respectively, while the electrodes S1, S2, DA10 and S3 were the most active for FRp. The SOZ determined by clinical observations was at S1, S2 and S3 electrodes, where the resective procedure was performed, leaving the medial-posterior lesion intact.
Conclusion: The epileptogenic zone as determined using standard clinical techniques included the regions showing the highest prevalence of HFO. Our patient remains free of major seizures 9 months post-surgery, suggesting that high frequency oscillations may indeed be a reliable biomarker of the epileptogenic zone.

References

[1] J Jacobs et al. Epilepsia 2008; 49(11):1893−1907
[2] B Crépon et al. Brain 2010, 133(Pt 1):33−45

Characteristics of evolving epileptiform activity in different cortical areas

Neela Codadu
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Newcastle University

Clinical evidence suggest strongly that different regions in the brain have different seizure susceptibility; the disproportionate number of epilepsy cases arising from temporal lobe pathology suggest that hippocampal circuits may be peculiarly epileptogenic. The reasons for this differential susceptibility, however, are not known. We therefore characterised how epileptiform events evolve in different regions of the brain in response to acute pharmacological challenges in brain slices from young adult mice.

Surprisingly, when bathing slices in 0 Mg artificial CSF, neocortex appeared more excitable than hippocampus: full ictal activity occurred earlier in neocortex than hippocampus, and furthermore, tonic-clonic like patterns were not typically recorded in hippocampal territories. Instead, the hippocampus showed characteristic spike and wave type discharges, which occurred in isolation, but with great regularity. These start relatively late, but have the effect of immediately entraining neocortical activity. We further show that this entrainment can occur independent of axonal pathways, and suggest that this occurs instead through local field effects.

Differential gene and protein expression changes induced by disparate patterns of epileptiform activity

Saif Haddad
Institute of Neuroscience,
Newcastle University

The genes and proteins expressed by a neuron determine its excitability and the neurons activity also influences these expression patterns. This two-way interaction regulates key homeostatic mechanisms in the brain. Various brain insults can trigger non-homeostatic changes, leading to epileptogenesis. The balance between homeostatic and non-homeostatic changes is likely to provide important clues as to how epilepsy develops.

Epileptogenesis can be triggered in vivo by periods of status epilepticus. It is not known though what roles are played by the different elements within the network, namely the pyramidal cells, glia and the different classes of interneurons. We set out to explore this utilizing several different in vitro models of epileptiform event. We will present evidence from patch clamp and Ca2+ network imaging to illustrate how these can be used to generate stable patterns of activity involving very different subsets of the cortical network.

We next show how we can use these in vitro models to separate out the homeostatic responses of different neuronal elements within the network. We present RT-PCR and immunohistochemical analysis showing how different epileptiform activity patterns can induce different acute changes in expression. These data suggest that induced gene expression is dependent on type of epileptiform activity.

Reduced seizure like events in neocortical slices prepared using sucrose based artificial cerebrospinal fluid

Anupam Hazra
Institute of Neuroscience,
Newcastle University

To understand how seizures originate and propagate during the epileptogenic state, it is critical to preserve excitatory and inhibitory neuronal network functions. The presence of inhibitory veto plays a significant role to decrease the speed of seizure propagation in rodent brain slices1. Brain slices used for in vitro studies are prepared using either one of the following protocols. In the majority of studies concerning epileptogenesis, cervical dislocation and removal of the brain using a standard artificial cerebrospinal fluid solution (stdACSF). An alternative approach is terminal anaesthesia followed by cardiac perfusion with a sucrose based ASCF (sACSF). Previous work has demonstrated that slices prepared using sACSF demonstrate higher levels of intact GABAA mediated inhibition with implications for the generation of long term potentiation in vitro2. We therefore aimed to examine the implications of the differing forms of brain slice preparation for the generation of acute epileptiform activity in vitro.

