

## REVIEW OF CURRENT RESEARCH

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### IMAGING OF BRAIN FUNCTION

#### *“Imaging the functions of the brain with fMRI”*

**S Bonelli, M Centeno, JS Duncan, MJ Koepp, J Stretton, MR Symms, PJ Thompson, C Vollmar.**  
**Collaborators: G Barker, V Kumari, J O’ Muircheartaigh, MP Richardson (King’s College London)**

*We are developing the use of the MRI scanner to visualize the site in the brain of crucial functions such as language and memory. This is very important when trying to determine the effects of brain surgery, and to understand the effects of epilepsy on brain functions. We can now use this method to predict, for individual patients, the likely effects of temporal lobe surgery on their memory.*

#### **Memory**

We have completed the analysis of a series of 54 patients with temporal lobe epilepsy, who have had language and memory encoding fMRI before and 3 months after anterior temporal lobe resection.

In left temporal lobe epilepsy, greater left than right anterior hippocampal activation on word encoding correlated with greater verbal memory decline after left anterior temporal lobe resection, while greater left than right posterior hippocampal activation correlated with better postoperative verbal memory outcome.

In right temporal lobe epilepsy, greater right than left anterior hippocampal functional MRI activation on face encoding predicted greater visual memory decline after right anterior temporal lobe resection, while greater right than left posterior hippocampal activation correlated with better visual memory outcome.

Preoperative memory functional MRI was the strongest predictor of verbal and visual memory decline following anterior temporal lobe resection. Activation asymmetry, language lateralisation and performance on preoperative neuropsychological tests predicted clinically significant verbal memory decline in all patients who underwent left anterior temporal lobe resection, so that we are now in a position to predict the likely effect of temporal lobe surgery on memory, for individual patients.

The finding that strong activation in the posterior ipsilateral hippocampus was associated with preservation of memory is a novel and important finding. This implies that reorganization of function within the ipsilateral hemisphere is an efficient process.

We are now following this up with analysis of memory fMRI studies acquired after temporal lobe resection to determine whether there is relocation of memory functions after surgery and, in particular, whether the posterior hippocampal remnant is activated.

In patients with frontal lobe epilepsy, in contrast, we have found that memory encoding activates hippocampi as it does in controls.

#### **Language**

This year, we translated language fMRI into clinical use prior to neurosurgery in the frontal and temporal lobes, so that the potential risk to language can be predicted and minimized. We are looking further into the factors that determine language dominance and, with language fMRI studies acquired after temporal lobe surgery, the post-operative changes in language networks that occur as function recovers. Up to 30-40 % of patients with TLE show a clinically significant decline in naming abilities after anterior temporal lobe resection of the language dominant hemisphere. We showed that naming ability correlated with left hippocampal activity in healthy controls and patients with right TLE, characterised by better naming scores in subjects with greater hippocampal fMRI activation, but this was not observed in left TLE patients.

In frontal lobe epilepsy, we observed more widespread and diffuse left frontal activation during verbal fluency and verb generation fMRI paradigms than observed in controls and in patients with TLE. Furthermore, increased activations were found in temporal areas bilaterally, particularly contralaterally and fronto-temporal connectivity was reduced compared to controls.

**Working memory**

We found that working memory results in co-activation within the motor cortex in patients with juvenile myoclonic epilepsy. In this group, left motor cortex activation correlated with increasing task demands and performance scores suggesting increased functional coupling between “frontal lobe” cognitive networks and motor cortex in juvenile myoclonic epilepsy patients. Evidence for hyperexcitability of motor cortex is an interesting finding, given the predominant clinical seizure type with myoclonic jerks which have been reported to be triggered by cognitive activity. During verbal processing tasks left FLE had more dispersed activation patterns than controls and juvenile myoclonic epilepsy.

We have initiated a study of working memory in temporal lobe epilepsy, and found that functional connectivity between both hippocampi was reduced in TLE but not in FLE.

**“Imaging epileptic activity”**

**L Lemieux, D Carmichael, U Chaudhary, B Diehl, JS Duncan, A McEvoy, R Rodionov, K Rosenkranz, R Thornton, A Vaudano, S Vulliemoz, MC Walker. Collaborators: F Bartolomei, P Chauvel, M Guye (Marseilles), R Elwes (KCH), S Lhatoo (Frenchay), C Michel (Geneva), C Falcon (Barcelona), M Siniatchkin (Kiehl)**

*We are working on increasing our ability to find brain regions responsible for the epileptic activity and increase understanding of the mechanisms that give rise to this activity using multi-modal imaging techniques, and in particular simultaneous scalp and intracranial EEG-functional MRI. This may help in the clinical management of some individuals with severe epilepsy.*

We have continued acquiring EEG-fMRI data in patients with severe epilepsy from 4 epilepsy centres (Queen Square, Kings College Hospital, North Bristol and Marseille) as part of an ongoing 5-year project on the validation of the localising information provided by the non-invasive technique. We have made further significant methodological advances in the analysis methods particularly quantitative EEG modelling and are preparing to analyse the bulk of the data acquired. We have successfully completed the safety testing for intra-cranial EEG-fMRI and acquired a completely new kind of functional imaging data in humans – this is a world first as no report of this technique has been published to date. We have undertaken a large scale study on the haemodynamic correlates of seizures in patients with focal and generalised epilepsy using the newly implemented technique of video-EEG-fMRI.

**IMAGING BRAIN STRUCTURE****“New MRI contrasts and image analysis”**

**JS Duncan, N Focke, R Samson, MR Symms**

*We are pursuing the automated analysis of MRI scans to improve the sensitivity to detect subtle abnormalities that may cause epilepsy.*

Automated analysis of MRI scans has the potential to demonstrate subtle cerebral abnormalities that are not evident on visual inspection of images. It is crucial to balance sensitivity and specificity and, in particular, to avoid false positive findings when considering surgical treatment in individual patients. The techniques do not replace visual analysis but provide a useful adjunct, highlighting areas for further review.

Applying this method to FLAIR scans identified abnormalities in 14% of patients with refractory focal epilepsies who were previously considered to have normal MRI scans, leading to further consideration of surgical therapy.

We are continuing to work on the implementation of T1 mapping on the 3T MRI scanner, that will also enable the analysis of quantitative magnetization transfer imaging and related MR contrasts.

**“Neuropathological basis of MRI findings”****SH Eriksson, JS Duncan, SM Sisodiya, M Thom**

*In vivo MR images can detect a wide range of cerebral abnormalities, but in patients with presumed normal MRI, there may be more subtle changes that are currently only identified histopathologically. Further, in patients with MR signal abnormalities, it may be difficult to infer the precise underlying pathology. Improved MRI-histopathology correlations are needed to improve the yield and interpretation of in vivo MRI.*

We have continued our studies correlating quantitative MR parameters from preoperative *in vivo* MR images with quantitative postoperative histopathological parameters. Using a 3T MRI we did not find any significant correlations between quantitative MRI and histopathology in a small area of normal appearing tissue in the resected temporal lobe. Next, we will analyse larger areas such as the whole resected lobe and evident abnormalities such as focal cortical dysplasia or tumours.

Using voxel-based morphology, we have shown that quantitative histological measures of grey matter do not correlate with in vivo MRI-derived grey matter probability values and that VBM cannot identify either cortical neuronal loss or hippocampal sclerosis as seen pathologically in individual patients with epilepsy. We are currently collaborating with Dr Sebastien Ourseline at UCL Centre for Medical Image Computing (CMIC) to determine cortical thickness.

Significant changes in tissue size occur during fixation and processing. We therefore developed methods for measuring changes in size of resected tissue during fixation and subsequent tissue processing. The method enables us to calculate correction factors for quantitative analyses and comparisons.

**“Quantifying Change in Brain Morphology”****L Lemieux, E Williams, J Burdett. Collaborators: V Brazdova (UCL) and M Chupin (Paris)**

*We are developing a new method to measure the volume of the hippocampus and its neighbour, the amygdala and developing a new computational model of cerebral volume change. This should allow us to improve our ability to study the relationship between the progression of epilepsy and structural changes in the brain and to increase our understating of the underlying cellular mechanisms.*

We have continued segmentation software development and evaluation using data from healthy subjects and patients with epilepsy. We are now working on methods to improve our ability to detect changes in the volume and shape of the hippocampus and on improved validation methods.

