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ADVANCES IN CLINICAL NEUROSCIENCE & REHABILITATION

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SPECIAL FEATURE

REGULARS

Front cover picture is from Headway Nottingham's awareness campaign #seaofissues, aiming to highlight the amount of subtle and profound effects following brain injury. Find them on

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for more information on the campaign.

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Michael Zandi, Co-Editor.

It is now the centenary of the publication by Constantin von Economo (1876-1931) of his description of encephalitis lethargica in *Wiener Klinische Wochenschrift*. Josephine Bicknell Neal (1880-1955) led the writing of the Matheson Reports from 1929, which with her subsequent 1942 monograph helped organise and advance an epidemiological understanding of the syndrome whose aetiology remains enigmatic. The Matheson reports were funded by the chemist and philanthropist William Matheson. It is interesting to reflect on the funding and organisation of neurological and medical research in the early 20th Century, in the current challenging political clime. The book *encephalitis lethargica: during and after the epidemic*, by Joel Vilensky and contributions by Sid Gilman and others (OUP 2011) is highly recommended, and contains self-reports of people with encephalitis lethargica (and variants and mimics). This issue of ACNR has a feature by Ava Easton of the Encephalitis Society, and we review her book, *Life after Encephalitis* which presents stories by and of people who have had encephalitis.

Elsewhere in this issue, Catherine Ashton and Merrilee Needham from Murdoch, Australia, provide an update on necrotising autoimmune myopathies, in particular those associated with signal recognition particle and HMGCR autoantibodies, which are increasingly recognised diseases.

Janine Ostick from Cambridge provides a primer on the game changer that is CRISPR targeted gene editing, a technology we all need to gain an understanding of and that holds much promise.

Mark Nowell and Wisam Selbi from Plymouth write in our neurosurgical article a comprehensive review of the role of surgery in epilepsy, from resections to deep brain stimulation.

Jasvindher Singh and Jack Wildman from Newcastle discuss the management of sleep disorders after traumatic brain injury. David Nicholl introduces this year's ABN meeting, and we look forward to seeing you there. We hope you enjoy this issue of ACNR, which includes as ever a collection of book and conference reviews.

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Necrotising Autoimmune Myopathy (NAM)

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Key Points

- NAM presents with subacute proximal muscle weakness and very high serum creatine kinase levels
- It is associated with anti-HMGCR and anti-SRP antibodies, connective tissue disease and malignancy
- It is responsive to immunotherapy, often requiring multiple immunosuppressive agents
- Rituximab and IVIG are being increasingly used in severe and refractory disease

Abstract
Necrotising Autoimmune Myopathy is a subacute proximal myopathy with high creatine kinase levels and biopsy findings of necrotic and regenerating fibres with minimal inflammation. It is associated with anti-SRP and anti-HMGCR antibodies, malignancy and connective tissue disorders, and is responsive to immunotherapy. This review aims to increase clinician awareness of this rare but potentially treatable condition, by describing the clinical presentation, serological and biopsy findings, and providing an overview of the currently utilised immunotherapy regimens.

Overview

Necrotising Autoimmune Myopathy (NAM) is a relatively newly recognised subtype of the immune-mediated myopathies, characterised clinically by the subacute onset of proximal muscle weakness, often with a significantly raised creatine kinase (CK) level. It is associated with 3-hydroxy-3-methylglutaryl–CoA reductase (anti-HMGCR) antibody (with or without statin medication exposure), Signal Recognition Particle (anti-SRP) antibody, connective tissue disorders, and malignancy.[1-3] In addition, there have been case reports of NAM associated with hepatitis C and HIV.[1] Electromyography shows increased insertional and spontaneous activity,[4] and muscle biopsy reveals necrotic and regenerating fibres, with minimal inflammation.[4] Although there are no prospective trials, treatment generally involves immunotherapy, with the majority requiring multiple immunotherapy agents, with high rates of relapse[5-7] (see Table 1 below).

