North East Epilepsy Research Network Meeting

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## Programme

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<td>09.30-10.10</td>
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<td><em>Epilepsy and Autism: the questions that clinicians and families want answered</em></td>
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<td>10.10-10.40</td>
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<td>11.10-12.00</td>
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<td>13.40-14.00</td>
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North East Epilepsy Research Network Meeting  Friday 30th September 2016
A recent report highlighted that people with autism are at increased risk of premature death, with epilepsy being one of the most common causes. This highlights the long standing view of the considerable overlap between both conditions. Parents and clinicians are often faced with similar questions viz: how often do they coexist? Is the epilepsy in people with autism different than in people who do not have autism? What are the causes for the co-existence? Are there ways of earlier detection? These questions and more will be addressed in this talk.
ERK and epilepsy in fragile X

Dr Emily Osterweil  
Centre for Integrative Physiology  
Edinburgh University

Fragile X syndrome (FXS) is a developmental disorder associated with a high incidence of autism, intellectual disability and epilepsy. FXS develops due to silencing of the FMR1 gene and subsequent loss of FMRP, a potent repressor of translation. It has been suggested that the protein synthesis downstream of mGluR5 significantly contributes to the synaptic pathophysiology of the disorder. Consistent with this, we find that hippocampal protein synthesis is excessive in the Fmr1 KO, and that acute pharmacological inhibition of either mGluR5 or the ERK1/2 signalling pathway is sufficient to normalize protein synthesis.

Interestingly, it had been shown that a mild reduction of ERK1/2 activity can be achieved by disrupting the posttranslational maturation of the upstream activator, Ras, using HMG-CoA reductase inhibitors such as lovastatin. Based on these findings, we tested the efficacy of lovastatin for correcting pathological phenotypes in the Fmr1 KO. Remarkably, we find that lovastatin, a drug in widespread use and approved to treat hypercholesterolemia in children, decreases Ras-ERK1/2 signalling, normalizes excessive protein synthesis, corrects exaggerated hippocampal mGluR-LTD, eliminates hippocampal epileptiform activity, normalizes neocortical hyperexcitability, and significantly ameliorates audiogenic seizures (AGS) in the Fmr1 KO mouse. These data suggest that lovastatin is potentially disease modifying, and could be a viable prophylactic treatment for epileptogenic symptoms in FXS.
John “Os” Walkinshaw Osselton (1928-2009)

John Osselton, or “Os” as he was generally known, spent his entire academic career at Newcastle University, where his lifelong research interest in EEG contributed significantly to our understanding of epilepsy.

Oz was born into a medical family in Newcastle in 1928. His mother had been something of a medical pioneer; not only was she the third female to qualify in medicine from Newcastle University (then part of Durham University), graduating in 1911, but one of the first female consultant anaesthetists in the UK. It was natural therefore that Oz, despite graduating from Newcastle University in 1949 with a BSc in Electrical Engineering, should embark upon a career in medical research.

His first appointment in 1949 was as Research Assistant in the Department of Psychological Medicine at the Royal Victoria Infirmary, in the section of “Applied Electrophysiology”. The then head of department, Professor Alexander Kennedy, keen to embrace the new technology of EEG dispatched Oz to the Burden Neurological Institute in Bristol, to learn about EEG from his former colleague William Grey Walter (Kennedy and Walter had been colleagues at the Maudsley Hospital before the war). Grey Walter had already built the first EEG system in the UK in the 1930s after visiting Hans Berger’s laboratory, improving greatly on the original design. With their shared interest in refining and improving EEG technology, Walter and Oz were destined to be lifelong friends. Oz was promoted to Lecturer in 1954 and then Senior Lecturer in EEG in 1965. He retired in 1984 and died after a long illness in 2009.