**“Imaging the connections of the brain”****JS Duncan, MJ Koepp, AW Mcevoy, C Micallef, MR Symms, S Vulliemoz, C Vollmar, G Winston, M Yogarajah. Collaborators: D Alexander, AW Mcevoy, GJ Parker**

*The white matter forms the pathways that connect the parts of the brain together into functioning units. We have developed methods to examine the structure of white matter in great detail and to visualize the connections in the brain that are necessary for vital functions to be carried out. We are now beginning to use this information to reduce the risk of neurosurgery.*

**Temporal lobe epilepsy surgery and language**

Serial diffusion tensor imaging (DTI) before and after temporal lobe resection shows that the surgery causes areas of disruption of the white matter in the vicinity of the resection. In the left hemisphere, after left anterior temporal lobe resection, we found an increase in fractional anisotropy (FA) in the white matter of the internal capsule and corona radiata. Importantly those individuals who had increases in FA in this area did not have declines in expressive language function. The implication is that the DTI is showing plasticity of the white matter in the pathways of the ventromedial language stream that is compensating for the surgical deficit. This is the first time that acute structural and functional changes have been shown following neurosurgery

and has profound implications for understanding the processes of cerebral reorganization and recovery from injury.

We are following this work up with taking serial DTI scans at intervals following surgery to determine the time course of recovery and the plasticity of white matter, and the use of pre-operative DTI parameters to determine the risk of surgery affecting language functions in individual patients.

#### **Temporal lobe epilepsy and memory**

Using a voxel –based analysis of the diffusion characteristics of white matter we identified the extent of abnormalities of the white matter, in temporal lobe epilepsy. These primarily affect the limbic system and the ipsilateral frontal and temporal neocortex and the contralateral temporal lobe.

These structural changes have a functional correlate, with abnormalities in the ipsilateral fornix being correlated with extent of impairment of verbal memory encoding. Our next step will be to determine the effects of temporal lobe surgery on the memory functions and connections of the limbic system.

#### **Temporal lobe epilepsy and vision**

We have developed tractography methods to demonstrate the optic radiation in vivo and used this to determine the likely compromise of the optic radiation and visual field deficit as a result of anterior temporal lobe resection.

We are now working to optimise these methods and the display of the optic radiation and other critical tracts in three dimensions for surgical planning, and to integrate the results with the BrainLAB iMRI neurosurgical navigation system that is used in the operating room during neurosurgery. This system is the only one of its kind in the UK and promises to greatly enhance the precision of neurosurgery and reduce the risks.

#### **Frontal lobe epilepsy**

The supplementary motor area (SMA) has a key role in the execution of movements and is often involved in epileptic seizures. Using DTI and tractography we have shown that the major tracks connecting the SMA with the rest of the brain are not affected by frontal lobe or juvenile myoclonic epilepsies. This is in contrast to the effect of TLE on white matter connections and reflects the fundamental role of the SMA in motor control and the robust nature of these connections.

## **POSITRON EMISSION TOMOGRAPHY TO PROBE THE CHEMISTRY OF THE BRAIN**

### ***“Imaging of drug-resistance”***

**MJ Koepp, JS Duncan, M Feldmann, J Jamnadas-Khoda, JW Sander, SM Sisodiya**

*We are using PET tracers labelled with radio-isotopes to investigate the chemical abnormalities which are involved in epilepsy and epileptic seizures and where these are located in the brain.*

In collaboration with the Wolfson Molecular Imaging Centre in Manchester we performed the first human study using [11C]-verapamil as a radiotracer for P-glycoprotein function in the UK. The main intention is to validate radiotracers for P-glycoprotein activity as biomarkers for drug resistance using drug-resistant and drug-responsive epilepsy as a biological model. The first (R)-[11C]verapamil after the administration of the P-glycoprotein inhibitor tariquidar scan was also performed in both a healthy volunteer and in patients with drug-resistant mTLE. Preliminary analysis supports the hypothesis of altered P-glycoprotein function in areas of seizure spread and differences between drug-resistant patients and healthy volunteers. The development of new PET tracers is also being pursued as part of this project in collaboration with the Free University and SEIN in the Netherlands.

### ***“Imaging excitatory and inhibitory transmission”***

**JS Duncan, MJ Koepp. Collaborators: DJ Brooks, A Hammers, C McGinnity**

*The excessive, synchronised discharge of nerve cells in the brain is fundamental to the causation of epileptic seizures.*

Excessive activation of cerebral neurones by excitatory neurotransmitters acting on the NMDA receptors may underlie the genesis of some forms of epilepsy. To date it has not been possible to visualise or quantify this activation in vivo. We are working with GE Healthcare and the Hammersmith PET Centre to implement the use of an  $^{11}\text{C}$ -labelled PET tracer of the NMDA receptor (GE179 AH113135) and are carrying out the first proof of principle study in individuals with severe, refractory focal epilepsies.

In parallel, we are collaborating with studies to investigate the binding of subtype specific benzodiazepine receptors and cannabinoid receptors in individuals with specific forms of epilepsy.

## MAGNETOENCEPHALOGRAPHY

### ***“Advanced neurophysiological techniques to localise epileptic discharges and map cognitive function”***

**FJ Rugg-Gunn, N Cashdollar, JS Duncan, E Düzel**

*We are using magnetoencephalography (MEG) to identify the locations of epileptic foci and important cognitive functions such as memory and language. This will aid planning of surgical treatment for epilepsy and may predict the effects of surgery on brain function.*

MEG data derived from patients with refractory focal epilepsy who are candidates for surgery are being integrated with other presurgical imaging and neurophysiological investigations with the aim of improving the localisation accuracy of epileptic foci. The demonstration that MEG could obviate the requirement for intracranial EEG recordings or guide the placement of intracranial EEG electrodes in more complex cases would be a significant advance in the presurgical evaluation of patients with epilepsy. Over the last year we have acquired MEG recordings from over 60 patients who are undergoing evaluation for epilepsy surgery. The results have been compared to data obtained from other modalities such as intracranial EEG, structural and functional MRI. The localisation of epileptic discharges has been shown to correlate well with localising information from other sources and as a result MEG has been integrated in the pre-surgical programme. Over the next year we will examine the accuracy of the MEG results further and evaluate the usefulness of more subtle epileptic abnormalities, such as slow waves, high frequency oscillations and local cortical hypersynchrony and directly compare these results with the ictal onset zone as defined by intracranial EEG recordings. This will be facilitated by performing simultaneous MEG and intracranial EEG recordings.

We are now acquiring MEG recordings from healthy control subjects and patients with temporal lobe epilepsy to investigate the localisation and propagation of brain activity and the synchrony of fronto-temporal brain regions during language and memory tasks. The ability to localise eloquent cerebral regions and map neural networks involved in cognitive function may lead to a more individualised surgical approach and may be able to predict post-operative memory and language decline.

### ***“A dynamic approach to characterising functional reorganisation and neuro-modulation”***

**E Düzel, N Cashdollar**

*Magnetoencephalography (MEG) has a number of advantages over EEG, which make it ideal to study functional organization of cognitive processes such as working memory and long-term memory and the reorganisation of these processes in patients with epilepsy.*

Using MEG, we have shown that a neural circuitry involving prefrontal, medial temporal and visual regions is critical for our ability to actively maintain visual information in working memory. The function of this network is disrupted by bilateral hippocampal sclerosis. Specifically, our results indicate that the hippocampi are necessary to synchronize (in the theta frequency range) these brain regions and that this hippocampus-dependent synchrony is particularly critical if working memory is required for the associative relationship between different items in a visual image.

One important shortcoming in human memory research is the inability to read out the mental content of memory from recordings of brain activity. We have now overcome this shortcoming by developing MEG based ‘pattern classification’ algorithms which can decode neural oscillation patterns in the gamma frequency range and thus reveal which information an individual is currently holding in mind. This allowed us

to establish that active maintenance is associated with the periodic replay of information. The periodicity, in turn, is controlled by theta oscillations and determines how well participants are able to hold information in working memory. We are now using these decoding methods in patients with bilateral hippocampal sclerosis to understand in what way their inability to maintain associative information is accompanied by a degraded coding of associative relationships.

Our findings support theoretical computational models of brain activity that maintenance requires the coordination of slow (theta) and fast (gamma) rhythms in the brain and we have developed new techniques to quantify this form of coordination.