In stdACSF slices the perfusion of zero magnesium (Mg2+[0]) ACSF elicits seizure-like-events (SLEs) which evolved rapidly. SLEs were observed in majority in the stdACSF slices (>80%) in contrast to only few sACSF slices (<20%) exhibited such events. Immunohistochemical staining of slices from both groups demonstrated a reduction in the density of parvalbumin containing interneurons in stdACSF slices. Using multi-electrode arrays, we observed that the propagation speed of stdACSF-SLEs was significantly faster when compared with sACSF-SLEs. In the case of sACSF-SLEs, the antagonism of GABAA receptors increases the mean propagation speed to values comparable to stdACSF-SLEs. We also compared preparation techniques using the 4-aminopyridine (4-AP) model. Our findings in the 4-AP corroborate the results obtained using the Mg2+[0] model. Together these data suggest that the use of sACSF preserves the inhibitory network in cortical slices for in vitro studies and can have important implication on network dynamics. We suggest that preparation of cortical slices using perfused sACSF merits serious consideration during in vitro epilepsy studies.

1. Trevelyan et al., (2006) J Neurosci. 26(48):12447-55.
2. Kuenzi et al., (2000) J Neurosci Methods. (1-2):117-22

Predicting surgery targets for Temporal Lobe Epilepsy

Frances Hutchings
School of Computing Science,
Newcastle University

Imaging techniques can be used to estimate connectivity between brain regions in individuals. We incorporate this patient-specific connectivity data into a simplistic model of epilepsy to predict regional vulnerability to seizures- and to estimate how modifying the connectivity may affect seizure likelihood. Simulations of surgery procedures show success rates comparable to those found in literature- and the model additionally predicts patient specific recommendations for improved surgical procedures.

Proposed Closed Loop Algorithm System Implementation for controlling focal epilepsy using Optogenetics

Soumyasanta Laha
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The proposed closed-loop concept will be continuously monitoring the brain activity in a patient with focal epilepsy for epileptic precursors and adapt a pulsed optical signal to prevent epileptic seizures from developing using the novel principles of Optogenetics. In the heart of the closed loop algorithm is essentially a digital FIR filter, as envisaged so far. This filter will be implemented in firmware using an ultra-low power DSP enabled microcontroller/FPGA which can be either be an ARM Cortex M4 or an M0+ microcontroller or a Flash FPGA. Currently the comparative performance of these different hardware devices to implement the algorithm in firmware are investigated, and is the subject of this presentation.

Fragile recurrent activity of local cortical networks shown by optogenetic manipulation of basket cells

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The role of specific subclasses of neurons in the dynamics of local cortical networks remains unclear. A well characterised recurrent activity in these networks is the "UP state", during which neurons are depolarised and their firing rate is increased. In vitro and in vivo experiments showed that pyramidal cells and inhibitory basket cells simultaneously enter and exit this state. This recurrent network activity was also shown to be self-maintained by a balanced input of excitatory and inhibitory conductances in each neuron. We hypothesised that any manipulation of the activity of the inhibitory populations involved would disturb the balance and force the network to a hyperpolarised state ("DOWN state") decreasing the network activity. One question we wanted to address was whether the balance was the key stabilising factor. If so, then this might suggest a surprising possibility, that transition from UP to DOWN states might happen even when the inhibition is decreased.

We explored this question using brain slice preparations, using ACSF which is known to facilitate UP / DOWN transitions (1.1mM Ca2+ / 1mM Mg2+). The PV- expressing basket cells were manipulated optogenetically either by increasing their activity with channelrhodopsin (ChR2) or by silencing them with halorhodopsin (Halo/NpHR). Both the increase and the decrease of inhibitory basket cell activity forced the network to a DOWN state for the duration of photostimulation as hypothesised. Interestingly the local network activity returns to the UP state as soon as the photostimulation ends. The results suggest that the recurrent activity found in local cortical networks is a fragile state that can be abruptly interrupted and restarted by manipulating the inhibitory currents and disturbing the balance between excitation and inhibition in the network. This implies, counter-intuitively, that in such regimes of activity, decrease of inhibition can result in lower network activity.