Oz published numerous teaching articles and scientific papers, but is probably best remembered internationally as the co-author of two of the first EEG textbooks: “clinical EEG” and “EEG technology” and co-editing both volumes of the more comprehensive textbook “Clinical Neurophysiology”. He is remembered locally in Newcastle for being an outstanding teacher, having trained many generations of neurologists, neurophysiologists and technicians in the mystery of EEG interpretation.
The brain contains an extremely complex network of neurons and their connections. We assume that neuronal dynamics operating in these networks gives rise to all the normal functions of the brain. It is tempting to assume that seizure arise either in isolated abnormal populations of neurons (in focal epilepsy) or in all brain areas simultaneously (in generalised epilepsy), but evidence suggests seizures emerge through a complex interplay between the dynamics of local neuronal populations and the networks that interconnect them. This contribution will discuss the ways in which human brain networks can be observed, new methods to describe and model the networks, and why epilepsy provides an exciting opportunity to develop simple but informative models of the human brain. Examples will be discussed to illustrate how models of brain network dynamics can contribute to our understanding of epilepsy, and may underpin future diagnostic and prognostic tools in clinical management.
The source of human focal seizures: evidence from single unit recording

Dr Catherine Schevon
Department of Neurology
Columbia University, New York

Despite over 50 years of electrophysiology investigations, the temporal and spatial structure of human focal seizures has never been clearly defined. We present findings from microelectrode recordings of seizures in epilepsy surgery patients that outline a structure with a slowly expanding core of seizing brain, and a surrounding "penumbra". Based on results from animal model experiments, we hypothesize that the penumbra is reacting passively to the seizure, despite being marked by EEG discharges that may be indistinguishable from those present in the seizure's core.
Active brain stimulation to suppress or prevent seizure activity is an active field of research. With some recent promising experimental and clinical advances, a real-time interaction with seizure activity is now technically possible, allowing for the development of closed-loop devices. However, strategies for how seizure activity can be controlled by such devices is currently lacking.

In my talk, I will discuss this problem from a theoretical/computational point of view, and also highlight the challenges that are specific to epileptic seizures in this regard. I will propose a possible strategy to address these challenges, and show initial results using such a strategy in silico.
Session 3, Epileptic Seizures
Instead of reversing a specific mutation, gene therapy in epilepsy can take a broader approach based on addressing the balance of excitation and inhibition. We have recently reported three different strategies for reducing excitation in non-genetic models of epilepsy, including over expression of an endogenous channel, expression of a light-activated chloride pump, and expression of a synthetic channel gated by an exogenous ligand. This talk will briefly summarise the three approaches and focus on the challenges of bringing the technology to clinical trials in human patients, as well as ideas for what future strategies might be most promising.
Seizure propagation in vivo in the cortex respects the functional connectivity underlying sensory processing

Dr Rob Wykes
Institute of Neurology
University College London

Focal epilepsy results from excessive and synchronous cortical activity that propagates both locally and to distant sites. Does this propagation follow the same routes as normal cortical activity? To answer this question, we induced focal epileptiform discharges in primary visual cortex (V1) of awake mice, and compared their propagation to the retinotopic organization of V1 and higher visual processing areas. We measured neural activity through simultaneous LFP recordings and wide-field imaging of a genetically encoded calcium indicator, and observed both seizure-like (ictal) events and brief interictal events. Interictal events elevated activity synchronously in the focal V1 region and in corresponding retinotopic locations in higher areas. Ictal events exhibited at first the same characteristics, but they persisted for much longer, and propagated both locally and into non-contiguous cortical regions. The distal regions matched the local regions in retinotopy, indicating that seizure propagation respects the functional connectivity underlying normal visual processing.
Metabolic underpinnings of tumour-associated epilepsy in a mouse model of malignant glioma

Dr Elizabeth Stoll
Institute of Neuroscience, Newcastle University

Glioma is the most common form of adult-onset primary malignant brain tumour, affecting approximately 4-5 per 100,000 people and representing 81% of all malignant brain tumours. Low-grade gliomas commonly manifest with a seizure, in approximately 75% of cases; high-grade gliomas, called glioblastomas, are associated with seizures in 29-49% of cases (Ostrom Neuro Oncology 2014). Tumour-associated epilepsy (TAE) significantly impacts on the quality of life of these patients.