This year we aim to establish recordings of intracranial data from patients undergoing invasive presurgical monitoring simultaneously with whole-head MEG. This will offer a new methodological perspective to relating medial temporal memory processing to distant cortical processing. At the same time, it will allow us to establish to what extent epileptiform discharges in the MTL can be detected non-invasively with MEG.

Using functional MRI, we investigate how hippocampal memory formation is modulated by the activity of dopaminergic midbrain structures. This is important because animal studies indicate that dopamine is critical for the long-term consolidation of newly formed hippocampus-dependent memories. To that end we study how dopaminergic drugs such as L-DOPA affect memory consolidation in healthy individuals. We also study the effect of L-DOPA on memory consolidation in older adults.

## NEUROGENETICS

### *“Genetic neuroimaging”*

**SM Sisodiya, M Matarin, JS Duncan, F Vargha-Khadem, D Hunt, T Moore**

Funded by the UCLH/UCL CBRC and GOSH/ICH and Moorfields/IOO SBRCS, we are investigating potential candidate genes for epileptogenic brain malformations, and genes involved more generally in brain development, maintenance and function. These studies integrate with our genome-wide genomic and post-genomic work, all seeking to define more precisely genes involved in brain disease, especially epilepsy, and consequences of variation in those genes.

### *“Genome-wide association studies”*

**SM Sisodiya, JW Sander, C Catarino, K Chinthapalli, L Clayton, D Kasperaviciute**

Funded by the Wellcome Trust and MRC, we have undertaken the largest genome-wide association study in the partial epilepsies so far completed anywhere in the world. Detailed analyses are underway. In addition, the data have revealed a new degree of complexity in epilepsy genomics, substantiating the role of rare variation in causation of epilepsy. It is likely that the genetic architecture of the epilepsies will be revealed as being more complex than imagined. We are exploring in detail the phenotypes of patients in whom rare variants have been found, including specific phenotypic tests driven by bioinformatic analysis of genomic results. The approach to testing has been honed over many years from our candidate-gene neurogenetic imaging project, and is being further enriched by neuropathological studies in very rare cases. It is likely that the next few years will bring a plethora of new genetic findings in the epilepsies.

### *“Vigabatrin and clobazam pharmacogenetics”*

**SM Sisodiya, JW Sander, L Clayton, J Acheson**

We have continued to collaborate on the important Department of Health funded study, coordinated by the Walton Centre in Liverpool on the pharmacogenetics of the drugs vigabatrin and clobazam. Genome-wide evaluation of response to these drugs is due shortly.

***“A Syndrome with established genetic causation”*****SM Sisodiya, C Catarino, J Liu, L Martinian, M Thom**

Funded by an MRC grant, we have undertaken a genetic and neuropathological study of Dravet syndrome in adults, adding new aspects to this condition, and exploring its consequences on brain tissue.

***“After Genomics: detailed phenotyping”*****S Sisodiya, L Clayton, K Chinthapalli, E Bartolini, JW Sander (and P Hammond, M Suttie at ICH)**

Funded by the Tuberous Sclerosis Association, we have explored the use of ocular coherence tomography (OCT) as a robust objective measure of field loss associated with vigabatrin use, to determine whether OCT can be an effective surrogate for both clinical use and pharmacogenomics.

***“The Genetic basis of epilepsy amongst the Roma Community in Bulgaria”*****JW Sander**

We are ascertaining people with epilepsy amongst large pedigrees in the Roma (Gypsy) community of Bulgaria, aiming to identify a possible genetic basis and causative genes. This work is done in collaboration with the Academy of Sciences of Bulgaria and the University of Western Australia. We have identified a large number of family groups with a high number of people affected by epilepsy. A full work-up (including a whole genome scan) has been undertaken in four of these families. In one family a novel locus was identified on 5q31.3-q32 and this was recently published. In another family, several deletions have been identified.

**CLINICAL PHARMACOLOGY*****“Long-term retention of recently launched anti-epileptic drugs”*****JW Sander, AW Yuen, GS Bell, PN Patsalos, A Neligan, C Catarino**

*There is a clear need for better understanding of antiepileptic drug treatment and when should each drug be used as this would improve antiepileptic therapy.*

We are currently assessing the long-term retention, a composite measure of safety and efficacy, of the recently launched antiepileptic drugs, zonisamide and lacosamide. This assessment is important in order to find the correct place of these drugs in the antiepileptic armamentarium and at which stage they should be deployed in the treatment of an individual patient. The results of the assessment of pregabalin have now been published. The data collection for zonisamide is nearly complete and the data collection for lacosamide is ongoing.

***“New anti-epileptic drugs”*****JW Sander, AW Yuen, GS Bell, MJ Koepp, PN Patsalos**

We are continuing to assess the potential antiepileptic efficacy of the omega-3 fatty acids. We are actively involved in the development of alternatives to the use of rectal diazepam as a rescue treatment for serial seizures and status epilepticus.

***“Open study of omega-3 fatty acid EPA in people with refractory epilepsy”*****A Yuen, G Bell, JW Sander**

In collaboration with D Flugel (St Gallen, Switzerland), an open trial of the omega-3 fatty acid EPA (eicosapentaenoic acid) has been completed in a small number of patients. Preliminary results suggest that there is efficacy in some patients and blinded studies are now needed.

***“Antiepileptic drug combination therapy in epilepsy – preclinical studies”*****N Ratnaraj, PN Patsalos. Collaborators: S Czuczwar and J Luszczki (Medical University of Lublin, Poland)**

We continue our work to identify rational antiepileptic drug combinations that may prove particularly efficacious in patients with intractable epilepsy. Our studies involve the use of seizure models combined with drug pharmacokinetic measurements and have included studies of the new antiepileptic drug levetiracetam in combination with gabapentin, tiagabine, vigabatrin, clonazepam, ethosuximide, phenobarbital and valproate.

***“Population pharmacokinetics of lacosamide, rufinamide, stiripentol and eslicarbazepine acetate”*****C Greenaway, B Staron, N Ratnaraj, JW Sander, P Patsalos.**

*During the last two years four new antiepileptic drugs: lacosamide, rufinamide, stiripentol and eslicarbazepine acetate have been licensed for the management of patients with epilepsy.*

New high performance liquid chromatographic analytical techniques have been set up for the measurement of these drugs and we are presently evaluating their population pharmacokinetics which will serve to enhance their therapeutic use. We will also evaluate their potential to interact with other medications and ascertain whether the use of saliva drug concentrations as opposed to blood drug concentrations can better help guide their use therapeutically in the clinic. We have recently established that lacosamide can be readily quantified in saliva and that saliva concentrations reflect blood concentrations.

***“Assessment of general health status in Chalfont residents using biomarkers”*****A Yuen, GS Bell, MJ Koepp, PN Patsalos, JW Sander**

*Current data suggest that reducing the markers of free radical damage or increasing antioxidant capacity might be expected to reduce seizures.*

Physical and biochemical health measures were collected from approximately half of all Chalfont residents in 2006 and 2007. A comparison of the health measures in 2006 with the UK general population showed that the Chalfont residents had increased weight, BMI, waist, waist-hip ratio, C-reactive protein, but surprisingly a lower BP and HbA1c (a measure of long term blood glucose levels and a potent predictor of all cause mortality).

***“Erythrocyte and plasma fatty acid profiles in patients with epilepsy”*****A Yuen, JW Sander, D Flugel, PN Patsalos, GS Bell, MJ Koepp**

The red blood cell and plasma fatty acid profiles from Chalfont residents who took part in the double blind omega-3 supplementation study were further analysed and the results suggest that Carbamazepine appears to lower Omega-3 Index (a risk factor for CHD mortality) whilst oxcarbazepine appears to be associated with a higher Omega-3 Index.

## COGNITIVE NEUROSCIENCE

### ***“Computational and in-vivo electrophysiological investigation of entorhinal ‘grid cell’ firing and EEG theta in freely moving rodent: effects of novelty and pharmacological intervention”***

**C Barry, A Jeewajee, N Burgess. Collaborators: J O’Keefe (Cell and Developmental Biology, UCL), C Lever (Leeds)**

*“Grid cells” recorded in the entorhinal cortex of freely moving rodents fire whenever the animal enters one of several locations arranged in a regular triangular grid across the animal’s environment.*

We have produced a computational model of how this firing might result from interference between sub-threshold membrane potential oscillations in the theta band. This makes predictions for theta-band modulation of cell firing as a function of running speed and grid size, and for the EEG theta frequency as a function of running speed.