Dissociative Seizures: A Psychobiological Perspective

Emma Robinson
NUTH NHS Foundation Trust

Epilepsy clinics are often referred people who appear to be having epileptic seizures however- on examination epilepsy is not present. These seizures have been known by many different names and more recently are called dissociative seizures or non-epileptic attack disorder- which is one condition within a group of symptoms called functional neurological disorder. It is estimated that 1 in 3 referrals to tertiary epilepsy centres receive a diagnosis of dissociative seizures (Bodde 2009). This condition has historically been an enigma which has resulted in the belief that they are fake or purely behavioural. This generally leads to a lack of treatment despite experiencing high levels of disability- leading to repeated A&E admissions- GP appointments and multiple investigations. Estimated financial costs of this disorder are high (Binder & Salinsky 2007; Salinksy 1995) and it is distressing both to the individuals and clinicians. We now have an increasing understanding of dissociative seizures largely based on trauma literature. It is widely reported that there is a high prevalence of trauma in those who have dissociative seizures- (Reuber 2008). Psychological therapy has been used with this client group with positive outcomes including- significant reduction or cessation of seizures.

The 100,000 Genomes Project & Epilepsy

Hannah Steele
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Newcastle University &
Department of Neurology,
NUTH NHS Foundation Trust

The 100,000 Genomes project is a DH funded initiative facilitating genomic sequencing for rare diseases and cancers (1). Many rare neurological disorders have a genetic basis (2), including many epilepsy syndromes (3).

Whilst most epilepsies are polygenic, approximately 1% arise due to variants in a single gene. The 100,000 Genomes project looks to recruit these families.

Phenotypes that can be included are:

De novo epilepsies	Familial epilepsies (min. 2 affected 1st deg rels)
epileptic encephalopathy	familial focal epilepsies
intellectual disability	familial generalised epilepsies
	genetic epilepsy with febrile seizures plus (GEFS+)

Newcastle was one of 3 pilot sites in England, recruiting 1085 participants between November 2013 and June 2015, including 500 with a neurological disorder.

Following a successful bid, the Newcastle upon Tyne Hospitals NHS Foundation Trust was awarded Genomics Medicine Centre status, enabling this work to be continued in the region.

This poster lays out the process and pipeline involved for participants.

Participation in the project does not guarantee results. However a handful of patients have received results with implications for their clinical care following the pilot study. Further results from the pilot scheme are expected to be fed back to clinical teams from October 2015.

References

1 - http://www.genomicsengland.co.uk/
2 - PMID: 26341866
3 - PMID: 23468209

Predicting neurosurgical outcomes in focal epilepsy patients using computational modelling

Peter Taylor
School of Computing Science,
Newcastle University

Around a third of patients continue to have seizures even after epilepsy surgery. Hence, reliable criteria for predicting patient outcomes are needed. Computational models, with appropriate parameters constrained by patient data, allow the opportunity to make patient-specific predictions based on the model dynamics.

In this study, non-seizure electrographic recordings were used to calculate connectivity between different cortical regions. This connectivity was used to construct patient-specific computational models. We simulated patients with intractable epilepsy, who underwent surgical treatment and made model predictions regarding their surgical outcome.

Using the model, brain regions with high epileptogenecity were predicted. We found that in some patients these regions are correlated with those identified clinically as the seizure onset zone. Moreover, it was found that the resection of these regions in the model reduces the overall likelihood of a seizure. Following removal of these regions in the model, surgical outcomes were predicted and compared to actual patient outcomes. The prediction was found to be 78% accurate. Intriguingly, in patients with unsuccessful outcomes alternative resection sites were proposed by the model.

Our model may aid clinicians in presurgical evaluation by providing a tool to explore various surgical options offering complimentary information to existing clinically used techniques.

Inhibitory synapse location and the propagation of seizure-like events

Chris Thornton
School of Computing Science,
Newcastle University

The aim of this work is to investigate how the location of inhibitory synaptic input on the post-synaptic cell affects the ability of a neuronal network to restrain the spread of activity. To do this we have used the Virtual Electrode Recording Tool for EXtracellular potentials (VERTEX), a Matlab tool, to simulate a network of 5000 multi-compartmental adaptive exponential integrate and fire neurons with conductance based synapses. We applied a current injection to a spatially restricted subset of the neurons and observed whether this resulted in a propagating wave of activity or whether the activity was restrained. This was done for a range of excitatory and inhibitory synapse strengths for networks with exclusively soma targeting or dendrite targeting inhibitory neurons. The result was that there is a far greater range of synapse strengths for which activity is restrained for the networks with soma targeting inhibitory neurons.