Initiating events underlying TAE are not well-understood, and may include mass effect during tumour growth, with attendant increases in intracranial pressure; loss of particular cell types, such as inhibitory interneurons; excess release of the excitatory neurotransmitter glutamate by the tumour or altered responses of cells to this factor; aberrant potassium ion channel expression within neurons, leading to depolarizing not hyperpolarizing responses to GABA signals; alterations in gap junctions between cells; or pH shifts due to the acidic environment created by tumour cells (Cowie & Cunningham Epilepsy & Behavior 2014).

A highly-reproducible, clinically-relevant animal model of malignant glioma which demonstrates TAE may help to elucidate the underlying mechanisms for this phenomenon, however few characterised models are currently available (Kirschstein & Kohling J Neurosci Methods 2015). Recently, a syngeneic mouse model of glioma has been developed which reproduces the histopathological and clinical characteristics of human glioma on a wild-type background (Mikheev et al. Aging Cell 2009). We observe that 26% of these animals manifest seizures, thereby providing a reliable, clinically-relevant context in which to evaluate mechanisms underlying TAE.

In this study, we conducted histological analysis in seizing and non-seizing animals to discern cellular and molecular features associated with this phenotype. Animals with seizures do not have significantly larger tumour size or greater infiltration of brain areas, nor do they demonstrate significant changes to interneuron population size in ipsilateral or contralateral regions to the tumour, although some cellular disorganisation is observed. Future studies will address mechanisms underlying TAE by using Utah Arrays to record single-unit activity and field potentials across tissue sections containing both tumoural and peri-tumoural region during pharmacological manipulations, to evaluate several hypotheses related to seizure generation in the vicinity of the glioma.
Session 5, Brain tumours and epilepsy
Evidence based management of epilepsy in patients with brain tumours

Symptomatic management of seizures in cancer patient is in principle not different from other causes for focal epilepsy. Antiepileptic drugs (AEDs) can be initiated after the occurrence of a single seizure attributable to a brain tumor. Epilepsy in patients with brain tumors (BTE) belongs to the type of partial epilepsy in adults, either with or without secondary generalized seizures. For this type of seizures, the International League against Epilepsy has updated the most appropriate AEDs based on a meta-analysis of large number of randomized controlled trials. As such, levetiracetam, carbamazepine, phenytoin and zonisamide score as class A anticonvulsants, based on trial quality for efficacy. Valproic Acid represents the only class B anticonvulsant. Gabapentin, lamotrigine, oxcarbazepine, phenobarbital, topiramate and vigabatrin are class C agents. Subsequently, the choice of the most fitting AED among the approved agents depends on individual patient factors, most importantly age, sex, weight, comorbidities, and concomitant therapy including drug interactions.

Levetiracetam as monotherapy demonstrates a high seizure control rate of 70-100% in low- and high-grade gliomas, although preceding surgery and associated anti-tumor treatment contribute to these excellent results. It is likewise effective for other primary or secondary brain tumours. The advantages of levetiracetam over other AEDs include good tolerability and lack of drug-drug interactions. Approx. 5% of patients develop irritability, aggression or psychosis, for which dose adjustment or withdrawal of levetiracetam is usually indicated. Intriguingly, cognition improves in around 25% of patients on levetiracetam in both general epilepsy as in BTE. Valproic acid monotherapy in BTE is extensively utilized for low- and high-grade gliomas and provides improved or complete seizure control in 55-78%. (3) Valproic acid is a broad-spectrum, well-tolerated AED although it may cause increased appetite, hand tremor, and thrombocytopenia. It is contra-indicated in pregnant women. In glioblastoma, valproic acid may be given as first line AED in based on the evidence as class B agent for focal epilepsy together with emerging activity of antitumor efficacy if combined with temozolomide.

With regard to class C agents, there is little information on gabapentin and lamotrigine in BTE, although both AEDs are generally well tolerated. Topiramate is a broad-spectrum AED that often causes substantial cognitive side effects. Oxcarbazepine monotherapy in BTE is associated with a relatively high rate of cognitive adverse effects.