We are now investigating the effects of novelty and pharmacological interventions on the relationship of theta to running speed – hoping to dissociate two components reflected in the intercept and slope of this relationship and concomitant changes in the spatial scale of the grid-like firing patterns. Drugs used so far include anxiolytics (Chlordiazepoxide and buspirone) and lamotrigine, which appear to affect intercept and slope respectively.

### ***“Understanding the neural mechanisms of spatial cognition: from rodent neurophysiology to human fMRI”***

**C D Doeller, C Bird, N Burgess**

*We have previously shown that the spatial firing of hippocampal “place cells” in rodent hippocampus are driven by neurons representing the distances and directions to environmental boundaries, and that the spatial firing patterns of “grid cells” are aligned with each other across entorhinal cortex.*

We are now investigating whether these properties of neuronal firing are conserved in the hippocampal formation of humans performing virtual reality navigation. Specific predictions for the pattern of fMRI data expected as a function of the number of environmental boundaries, or the speed and direction of running are derived from the rodent data. Looking for these patterns in fMRI data will help to establish whether similar neuronal representations are present in human and rodent spatial cognition, and help to identify the spatial distribution of these neuronal representations throughout the brain. We have found an entorhinal signal consistent with the presence of grid cells, and this signal was also found in a network of regions typically associated with autobiographical memory. We have also found that, when imagining a spatial scene, hippocampal activation corresponds to the number of environmental walls (but not towers) in the scene.

### ***“Theta rhythmicity in MEG studies of human spatial navigation in virtual reality”***

**R Kaplan, C D Doeller, N Burgess**

*We have combined fMRI with adapted virtual reality video games to demonstrate the correspondences between human’s spatial cognition and neuronal firing in freely moving rodents: is there similar dynamical structure?*

We now wish to examine the potential correspondences between the MEG signal from human participants navigating in virtual reality and the movement-related theta rhythmicity found in the EEG of freely moving rodents. We have found a robust 4-8Hz theta signal associated with navigation, and will be investigating its source within the brain and predicted relationships between theta frequency, environmental novelty and running speed.

***“Separating hippocampal and striatal contributions to spatial memory”*****C D Doeller, N Burgess**

*We have previously combined fMRI with adapted virtual reality video games to demonstrate the correlation between hippocampal activation and navigational accuracy.*

We have now shown that the location of an object in a complex environment can be remembered relative to extended environmental boundaries and to discrete landmarks in parallel. Memory relative to boundaries correlates with activation of the right hippocampus, consistent with studies of the firing of hippocampal place cells in rodents. Memory relative to landmarks correlates with activation of the right dorsal striatum. In addition, these two systems use different learning rules, memory for locations relative to landmarks obeys reinforcement learning, consistent with a proposed role for striatal dopamine, while memory for locations relative to boundaries is incidental, consistent with a proposed role for hippocampal novelty detection.

***“The hippocampal role in episodic and autobiographical recollection”*****I Trinkler, C D Doeller, N Burgess**

In an fMRI study of recognition memory for the faces of friends, famous people and unfamiliar people we compared the activation resulting from recollection of the prior presentation of a face with the activation resulting from the participant’s pre-experimental autobiographical knowledge of the face. The hippocampal, retrosplenial and medial prefrontal network associated with ‘episodic’ memory was strongly activated by autobiographical knowledge, but not activated by recollection of recent prior occurrence *per se*. This suggests that the hippocampus contributes to recollection by supporting incidental autobiographical associations to stimuli which in turn aid recollection.

***“Differential hippocampal dependence of memory for faces, scenes and words, and for known versus unknown faces”*****C Bird, N Burgess**

*The human hippocampus is generally thought to provide a domain-general long-term memory function: supporting ‘episodic’ or ‘declarative’ memory.*

However, focal hippocampal damage appears to affect memory differently for different types of stimuli. We previously showed that memory for the topographical layout of spatial scenes is impaired by focal hippocampal damage, even for intervals as short as one or two seconds. We have now shown that focal hippocampal damage does not impair recognition memory when tested with lists of unfamiliar faces, in contrast to lists of scenes or words.

In an fMRI study of recognition memory for the faces of friends, famous people and unfamiliar people we compared the activation resulting from recollection of the prior presentation of a face with the activation resulting from the participant’s pre-experimental autobiographical knowledge of the face. The hippocampal, retrosplenial and medial prefrontal network associated with ‘episodic’ memory was strongly activated by autobiographical knowledge, but not activated by recollection of recent prior occurrence *per se*.

These results suggest that the hippocampus contributes to recollection of faces by supporting incidental autobiographical associations, recollection of words (cf non-words) by supporting incidental semantic associations and places by supporting incidental spatial associations. Thus the results of using memory for a recently-presented list of memoranda to test for hippocampal function will be highly dependent on the nature memoranda chosen.

***“Using spatial processing to identify Hippocampal deficits”***

**C Bird, C D Doeller, N Burgess. Collaborators: M Rossor (UCL, IoN), D Chan (Sussex), R Barker, P Nestor (Cambridge)**

*Our tests of spatial memory show some very specific dependence or lack of dependence on the hippocampus, and (to a lesser extent) striatum.*

In our “Four Mountains” test memory for topographical layout, but not the other visual properties, of scenes is sensitive to hippocampal damage. We have now shown that this test is predictive of patients progressing from “Mild Cognitive Impairment” (MCI) to Alzheimer’s Disease (AD). Importantly, patients with frontotemporal lobar degeneration are unimpaired at the task. We are now using the same test to investigate the early impairment of hippocampally mediated memory processes in Huntingdon’s disease, and a modified virtual navigation test to look at the progression from MCI to AD.

In our “landmark-boundary” test we have shown that the location of an object in a complex environment can be remembered relative to extended environmental boundaries and to discrete landmarks in parallel. Memory relative to boundaries correlates with activation of the right hippocampus, consistent with studies of the firing of hippocampal place cells in rodents. Memory relative to landmarks correlates with activation of the right dorsal striatum. In addition, these two systems use different learning rules, memory for locations relative to landmarks obeys reinforcement learning, consistent with a proposed role for striatal dopamine, while memory for locations relative to boundaries is incidental, consistent with a proposed role for hippocampal novelty detection. We have now developed a simplified version of this test, previously used in functional brain imaging experiments, to further investigate spatial memory in patients with neurodegenerative conditions, including Huntingdon’s disease.

**NEUROPSYCHIATRY AND NEUROPSYCHOLOGY*****“Psychiatric disorders and relationship to cognitive function following epilepsy surgery”***

**J Foong, PJ Thompson**

*Psychiatric disorders can develop for the first time, or pre existing symptoms be exacerbated following epilepsy surgery, even in patients with a good postoperative seizure outcome. We are interested in determining the psychiatric morbidity after epilepsy surgery and predicting factors.*

We have been funded for 3 years by the Henry Smith Charity to study pre-surgical and post-surgical psychiatric and cognitive function in patients undergoing epilepsy surgery at the National Hospital. This research would help to advance our understanding of the relationship between psychiatric symptoms and cognitive function. This research may also help to identify patients at high risk of developing psychiatric disorders after surgery for temporal lobe epilepsy.

***“Temporal Lobe Surgery”***

**SA Baxendale, PJ Thompson**

*We have continued to explore the factors that govern the nature and extent of cognitive changes following surgery and apply our findings to improve the clinical value of the neuropsychological assessment in the pre and post surgical evaluation of patients with epilepsy.*

**The Long Term Effects of Epilepsy Surgery**

Our surgical database continues to expand and develop. We are using these findings to modify our pre-operative counselling and advice to prospective surgical candidates. We have now completed long term follow-up assessments (average 10 years) on 70 patients and are examining this data to look for early indicators of poor outcome in the long term. We are also working to examine the impact of aging on memory function, following temporal lobe surgery. We have completed an audit of surgical team decision making and the factors that influence the estimates given of a successful outcome.

**Aging & Cognitive Decline**

We have investigated how normal age related cognitive decline affects people with medically intractable epilepsy. Our work has demonstrated that there appears to have been a steady improvement in the visual memory skills of the general population, year on year. This pattern is not evident in people with hippocampal pathology, suggesting that their memory deficits may put them at an increasing disadvantage compared to the general population as time goes on.