Clinical Presentation

NAM presents sub-acutely with symptoms of hip and shoulder-girdle muscle weakness, such as difficulty rising from low chairs, climbing stairs or lifting weights above the head, and is clinically very similar to polymyositis,[8] although patients often appear to have more muscle atrophy on presentation.[1,9] The clinical criteria for the diagnosis of NAM, from the 119th ENMC International Workshop on Idiopathic Inflammatory Myopathies, requires a subacute or insidious onset of proximal muscle weakness, with neck flexor rather than extensor weakness, associated with an elevated serum CK level, and no ocular weakness.[4] NAM can also be associated with dysphagia, dyspnoea and myalgia,[1,3,5,9] and there have been reports of cardiac involvement and interstitial lung disease, especially in anti-SRP positive patients.[1,5,9] It is important to exclude toxic myopathies, thyroid disease and muscular dystrophies, as these conditions can have similar biopsy findings. CK levels are generally very high, often more than ten times the upper limit of normal.[3,10] Electromyography

Table 1: Necrotising Autoimmune Myopathy

Clinical presentation	Subacute proximal muscle weakness Additional symptoms: dysphagia, dyspnoea, myalgia Markedly elevated creatine kinase
Biopsy findings	Myocyte necrosis and regeneration Minimal or absent inflammatory cell infiltrate MHC-I immunostaining
Associations	Anti-HMGCR antibody (with statin exposure or statin naïve) Anti-SRP antibody Malignancy Connective tissue disease
Treatment	Prednisolone Steroid-sparing agents (methotrexate, azathioprine, mycophenolate) IVIG Rituximab
Poor prognostic features	Statin naïve anti-HMGCR positive Anti-SRP positive Possibly MHC-II and MAC immunostaining on biopsy

is consistent with an inflammatory myopathy, showing increased insertional activity, fibrillation potentials, positive sharp waves or complex repetitive discharges, as well as short, small amplitude, polyphasic motor unit potentials.[4]

Aetiological Associations

All patients with suspected NAM should have serology performed for anti-HMGCR, anti-SRP and myositis specific antibodies, as well as ANA and ENAs, and blood-borne viruses including HIV and Hepatitis.

HMGCR Antibodies

Christopher-Stine et al first discovered the presence of an autoantibody in a subset of statin-exposed patients with NAM,[11] which was subsequently identified as the HMGCR autoantibody by Mammen et al.[12] The commercially available anti-HMGCR ELISA has a sensitivity of 94.4% and specificity of 99.3%, and to date there have not been any published cases of a positive anti-HMGCR antibody without associated muscle disease.[13] A new diagnostic algorithm, published by Andrew Mammen in 2016, suggests in patients over the age of 65 years with proximal muscle weakness and a high CK level that does not resolve within two months of statin cessation, anti-HMGCR serology should be performed, and if positive, a presumptive diagnosis of NAM may be made.[10] This can then be confirmed by muscle biopsy. The anti-HMGCR antibody has also been found in patients without prior statin exposure.[13] These statin naïve patients tend to be younger with severe muscle weakness, which is more refractory to immunotherapy than the statin-exposed patients.[14] In the statin exposed patients, the development of NAM is not always temporally associated with statin commencement,[15] often starting years after first exposure, so proving causality is difficult. Indeed some have questioned whether statins play a role, however most case series agree that when these generally older statin-exposed patients develop this disease, it is milder and easier to treat than the younger statin-naïve cohort.

Anti-HMGCR associated NAM has been strongly associated with HLA-DRB11*01(16,17), confirmed again in a recent Japanese series,[18] who also reported an association between HLA-DRB1*0803 and statin-associated NAM. The proposed pathogenic pathway is shown in Figure 1: statin exposure upregulates HMGCR expression in muscle cells via both the drug's direct effect and via muscle injury with resultant muscle fibre regeneration, as HMGCR expression is increased in regenerating muscle fibres compared with resting myocytes. In genetically predisposed individuals, (those that have HLA-DRB1*1101) it is postulated that the presentation of HMGCR-derived peptides to the immune system is a possible pathogenic pathway leading to autoimmunity against HMGCR, which is then sustained in a vicious cycle, months to years after statin cessation, due to the ongoing HMGCR expression in the regenerating myocytes, as suggested by Mammen et al.[10,18,19]