Mechanisms underlying different focal seizure onset patterns

Yujiang Wang
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Newcastle University

With the rise of new recording techniques in the last decade, clinical, experimental, and theoretical works have started to uncover a new understanding of neocortical focal seizure onset [1]. However, a long-standing observation has not been discussed in the context of the new discoveries yet: neocortical focal seizures typically begin with one of two typical waveform patterns -- low amplitude fast oscillations (LAF), or high amplitude spikes/sharp waves (HAS) [2]. Interestingly, only the former of the patterns is associated with a good surgical outcome [3].
Based on previous work [1] we replicate these different onset patterns of intracranial recordings in a spatio-temporal computational model of a neocortical patch of tissue, and show that they are associated with different spatio-temporal patterns at the finer mesoscopic scale (Fig. 1). The LAF is generated by initially independent patches of localized activity, which slowly evolve to a network of epileptic activity over time. In contrast, the HAS occurs as a transition to a globally bistable seizure state triggered by a local event. This indicates a difference in the spatial extent of the underlying pathology, which could explain the different surgical outcome associated with these two seizure onset patterns. Based on the results, we propose alternative treatment strategies for patients with the HAS onset pattern. Finally, we also discuss the implications of the different mechanisms on seizure prediction.

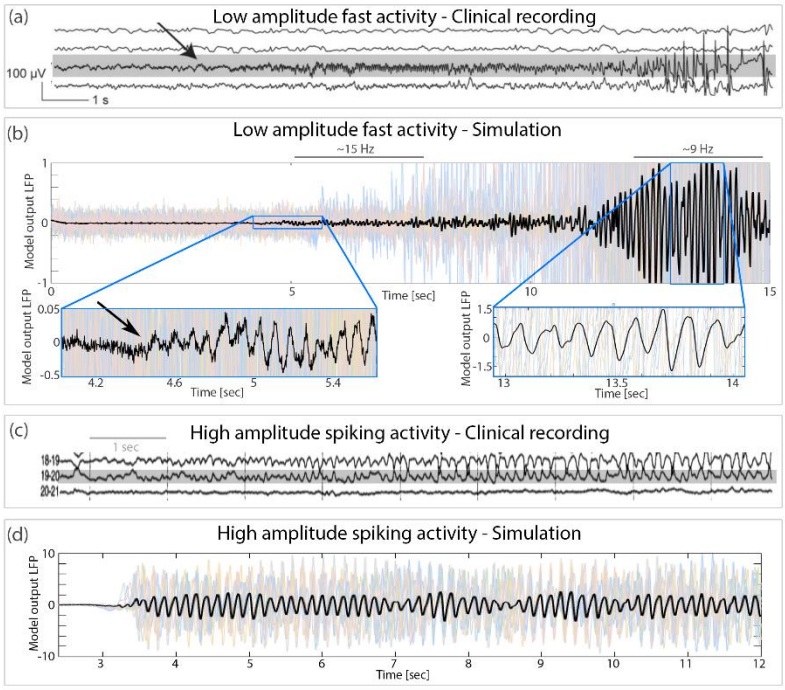

Fig. 1: Spatio-temporal model of two types of different focal seizure onset patterns.
(a) An example clinical recording of the LAF type of focal seizure onset (adapted from [2]). **(b)** Simulation of the low amplitude fast onset pattern (thick black line) calculated as the mean LFP activity from the underlying cortical columns (example traces shown in pastel colours). **(c)** An example clinical recording of the HAS pattern of focal seizure onset (adapted from [3]). **(d)** Simulation of high amplitude sharp waves pattern (thick black line) calculated as the mean LFP activity from the underlying cortical columns (example traces shown in pastel colours).

[1] Wang Y, Goodfellow M, Taylor P.N, and Baier G (2014) Dynamic mechanisms of neocortical focal seizure onset, *PLoS CB*, e1003787
[2] Perucca, P, Dubeau F, and Gotman J (2014) Intracranial Electroencephalographic Seizure-Onset Patterns: Effect of Underlying Pathology, *Brain* 137 (1): 183–96
[3] Lee S-A, Spencer D.D, and Spencer S.S (2000) Intracranial EEG Seizure-Onset Patterns in Neocortical Epilepsy, *Epilepsia* 41 (3): 297–307