**The effect of medically intractable seizures on cognition throughout the lifespan**

We have completed a large cohort study looking at the effects of intractable seizures on cognition from age 18 to 65 years. Our findings suggest that the profile of cognitive deficits associated with mesial temporal lobe epilepsy is already established as children with epilepsy enter adulthood. Whilst memory and language skills are maximally affected, intellectual function is also compromised in mesial temporal lobe epilepsy. This profile appears to remain stable across the adult lifespan, at least until 65 years of age, despite the intractable nature of the seizures. Side of pathology and gender are significant mediating factors in shaping the profile of cognitive deficits; people with left hippocampal and females being particularly vulnerable.

***“Temporal lobe surgery: Executive functions and mood”***

**J Stretton, R Cleary, J Foong, SA Baxendale, PJ Thompson**

*We are broadening our assessment of changes following surgery to include processes such as decision-making and attention and also mood to help us identify people who may be at risk of developing deficits after surgery.*

Cognitive assessments and psychiatric evaluations are undertaken prior to surgery and 3-6 months and one year post-resection. Assessment measures include standard clinical neuropsychological tests, fMRI paradigms, mood and personality rating scales. A retrospective review of psychiatric status pre and post-operatively is also underway in more than 300 surgical cases.

***“Temporal Lobe Surgery: Pre-emptive Memory Rehabilitation”***

**L Koorenhof, SA Baxendale, PJ Thompson**

*The aim of the research is to assess whether memory training can offset the decline in memory that occurs as a consequence of temporal lobe surgery and whether such training is better given before rather than after the operation.*

This study explores whether surgical candidates with unimpaired pre-operative memory skills can be taught memory support strategies prior to surgery thereby offsetting the expected memory decline. Findings indicate improved memory test performance following training in the controls but no clear support for the benefit of computerised home training exercises. Findings with patients have been variable but, contrary to our prediction, with pre-operative training showing no clear advantage over post-operative programme delivery.

***“Epilepsy in a Wider Context”***

**SA Baxendale**

*The way epilepsy is portrayed in the media is important as it can have a direct influence on the stigma and stereotypes associated with the condition*

ILAE Film Festival & Centenary Award for Film 2009

This year we coordinated a major film festival with epilepsy as the central theme as part of the celebrations for the Centenary of the ILAE in Budapest. In collaboration with the British Film Institute, we were able to screen films made between 1929 and 2007 during the festival. The themes in each film were debated by an international audience following each screening.

As part of the film festival we also launched the ILAE Centenary award for film in epilepsy. The competition attracted over 20 entries from around the world and we chaired the international judging panel. The winners in the short, documentary and feature length categories all represented innovative and thought provoking approaches to the portrayal of epilepsy in the 21<sup>st</sup> century.

## CLINICAL EPILEPTOLOGY

### ***“Monitoring of critical life functions”***

**JS Duncan, SJM Smith. Collaborator: J Radcliffe, N Hirsch (NHNN MITU), E Rodriguez (Imperial College)**

*Sudden death in epilepsy is thought to be the result of cardiac or respiratory arrest. We have developed a miniaturized wearable device for detecting cessation of breathing and dangerous abnormalities of heart rhythm, and are carrying out the first clinical trials of the device.*

With Dr Esther Rodriguez (Electronic Engineering, Imperial College) we have developed a miniaturized wearable apnoea detection device (WADD) that detects the acoustic signal of breathing and cardiac activity and have tested this in healthy volunteers. The microchip in the device identifies apnoea and serious tachycardias and bradycardias. The device has been patented and approved by MHRA for clinical investigations, and received the new IT award at the Institution of Engineering Technology Awards in 2009.

The first clinical trial of the WADD is underway with overnight studies in healthy volunteers and those with sleep apnoea. This study is designed to compare the performance of the device with conventional Somnoscreen cardiorespiratory monitoring equipment in the sleep laboratory at NHNN (Drs Jeremy Radcliffe, Nick Hirsch).

We are also working on a wireless EEG telemetry system. As a key part of this, “smart” scalp EEG electrodes contain microchips that process the EEG signal and transmit only epochs that are of clinical interest, using a low power radio transmitter to a base-station. The aim of this project is to develop a wearable EEG telemetry system that is low maintenance, reliable, cheap, non restricting on patients and hence will be accessible to many more patients.

### ***“The long-term outcome of epilepsy surgery”***

**GS Bell, J de Tisi, SA Baxendale, AW McEvoy, PJ Thompson, JW Sander, JS Duncan**

*Epilepsy surgery can be curative for those with refractory focal seizures. We are determining the long-term outcome of all those who have had epilepsy surgery at NHNN do ascertain whether it is possible to predict and improve outcomes.*

We have now obtained direct annual follow-up data on 698 patients who have had epilepsy surgery at NHNN since 1990. We showed that epilepsy-related premature mortality is much reduced in those who become free of all seizures or who only experience auras. 42% of patients remain entirely seizure free from the date of surgery and a further 10% only have auras, but 65% have been seizure free for the last year. We are now evaluating the patterns of seizure remission and relapse following surgery, and the factors that affect these patterns.

### ***“Treatment of status epilepticus”***

**SD Shorvon. Collaborators: HR Cock (St George’s), E Trinkla (University of Innsbruck), other European and American centres**

There are many off label therapies used in the treatment of status epilepticus and few controlled studies. A large scale multicentre randomized and controlled study of the treatment of status epilepticus is currently in the planning stage, comparing therapies in the established stage of status epilepticus.

**“Sunlight & Seizures”****SA Baxendale, DC Heaney**

*An audit of the pattern of seizures recorded on the Sir William Gowers Assessment Centre at the NSE suggests that seizures are less likely to occur on bright sunny days.*

We have conducted a review of the roles that melatonin and vitamin D play in regulating seizure thresholds and have hypothesised that light box therapy may possibly be a palliative treatment for some people with epilepsy. We have secured a grant to conduct a pilot study to investigate this possibility further.

**CLINICAL NEUROPHYSIOLOGY****“ECG changes in seizures”****R Surges, P Adjei, GS Bell, C Scott, SD Shorvon, JW Sander, MC Walker**

*Sudden unexplained death in epilepsy (SUDEP) occurs frequently in people with drug resistant epilepsy who have been referred for presurgical assessment, yet the mechanisms and risk factors associated with this are not clear.*

We have been carrying out a case control study of people who have been admitted to the video-EEG telemetry unit and later died from SUDEP to identify cardiac parameters both between and during seizures that may be used to predict risk of SUDEP. In addition, we have been looking at the influence of seizures on ECG parameters.

**“Changes in autonomic function during seizures”****R Surges, P Adjei, B Diehl, C Scott, SJM Smith, SD Shorvon, MC Walker**

*Seizures can alter autonomic function and these changes may help to lateralize or localize seizure activity. Moreover such changes may contribute to sudden unexplained death in epilepsy.*

In collaboration with the autonomic function unit at National Hospital of Neurology and Neurosurgery (Professor Mathias), studies of alterations in autonomic function in epilepsy are underway.

**“Semiology of seizures and sleep disturbances”****R Surges, SJM Smith, B Diehl, MC Walker**

*Events that occur at night can be very difficult to diagnose due to a poor collateral history and so these patients are often referred for video-EEG telemetry.*

Studies are underway to see if we can improve the diagnostic yield by identifying clinical features that are strongly predictive of specific diagnoses.

## **EPILEPSY NURSING**

### ***“Efficacy of Buccal midazolam”***

#### **A Smith**

Andy Smith is continuing to audit the efficacy of buccal midazolam in outpatients at both Chalfont and NHNN who are switching to this from other rescue medications. Patients are providing information over a period of 12 months. The expected completion date is June 2011.

### ***“Epilepsy Text Messaging Service”***

#### **A Linklater**

A pilot project has now started which offers support to people with epilepsy through their mobile phones. For those signing up to the service, reminders to take medication will be sent in the form of text messages at appropriate times. Patients will be able to opt in to a higher level of support whereby they will be able to confirm that they have taken their medication by reply text. If this reply text is not received, an alert will be sent to their nominated carer. Patients can also be supported through changes to their medication with text messages sent to remind them to adjust dosages when planned changes due to take place. This pilot project is planned to run throughout 2010.