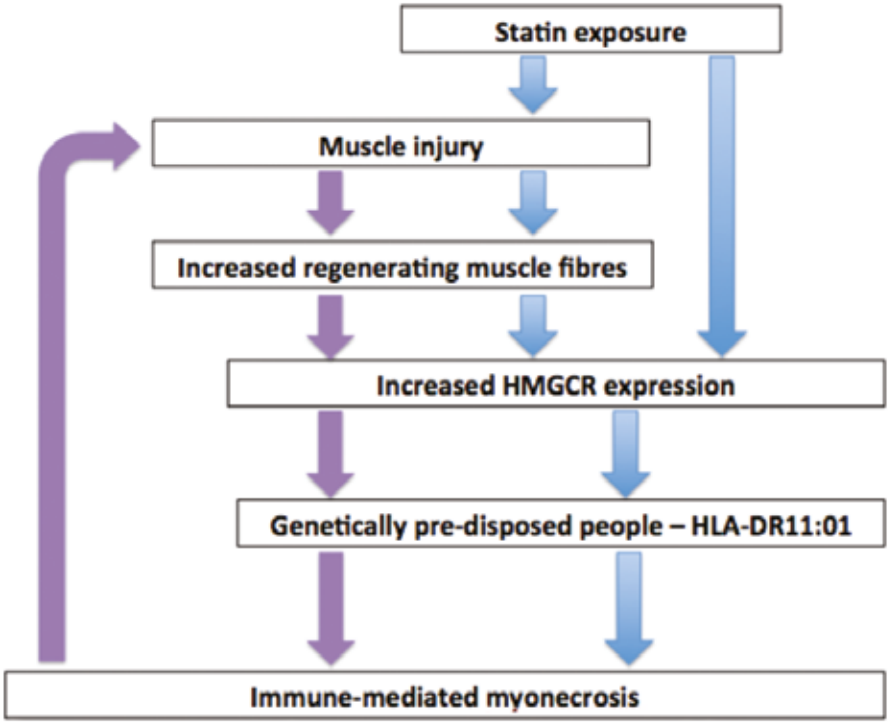

Figure 1: Proposed Pathogenesis of Statin Associated NAM

SRP Antibodies

Antibodies against the Signal Recognition Particle are not specific to NAM and have been found in patients with systemic sclerosis and anti-synthetase syndrome.[20,21] Patients with NAM and positive anti-SRP antibodies tend to have a rapidly progressive disease course with severe weakness and disability,[1] although there have been case reports of a more insidious disease course that can mimic muscular dystrophy.[9] Interstitial lung disease and cardiac involvement are most frequently reported in NAM patients with anti-SRP antibodies.[1] Patients with anti-SRP associated NAM tend to have more refractory disease and are less responsive to single agent immunotherapy.[9] Ohnuki et al found a significant association between HLA DRB1*0803 and anti-SRP associated NAM in their Japanese cohort.[18]

Connective Tissue Disease

Rheumatological conditions can present with necrotising myopathy in an overlap syndrome.[21] There have been case reports of NAM in association with Sjogren's disease, Scleroderma, and Systemic Lupus Erythematosus,[3,22] although connective tissue disease associated NAM is thought to be less common than anti-HMGCR and anti-SRP antibody associated NAM.[3,5]

Malignancy

According to the literature, approximately 10% of all NAM cases are paraneoplastic.[5,23] While there are insufficient patient numbers to specify which cancers are most culpable, there have been numerous reports of NAM associated with gastrointestinal, breast and lung cancers.[3,24,25] A large cohort study (Allenbach et al, 2016) found a significantly increased incidence of cancer within three years of diagnosis in patients with anti-HMGCR antibodies, as well as NAM patients with no myositis specific antibodies, and on the basis of these results, recommended formal malignancy screening in patients over 50 years with these serological results.[25] Anti-SRP associated NAM does not appear to be associated with malignancy.[25]

Biopsy

Muscle biopsy, usually of the vastus lateralis or deltoid, should be performed prior to immunotherapy commencement to facilitate accurate diagnosis. Typically, NAM histologically shows a pauci-immune necrotising myositis, characterised by necrotic and regenerating fibres with minimal or absent inflammatory cell infiltrate, with CD163+ macrophages being the most prominent cell type.[3,26] The ENMC criteria specify that only sparse perivascular inflammation may be present, with perimysial inflammation excluded.[4] Further studies have found an association with MHC-1 sarcolemmal deposition.[26,27] MAC sarcolemmal deposition is also increasingly recognised,[3,27] particularly in cases associated with anti-SRP antibodies,[28] and may be a marker of more severe disease.[29]