When the initial anticonvulsant provides insufficient seizure control, one can switch to a second agent as monotherapy, though there is a trend to rather apply polytherapy as the next step by adding a second AED to the first one. In drug-resistant epilepsy add-on levetiracetam is remarkably effective both in general epilepsy as in BTE, producing 50+% seizure reduction in 65% of patients. (2, 3) Apart from the use of combined levetiracetam and valproic acid, a good alternative anticonvulsant is lacosamide based on efficacy, good tolerability and absence of drug interactions. In BTE, 43% of patients on add-on lacosamide became seizure-free, and 40-50% of patients showed a 50+% seizure reduction. Adjunctive perampanel in drug-resistant partial seizures produces about a 40% response rate and sustained seizure frequency improvement with a generally favorable safety profile.

If either levetiracetam or combinations with VPA or lacosamide are insufficiently effective, one can choose lamotrigine for its good tolerability and its potential of synergistic activity with VPA, perampanel for its efficacy and tolerability in refractory partial epilepsy or zonisamide considering its recent designation as class A agent for the partial epilepsies. Duration of AED therapy depends on the underlying cause of seizures. For seizures associated with metabolic or toxic encephalopathies, we recommend to continue AEDs therapy as long as the underlying cause remains present or can easily recur. In the case of a structural lesion as cause of the epilepsy as with gliomas, we advocate continuing antiepileptic treatment for at least two years following seizure control. In patients with long-term good seizure control on polytherapy, it is reasonable to try to gradually taper the patient down to monotherapy.

It is uncertain whether there is any role for AED prophylaxis in brain tumor patients without a history of seizures. A notable exception is that prophylactic AEDs may be considered for the first weeks after surgical resection, given the frequency of immediate post-operative seizures. Although peri-operative AED prophylaxis is common practice among neurosurgeons for brain tumor patients, evidence is lacking.
Posters

- A role for NMDA receptors subunits NR2A/B in human cavernoma epileptogenesis?
  Anderson Brito Da Silva, Institute of Neuroscience, Newcastle University

- Utilizing analytical biochemistry techniques to interrogate the state of tissue metabolism during mitochondrial epilepsy
  Felix Chan, Institute of Neuroscience, Newcastle University

- Using optogenetics to characterise the evolution of epileptiform activity in rodent brain slices.
  Neela Codadu, Institute of Neuroscience, Newcastle University

- Development of a lentivirus-based gene therapy for the treatment of epilepsy for the CANDO project - Controlling Abnormal Network Dynamics using Optogenetics
  Carolina Gándara, Institute of Neuroscience, Newcastle University

- Seizure self-prediction; limitations and possibilities.
  Michael Mackay, Clinical Research Associate, Newcastle University

- Disparate patterns of epileptiform activity result in differential acute responses within interneurons.
  Ryley Parrish, Institute of Neuroscience, Newcastle University

- Stimulus evoked layer-specific activity in vitro and in silico in the rat somatosensory cortex.
  Christopher Thornton, School of Computing Science, Newcastle University
Cavernoma or cerebral cavernous malformations (CCM) are cerebrovascular abnormalities and seizures are the most frequent clinical symptoms. Despite being well localised- only 75% of patients with CCM-related epilepsy became seizure free after the lesion resection. The high recurrence is probably caused by changes in the tissue surrounding the lesion. Evidence suggests that there is a upregulation of nitric oxide synthase (NOS) isoforms and the N-methyl-D-aspartate (NMDA) receptors- specially subunits NR2A/B- adjacent to CCM resected tissue (Kamida et al- 2007). - We investigated the role of the NMDA receptors in the generation of ictal activity- focusing on specific subunits of NMDA- in the perilesional tissue from human CCM. - The NR2A blocker reduced significantly the ictal activity induced by modified aCSF- decreasing the spectral power- spike rate and burstiness. - This results suggest that despite the evidence of upregulation of both subunits- NMDA receptos 2A seems to play a more important role in the epileptogenesis of CCM-related epilepsy.
Utilizing analytical biochemistry techniques to interrogate the state of tissue metabolism during mitochondrial epilepsy