## **NEUROPATHOLOGY**

### **SM Sisodiya, M Thom, C Catarino, J Liu, L Martinian, JW Sander**

We have continued our research into the neuropathology of epilepsy, focusing on temporal lobe epilepsy associated with hippocampal sclerosis, focal cortical dysplasia and specific pathways, such as cdk5 and its substrates. We showed extensive alteration within this pathway, suggesting links between neurodevelopment and neurodegeneration through disruption of the cell cycle and its regulation, leading, in focal cortical dysplasia, to accelerated neuronal loss through tau-mediated processes. We secured funding for research with our valuable post mortem brain archive from patients with well-characterised epilepsies, which will be studied intensively to explore mechanisms of drug resistance, neuronal loss, gene expression, somatic mutation and recovery from epilepsy, as well as the long term consequences of epilepsy.

We have continued to assess the long term effects of seizures on the brain through the MRC funded study of a large post mortem series. We made the novel observation in humans of bilateral damage and axonal re-organisation. We have also studied regional cortical atrophy, neurodegenerative changes and pathological aging in this epilepsy post mortem series using quantitative immunohistochemistry. We are evaluating immature, progenitor and undifferentiated cell types in epilepsy surgical tissues, in particular focal cortical dysplasia and hippocampal sclerosis in order to further characterise and distinguish dysplasia types in focal epilepsy. We characterised the pathological features of temporal lobe sclerosis, as distinct from focal cortical dysplasia, in association with hippocampal sclerosis. A work package in an EU-funded FP7 collaboration has examined multidrug transporter expression in post mortem brain tissue, taking advantage of the unique insight available from this valuable resource.

## EPIDEMIOLOGY AND HEALTH SERVICE RESEARCH

The study of the dynamics of epilepsy in the community is important in understanding the causes of the condition and impact of the treatment, and in planning the delivery of healthcare.

### ***“The National General Practice Study of Epilepsy (NGPSE)”***

**A Neligan, GS Bell, SD Shorvon, JW Sander**

The NGPSE is one of the longest prospective studies of prognosis of people with epilepsy in the general population in existence. The study is now contacting GPs after more than 7 years to determine the outcomes of the people in the original cohort with regard to seizure outcome and survival. We are currently in the process of analysing the mortality data of the cohort after 20-23 years follow-up. Initial analysis continues to confirm the increased premature mortality in people with epilepsy. Studies of prognosis in the community are very important to put the risk into perspective as this is often exaggerated in hospital-based studies.

### ***“The association between neurocysticercosis and Hippocampal Sclerosis: a longitudinal study”***

**G Singh, JS Duncan, JW Sander**

Neurocysticercosis (NCC) is the most common parasitic infestation of the brain worldwide associated with epilepsy. Hippocampal sclerosis (HS) is an important cause of poorly-controlled epilepsy which has disabling medical and psychosocial consequences. Based on anecdotal reports of an association between NCC and HS, we hypothesize that there might be a causal relationship between two conditions. We are planning a longitudinal MRI study to take place in Ludhiana, India to assess whether or not there is an association between NCC and HS and whether NCC or seizures due to NCC can lead to structural changes in the hippocampus that may be potentially epileptogenic.

### ***“The impact of suicide and drowning in the life expectancy of people with epilepsy”***

**GS Bell, JW Sander**

*A large meta-analysis of studies of mortality in epilepsy with a particular emphasis on reports of suicide and drowning has been carried out. This was supplemented by an estimation of death due to these two causes from national death registries.*

We have found that people with epilepsy have a risk of drowning that is almost twenty-fold that of their peers in the general population whilst the risk of suicide in people with epilepsy is increased by at least three times. Further analysis in this data set will be carried out to estimate SMRs using direct standardisation instead of indirect methods.

### ***“Patterns of Relapse and Remission in Epilepsy”***

**A Neligan, JW Sander, SD Shorvon**

*There are current debates about the chance of people with epilepsy entering remission once chronicity has been established.*

We are carrying out a clinic-based study in a cohort of patients with chronic epilepsy attending a tertiary referral centre to establish accurately the patterns of seizure occurrence and to categorise them using the results of previous investigations and classification of epilepsy. We hope to establish possible predictors of different patterns of seizures.

***“Premature mortality of Epilepsy in Rural China”*****GS Bell, JW Sander**

*Premature mortality is thought to play an important role in the global burden of epilepsy to society. Little is known, however, about the risk of premature mortality in people with epilepsy in rural areas of resource-poor countries.*

We have been ascertaining this in a large cohort of people with epilepsy identified over 7 years ago in rural areas of 6 different provinces of China. Preliminary findings are that having epilepsy is a major risk factor for premature death particularly in the 20 – 40 years age group. We are currently assessing the causes for this increase in mortality and how it may impact on prevalence figures.

***“A Prospective Study of the Impact of New Anti-Epileptic Medication in Chronic Epilepsy”*****A Neligan, JW Sander, SD Shorvon**

*It has been suggested that there is little chance of people achieving remission from seizures once two anti-epileptic drugs have failed to control their seizures. A previous retrospective study at our centre suggested that this view is overly pessimistic.*

We are carrying out a clinic-based study to determine prospectively the impact on seizure control and remission of the initiation of new anti-epileptic medication in a cohort of patients with refractory epilepsy. Outcome will be determined after one year of follow up. Active recruitment for this study is currently ongoing.

***“Adherence to epilepsy guidelines in general practice”*****GS Bell, JW Sander**

An audit of documented care for people with epilepsy was carried out in one of 12 General Practices which had been audited previously. The audit found that more patients had had an epilepsy review in accordance with guidelines than in the previous audit in 2001; it appeared, however, that some patients had not had an epilepsy review in accordance with the guidelines. Over two thirds of patients were documented as being seizure free in the current audit. Information provision was documented in few of the records. Only a minority of women had documented information provision about women's issues. Information may have been given but not documented. This information will help assess the impact of guidelines in the management of epilepsy and instruct future changes to the guidelines.

***“Seasonality in the outcome of epilepsy surgery: the potential role of vitamin D”*****AW Yuen, GS Bell, JW Sander**

*Seasonality has been observed for a number of clinical conditions. Some suggest that there might be an effect of seasonality of birth in the development of epilepsy. As the seasonality factor may be related to Vitamin D levels, winter months were defined as those with the lowest vitamin D levels found in a British population cohort.*

Analysis of the epilepsy surgery database showed a four fold difference in mortality between patients who had surgery in the summer and winter. There were 11 deaths following winter surgery and 2 deaths following summer surgery. The number of cancer deaths appears to contribute to this difference. It is possible that lower vitamin D levels during winter surgery might have led to the difference through an effect on cancer susceptibility. The data are being further analysed.

## GLOBAL HEALTH

Our commitment to advance the understanding of epilepsy worldwide and to improve service delivery is part of UCL's global health pledge and will hopefully help fulfil the aim of WHO's Global Campaign against Epilepsy to bring epilepsy out of the shadows.

### ***“Epilepsy management in resource-poor settings”***

**GS Bell, JW Sander**

In conjunction with the World Health Organization's Global Campaign against Epilepsy, we have completed large-scale projects assessing the delivery of care for people with epilepsy in the context of primary care in rural areas of both China and Brazil. The two projects have provided the embryos for National Epilepsy Programmes in both Brazil and China and have been assessed by the WHO as highly successful. In China alone over 30,000 people in 12 provinces have now been treated as part of the programme which is being extended nationally. In Brazil, epilepsy management has been incorporated into the Family medicine programme and has reached a third of Brazilian municipalities.

### ***“The epidemiology and treatment gap of epilepsy in the Republic of Georgia”***

**JW Sander**

*In many areas of the developing world, the majority of people with epilepsy do not receive anti-epileptic treatment; this is known as the so called epilepsy treatment gap.*

We have recently started a study of the epidemiology of epilepsy in four districts of Tbilisi, the capital of Georgia in which we will estimate the prevalence and the treatment gap of epilepsy. In tandem with this effort, we will assess the delivery of care for epilepsy, establish referral networks and look into the provision of antiepileptic drugs. The aim of this project, funded by the WHO, is to see whether epilepsy management can be provided in its incipient primary-care system and, if the model is successful, deploy it in other countries of the region.

### ***“Health delivery and health seeking strategies for epilepsy in Roma community of Bulgaria”***

**JW Sander**

*The Bulgarian Romas (gypsies) are the ethnic minority subject to the highest degree of social and health deprivation in Europe. There is accumulating evidence that epilepsy is the most common serious neurological condition in this population with a prevalence that is higher than expected. The management of epilepsy in this community is inadequate at both the level of public health policies and in individual patients.*

Together with colleagues from Bulgaria and from the University of Western Australia, we are assessing health delivery amongst this community from an integrated medical, epidemiological, sociological and public health point perspective. The results, likely to be applicable to other Roma communities across Europe, will inform public health decisions in general and improve management of epilepsy in particular.

### ***“Epilepsy in Africa – clinical and epidemiological aspects”***

**C Newton, JW Sander**

Together with colleagues at UCL Institute of Child Health, we are carrying out a large project focusing on the epidemiological, clinical, genetic and health delivery aspects of epilepsy in several African countries including Kenya, Tanzania, Uganda and South Africa. This major effort to characterise epilepsy in different regions of Africa with probable different infectious risk factors may contribute to the understanding of the aetiopathogenesis of epilepsy associated with tropical infectious diseases and may have major implications for the delivery of epilepsy care in other African settings.

## EXPERIMENTAL EPILEPSY AND FUNDAMENTAL NEUROSCIENCE

All research involving animals is carried out at UCL Institute of Neurology and is not conducted at the NSE

### ***“D-serine released by astrocytes plays a critical role in NMDA receptor-dependent synaptic plasticity”***

**C Henneberger, DA Rusakov. Collaborators: SHR Oliet, T Papouin (INSERM Bordeaux)**

*A classical form of synaptic plasticity that underlies memory formation, long-term potentiation (LTP) in the hippocampus, relies on postsynaptic calcium entry through the NMDA subtype of glutamate receptors. Although activation of these receptors partly depends on glutamate glial uptake, the importance of glia in synaptic plasticity is controversial.*

We have shown that disrupting calcium signalling or calcium-dependent release in an individual glial cell (astrocyte), or pharmacological suppression of glial function, blocks LTP induction at local synapses. This blockade is completely reversed by adding the NMDA receptor co-agonist D-serine to the extracellular medium. We conclude that calcium-dependent release of D-serine from astrocytes regulates activation of neuronal NMDA receptors by glutamate, thus modulating synaptic plasticity.

### ***“Astroglial interactions in Down Syndrome”***

**P Ragunathan, DA Rusakov. Collaborators: R Scott (Alicante Inst Neurosci), E Fisher (IoN), Victor Tybulewicz (NIMR)**

*A mouse model of Down syndrome recently developed by E Fisher and V Tybulewicz promises important insights into the cellular mechanisms underlying this disorder.*

We combine two-photon excitation microscopy and single-cell electrophysiology in an attempt to understand the phenotype of mossy fibre connectivity in the CA3 sub-field of the hippocampus. Preliminary data indicate a striking loss of mossy fibre synaptic input to CA3 pyramidal cells.

### ***“The optimal glutamate content of synaptic vesicles”***

**LP Savtchenko, S Sylantyev, DA Rusakov**

*The amount of glutamate released by individual synaptic vesicles is an important determinant of excitatory signals in the brain. This fundamental quantity, and the principles underlying its formation, remain however poorly understood.*

We examine the effects of fast-dissociating antagonists on glutamatergic transmission and carry out outside-out patch measurements of rapid glutamate receptor kinetics to estimate that, in hippocampal pyramidal neurons, 2400-2600 glutamate molecules are released in a single synaptic discharge. This amount is similar to the theoretically maximal response per released molecule at such synapses, suggesting that a simple fundamental principle underlies neurotransmission: ‘maximal action at minimal expense’.

### ***“Nanodiffusion in the brain extracellular space: measurement and implications”***

**K Zheng, DA Rusakov. Collaborators: JA Levitt, N Sergent, K Suhling (King’s College London)**

*Signal transfer in the brain relies on rapid diffusion of transmitter molecules in the extracellular space. Although extracellular diffusivity is thus of a fundamental importance for neural communication, it has hitherto been evaluated only at relatively large scales.*

We have developed time-resolved fluorescence anisotropy imaging microscopy to measure extracellular diffusivity in the neuropil on a scale that is much smaller than extracellular gaps. We have applied this approach to ex-vivo brain tissue (acute hippocampal slices) using a small fluorescent probe. The results provide previously unattainable insights into the fundamental physical properties of the extracellular medium in the brain.

***“Presynaptic cannabinoid receptors and multi-vesicular release at excitatory synapses in the hippocampus”***

**T Jensen, S Sylantsev, DA Rusakov**

*At many central synapses, endogenous cannabinoids released from depolarised postsynaptic cells activate presynaptic cannabinoid receptors which in turn reduce the probability of neurotransmitter release. The molecular mechanisms of presynaptic cannabinoid action and their cellular specificity are intensely debated.*

We examine glutamate transients inside the synaptic cleft and apply optical quantal analysis at excitatory synapses in the hippocampal area CA1. The preliminary results show that activation of presynaptic cannabinoid receptors selectively interacts with multi-vesicular release associated with elevation of presynaptic calcium. This mechanism sheds light on a use-dependent function of cannabinoid receptors.

***“Presynaptic calcium channels in evoked neurotransmitter release at individual synapses”***

**C Henneberger, Y Ermolyuk, DM Kullmann, DA Rusakov, K Volynski**  
**Collaborators: Y Korchev, Y Gorelik (Imperial), G Moss (UCL Pharmacology)**

*Calcium-dependent neurotransmitter release is largely restricted to the synaptic active zone. How different presynaptic Ca<sup>2+</sup> channels contribute to triggering exocytosis is unclear.*

We have monitored vesicular exocytosis and presynaptic calcium signalling in individual axonal boutons of hippocampal neurons by combining different fluorescence imaging modalities. We show that, across the synaptic population, release probability varies with the magnitude of presynaptic calcium entry. By applying ion conductance scanning microscopy, we have found that calcium channels are confined to the active zone, providing for direct coupling of calcium influx to neurotransmitter release.

***“Modulation of synaptic transmission by metabotropic and ionotropic glutamate and nicotinic acetylcholine receptors”***

**I Oren, C Le Duigou, E Nicholson, DM Kullmann. Collaborator: KP Lamsa (Oxford)**

*Inhibitory interneurons play a central role in regulating circuit excitability and precise timing of activity in the brain. We have previously reported an interaction between acetylcholine and GABA receptors expressed in hippocampal interneurons, which may contribute to modulating their recruitment, as well as two distinct forms of use-dependent long-term potentiation (LTP) of excitatory synaptic transmission.*

We have extended these findings by examining the roles of metabotropic glutamate receptors in the induction of LTP, and explored the potential physiological and pathological consequences of alpha7 nicotinic receptor activation in distinct types of interneurons. The results are helping to shed light on how reversible and long-term changes in feed-forward and feed-back inhibition can be induced.

***“Computational properties of oscillatory hippocampal population activity, and optogenetic manipulation of populations of neurons”***

**T Akam, L Mantoan, DM Kullmann. Collaborators: S Schorge (Molecular Neuroscience) E Ferenczi (Academic Clinical Fellow)**

*The hippocampal formation is able to sustain several distinct patterns of network activity characterized by population oscillations at different characteristic frequencies. These oscillations involve different populations of interneurons, and are thought to be important for encoding information.*

We have used an in vitro model of gamma oscillations to explore how different areas of the brain can oscillate either independently or together. We are complementing electrophysiological methods with optical manipulation of neuronal activity, using virally-mediated expression of light-sensitive ion channels. This ‘optogenetic’ approach is potentially very powerful if defined populations of neurons can be manipulated. In parallel, we have used computational simulations to explore how gamma-band population oscillations can be exploited to achieve flexible routing of information flow among different connected brain areas.

***“Modulation of neurotransmitter release by presynaptic GABA<sub>A</sub> receptors”***

**E Campanac, DA Rusakov, DM Kullmann. Collaborators: A Ruiz (School of Pharmacy), R Scott (Alicante)**

*We have previously identified presynaptic GABA<sub>A</sub> receptors in mossy fibres in the hippocampus. This is a highly unexpected novel form of modulation of transmission, which has since been identified in several other sites in the brain.*

We have used direct recordings from presynaptic boutons and multiphoton fluorescence imaging to show that tonically active GABA<sub>A</sub> receptors facilitate synaptic transmission at mossy fibre synapses. Paradoxically, activation of presynaptic GABA receptors facilitates the induction of a form of LTP of excitatory transmission. This challenges the view that GABA receptors generally inhibit the excitability of cortical circuits.