**Felix Chan**  
Institute of Neuroscience, Newcastle University

We have developed a novel in vitro brain slice model for mitochondrial epilepsy based on neuronal respiratory chain inhibition using rotenone (complex I inhibitor) and cyanide (complex IV inhibitor) as well as astrocytic Krebs cycle inhibition using fluorocitrate (astrocyte-specific aconitase inhibitor). We aim to characterize the metabolic state of the tissue during the seizure state by labelling with [U-13C] glucose. Quantification of the amount of relevant amino acids is performed using HPLC and tracing of the metabolic labelling of the 13C using GC-MS.

There is significant increase in alanine and lactate pool in the epileptic slices, suggesting significant upregulation of glycolytic activity. 13C labelling indicates that in addition to upregulation of glycolysis, there is also significant increase in the pentose-phosphate-pathway suggesting the generation of NADPH, an important cellular reducing-agent against oxidative stress. Krebs cycle activity is significantly reduced, as demonstrated by reduced labelling in α-ketoglutarate, fumarate, malate, and succinate. Accumulation of labelled citrate confirmed a severe block in aconitase. Glutamate and GABA pool is increased, suggesting the lack of use of these metabolic substrates for energy production. Interestingly, glutamine pool is significantly depleted in epileptic slices, showing a preferential use of glutamine as metabolic fuel during a seizure state. Pool size of branched chain amino acids (leucine, valine, and isoleucine) is also increased, again suggesting the inability to utilize these amino acids as energy source.

Our results indicate severe metabolic changes that occur during the seizure state in mitochondrial epilepsy. In particular, several pathways are implicated such as the astrocytic glutamate-glutamine cycle and anaerobic glycolysis. Analytical biochemistry techniques represent a novel approach towards interrogating changes in tissue metabolism during a seizure state.
Using optogenetics to characterise the evolution of epileptiform activity in rodent brain slices

Neela Codadu
Institute of Neuroscience, Newcastle University

There are a disproportionate number of epilepsy cases arising from temporal lobe pathology, indicating that hippocampal circuits may be particularly epileptogenic. Using brain slices from young adult mice, we therefore characterised how epileptiform events evolve in different brain regions in response to acute pharmacological challenges. Local field potentials (LFP) were recorded simultaneously from CA3 pyramidal cell layer and deep layers of neocortex.

Surprisingly, when bathing slices in 0Mg2+ artificial CSF, neocortex appeared more excitable than hippocampus, with full ictal activity occurring earlier and with tonic-clonic like patterns apparent. In contrast, hippocampal territories exhibited spike and wave type discharges, which occurred in isolation, but with great regularity. Although hippocampal activity starts relatively late it immediately entrained neocortical activity. This entrainment occurred independently of axonal pathways, implicating local field effects. We further characterised how changes in excitatory synaptic transmission contributed to the evolution of epileptiform activity in neocortex. Brain slices were prepared from mice expressing Channel rhodopsin under the Emx1 promoter. Downstream postsynaptic LFPs were recorded in response to brief optical activation of layer 2/3 pyramidal cell populations. These experiments showed changes in the excitatory synaptic connectivity in tandem with the evolution of network dynamics in the 0Mg2+ model.
Development of a lentivirus-based gene therapy for the treatment of epilepsy for the CANDO project - Controlling Abnormal Network Dynamics using Optogenetics

Carolina Gandara
Institute of Neuroscience, Newcastle University

The use of viral vectors to deliver genetic material into cells is the most effective means of gene transfer in vivo. Lentivirus infects both dividing and non-dividing cells, has a high insert-size capacity and integrates recombinant DNA into the host cell genome to achieve long-term stable gene expression. In contrast to other viral vectors, such as adenovirus, lentivirus induces low levels of immune response. Therefore, lentiviral vectors are the vehicle of choice for gene therapy in the treatment of neurological disorders, such as epilepsy; the combination of lentivirus-mediated gene therapy and an implantable biomedical device with recording and optical stimulation capability represents a full tool-kit for closed-loop optogenetic control of neuronal activity in vivo.