***“Inherited ion channel mutations (channelopathies) in neurological disease”***

**J Heeroma, S Rajakulendran, R Begum, S Tomlinson, DM Kullmann. Collaborators: E Fletcher, C Farmer, E Matthews, J Burge, S Schorge, MG Hanna (Molecular Neuroscience), H Bostock (Sobell Dept), A Ruiz (School of Pharmacy)**

*Several ion channel mutations are associated with epilepsy and other CNS diseases characterised by paroxysmal symptoms (such as migraine and episodic ataxia). Ion channel mutations also underlie inherited diseases of muscle excitability (periodic paralysis and myotonia). The genetic and biophysical mechanisms of these diseases are incompletely understood.*

We have expressed potassium channel mutations with lentiviral vectors in neuronal cultures. Mutations associated with distinct syndromes alter neuronal excitability and neurotransmitter release probability in different ways. In parallel, we are examining the consequences of analogous mutations in defined pathways in the hippocampus using advanced electrophysiological methods. We have identified several novel mutations in potassium, sodium and calcium channels. We have shown that almost all mutations associated with hypokalaemic periodic paralysis affect arginine residues in voltage-sensors of sodium or calcium channels. We have also found that the effects of ion channel mutations on peripheral nerve excitability can be detected using non-invasive methods in humans. This work may lead to new diagnostic or monitoring tools to assess the function of ion channels in situ. Finally, we have found that, by systematically analysing the functional consequences of genetic variants in a candidate gene (*CACNA1A*) identified in a cohort of patients with ataxia and epilepsy, a significant association emerges between disease status and loss-of-function variants. An analogous stratification of variants in other candidate epilepsy genes may shed light on the genetic architecture of idiopathic generalised epilepsy.

**“Mutations in P/Q-type calcium channels and molecular mechanisms of migraine”**

**R Surges, F Alder, I. Pavlov, DM Kullmann, K Volynski. Collaboration: A. van den Maagdenberg (Netherlands)**

*Migraine affects over 10% of the general population. Inherited mutations in the CACNA1A gene (which encodes a brain calcium channel) account for a rare form, Familial Hemiplegic Migraine (FHM). This provides a unique insight into the mechanisms underlying this common debilitating disease. Calcium channels encoded by CACNA1A have a dominant role in triggering synaptic release of neurotransmitters. Therefore a detailed knowledge of how FHM mutations destabilise synaptic signalling is vital for understanding of migraine mechanisms.*

We are studying the effects of FHM mutations on neurotransmitter exocytosis in hippocampal neurons from CACNA1A knock-in mice using optical techniques. We show that expression of ‘leaky’ mutant channels increases the rate of spontaneous neurotransmitter release. This suggests that spontaneous opening of a single calcium channel can trigger exocytosis of synaptic vesicles.

**“Modulation of tonic GABA(A) receptor-mediated conductances in epilepsy”**

**I Pavlov, MC Walker**

*Tonic GABA<sub>A</sub> receptor-mediated inhibition is an important regulator of cell excitability and may represent a target of antiepileptic drugs that are designed to increase the extracellular GABA concentration in the brain. However, such an approach could have the undesired consequence of dampening excitability of inhibitory interneurons, thereby paradoxically decreasing synaptic inhibition and exacerbating any imbalance between excitation and inhibition in epilepsy.*

Using *in vitro* electrophysiological methods we are investigating the pharmacologies of tonic GABA<sub>A</sub>R-mediated currents in hippocampal CA1 pyramidal cells and interneurons in order to establish cell type-specific differences in tonic conductances. This will allow us to develop means of enhancing tonic inhibition in pyramidal cells but not interneurons, thus allowing more refined control over network excitability in epilepsy.

**“Synaptic mechanism of action of levetiracetam”**

**R Surges, MC Walker, K Volynski**

*Levetiracetam is a novel antiepileptic drug with broad antiepileptic potential, negligible metabolic effects and a low propensity for pharmacokinetic drug interactions. Although it is widely used in the treatment of focal and generalised epilepsy, its cellular mechanism of action is elusive.*

We are studying how levetiracetam modulates the release of neurotransmitters and presynaptic calcium dynamics at the level of individual excitatory and inhibitory hippocampal synapses, both under control conditions and in experimental models of increased network activity. This may lead to the development of even more potent antiepileptic drugs, as well as shedding light on mechanisms of epilepsy.

**“Mechanism of action of valproate and valproate analogues”**

**MC Walker, Pi-Shan Chang**

**Collaborators: R Williams (Royal Holloway), J Quinn (Liverpool)**

*Sodium valproate is a broad spectrum and effective antiepileptic drug that is also used as a mood stabiliser and in the treatment of migraine. It may also regulate gene expression and has been proposed as a candidate treatment for cancer and has neuroprotective effects. Despite, its wide range of uses and its long clinical use for thirty years, its mechanism of action has not been fully elucidated.*

In collaboration with Dr Robin Williams we are investigating biochemical effects of valproate. We are also determining the effects of valproate on gene expression following status epilepticus in particular the expression of REST (a regulator of gene expression) and its isoforms with Professor Quinn.

***“Mechanisms underlying epileptogenesis and regulating network excitability”***

**MC Walker, I Pavlov, S Schorge, Yu-Wei Wu, Pei-Yu Shih. Collaborators: A Semyanov (Tokyo), K Hashemi (Open Source Instruments, Brandeis University), A Pitkanen (Kuopio), G Sperk (Innsbruck), M Shah (School of Pharmacy), R Scott, M Lythgoe (UCL ICH)**

*Many people develop epilepsy after a specific brain injury, such as a stroke, brain tumour, head injury or status epilepticus. We are investigating the changes in the brain that lead to epilepsy (epileptogenesis). We are specifically interested to know how communication between neurons changes following status epilepticus and how this makes the brain predisposed to spontaneous seizures.*

We have completed the final stages of the development of a wireless animal telemetry unit at the Institute of Neurology. We can now continuously monitor seizures in animals for weeks, so facilitating the careful mapping of the development of epilepsy following a brain insult. In a series of studies, we are investigating further the mechanisms underlying the development of epilepsy. In particular, we are studying changes in GABAergic inhibition that occur during the development of epilepsy both in status epilepticus and following head injury. We have also involved in studies surrounding the role of changes in the cationic current I<sub>h</sub> in the entorhinal cortex, and the role of inflammation in epileptogenesis.

***“Experimental treatments of epilepsy”***

**MC Walker, J Heeroma, L Mantoan, S Schorge, DM Kullmann  
Collaborators: M Richardson (KCL), JR Terry, B Krauskopf, M Di Bernardo (Bristol)**

*Approximately 30% of people with epilepsy are not adequately controlled by medication and these people have a significant mortality and psychosocial morbidity. Novel treatment approaches are therefore urgently required.*

We are looking at a range of local treatments. Over the last year we have started a collaborative project (with Bristol and KCL) investigating stimulation paradigms of the thalamus that could translate onto novel stimulation approaches for the treatment of frontal lobe epilepsy. We also have an animal model of neocortical epilepsy and we have started to investigate the feasibility of viral vector approaches for treatment. Two main molecular tools are currently under investigation: we will use our insights into the consequences of human potassium channel mutations to manipulate the excitability of individual neurons and neurotransmitter release from their terminals; and we will attempt to use recently-developed light-activated ion channels to permit neuronal firing to be switched at high temporal resolution.

***“GABAergic inhibition in controlling brain excitability”***

**MC Walker, I Pavlov, DM Kullmann, LP Savtchenko, A Wlodarczyk  
Collaborators: A Semyanov (Tokyo), A Linthorst (Bristol) V Pachnis (NIMR)**

*GABA is the major inhibitory neurotransmitter in the brain. Much remains to be understood in the functions of GABAergic inhibition in controlling the excitability of individual neurons, and understanding how it regulates pathological and physiological network activity.*

We have continued to study tonic inhibition, in which extracellular GABA acts on extrasynaptic GABA<sub>A</sub> receptors on pyramidal neurons. We have found that this tonic inhibition has unexpected biophysical properties that have unique effects on neuronal excitability and on the temporal fidelity of neuronal transmission. We are now asking what are the possible sources of GABA that contribute to tonic inhibition. We are now, in collaboration with NIMR, contributing to work to determine the mechanisms underlying the development of epilepsy in mice that have genetic defects resulting in abnormalities of inhibitory neuron development.