Our group is currently developing such a lentivirus-based optogenetic gene therapy for the treatment of epilepsy (the CANDO project). We design and manufacture high-titre third-generation lentivirus and validate the constructs with a wide range of methods. We have also built a collection of lentivector plasmids that contain different combinations of promoters (to drive ubiquitous or cell-specific gene expression), light-sensitive ion pumps or channels (e.g. channelrhodopsins), and fluorescent reporters. This report summarises our workflow for producing and validating lentiviral vectors in our laboratory for the CANDO project.
Evidence suggests that patients have some awareness of their risk of an upcoming seizure and gain a degree of predictive ability from this information. Here we investigate the implications for seizure self-prediction. To have any predictive ability the underlying seizure risk must fluctuate, and the patient must have some awareness of this. The extent of predictive ability is dependent on the underlying distribution of seizure risk, and the accuracy of the patient's estimate of risk. Monte Carlo simulation of seizure occurrence and prediction suggest study lengths of greater than a year would be required to reliably detect all patients who have significant predictive ability and thus we may be dramatically underestimating this capability within the population of patients with epilepsy (PWE). In addition, utilising a classifier to predict seizures on the basis of predictive information can dramatically improve performance, suggesting there is scope for improving seizure prediction on the basis of patient derived information, and that this may be applicable to an appreciable proportion of PWE.
Disparate patterns of epileptiform activity result in differential acute responses within interneurons

Ryley Parrish  
Institute of Neuroscience, Newcastle University

Genes expressed by a neuron determine its excitability, and neuronal activity influences gene expression. This two-way interaction maintains functional stability; a key homeostatic mechanism. Non-homeostatic changes will occur during development and learning. Similarly, various brain insults can trigger non-homeostatic changes, leading to a long-lasting change in excitability, manifest as a tendency to suffer epileptic seizures. During this process, interneurons may experience a “homeostatic conflict” as the network becomes increasingly excitable, requiring the interneurons to increase their excitability. Such a response may be at odds with their own homeostatic needs as a cell autonomous population.

To investigate whether there are conflicting homeostatic drives in these inhibitory neuronal populations, we used acute pharmacological manipulations in brain slices from young adult wild-type mice, to induce epileptiform discharges in different subsets of cortical neurons, followed by analysis of gene expression changes. The experimental design aimed to test whether the gene expression changes in interneuronal populations was different in two conditions:

(1) Interneuron activation in relative isolation (4-aminopyridine with glutamatergic blockade) or

(2) Interneuron activation in tandem with pyramidal population (0 Mg2+).

Activity from these pharmacological manipulations were recorded for an hour, and then the tissue was prepared for post hoc analyses of gene expression.
Stimulus evoked layer-specific activity in vitro and in silico in the rat somatosensory cortex

Christopher Thornton
School of Computing Science, Newcastle University

Detailed maps of cell type-specific synaptic connectivity in the cortical microcircuit - are now available for various regions and species - including that of rat somatosensory - cortex provided by The Neocortical Microcircuit Collaboration Portal. Using this map - and VERTEX (the Virtual Electrode Recording Tool for EXtracellular potentials) we - generated a three-dimensional multilayered network representative of an in vitro slice - preparation. We wished to investigate the relationship between the synaptic connec- - tivity described here and the dynamics one would record in vitro. So- we simulated the - neuronal dynamics and local field potential generated by this network after transient - stimulation of layer 4 cells and then compared this to the layer-specific - local field potential and mulit-unit activity recorded in vitro as a result of electric field - stimulation. These data were recorded using a multi electrode array from slices made - hyper-excitable by perfusion with 4-amino-pyridine and stimulated in layer 4 using a - bipolar electrode. Both in vitro and in silico we see a larger response in the deeper layers - in particular in the multi-unit activity.