Treatment

There are no randomised controlled trials to direct management, and therefore we are guided by case series and expert opinion. Where there is an obvious underlying cause, such as malignancy, this needs to be treated. NAM appears responsive to corticosteroids, IVIG and rituximab, with many patients requiring multiple agents, particularly the statin-naive anti-HMGCR and anti-SRP positive patients.[29,30] Treatment is moving towards early aggressive immunotherapy, particularly in these sub-groups. Kassardjian et al found that treatment with two or more immunotherapeutic medications within the first three

months of onset predicted a more favourable outcome.[5]

The agents used vary between case series, influenced by individual experience and local financial constraints. Our general approach in Australia is to initiate high dose corticosteroids in combination with a steroid-sparing medication (such as methotrexate, azathioprine or mycophenolate), with dosage adjustments determined by clinical and biochemical response. If at three months the response is incomplete, or if the patient is in one of the poorer prognostic groups with a florid clinical presentation, then IVIG and/or rituximab is added. Some patients relapse on steroid weaning, requiring an additional agent (such as IVIG, Rituximab or cyclosporine). Prospective studies are needed to confirm the most effective regimens for the different subtypes.

Conclusion

Increasingly NAM is recognised as one of the most common immune-mediated myopathies. It is associated with specific antibodies in the majority of cases, most commonly anti-HMGCR and anti-SRP. These antibodies form a central part of the subtype diagnosis, predicting clinical course and possible complications. It is an important condition to recognise and distinguish from other forms of myocyte necrosis and regeneration, as it is responsive to immunotherapy.

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CRISPR for gene editing in neuroscience and neurological disease

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Key Points

- CRISPR is an efficient, targetable gene editing tool which can be used to make genetic or epigenetic modifications, modulate gene expression or label gene loci.
- Cell and animal models created using CRISPR have provided insights into neurological disorders including autism, Parkinson's disease and schizophrenia, and into neurological processes such as synapse formation.
- The use of CRISPR in a living brain involves challenges including delivery of CRISPR components, off-target effects and inefficient DNA repair machinery.

Introduction

Since it was first used to edit the mammalian genome,[1] the targetable gene editing tool CRISPR (clustered regularly interspaced short palindromic repeats) has become widely accessible to researchers. Compared to older gene editing technologies, such as zinc-finger nucleases (ZFNs) and transcription activator-like effector nucleases (TALENs), CRISPR has significant advantages: it is more efficient, faster to set up, and can be multiplexed: several DNA loci can be targeted in one experiment.[2] CRISPR's potential in neuroscience ranges from investigating fundamental processes underlying brain function and development, to modelling neurological diseases in both animals and cells, and perhaps to CRISPR-based therapies. This review discusses CRISPR's current applications in cell and animal models aiming to clarify brain function and dysfunction, and some of the challenges that currently limit CRISPR's use in neuroscience.

What is CRISPR?

The CRISPR gene editing system has been identified in and is derived from part of the prokaryote adaptive immune system, which defends against invading viruses or plasmids by specifically cleaving exogenous DNA. Adapting CRISPR for gene editing exploits the ability of CRISPR nucleases to make predictable DNA breaks at specifically targeted sequences. There are three types of CRISPR system (I, II and III) of which type II is most widely used in gene editing (see Figure 1).

First, guide RNA is designed complementary to a DNA target. Next, the guide RNA complexes with Cas9 nuclease (the CRISPR effector), followed by base-pairing between the guide RNA and its DNA target, which directs Cas9 to cleave the DNA. Finally, double stranded DNA breaks are repaired by either non-homologous end-joining (NHEJ) or homologous recombination (HR). NHEJ makes insertion or deletion mutations (indels) of varying lengths, usually resulting in a premature stop codon and gene knockout. Alternatively, DNA with the desired insertion, deletion or point mutation can be introduced to act as a repair template during HR, leading to precise mutations in the DNA.[3]

Cas9 is a nuclease, but CRISPR is not limited to nuclease activity. Inactivation of both catalytic domains in dead (d)Cas9 renders the nuclease unable to cleave DNA, but it can prevent transcription by steric hindrance in CRISPR interference (CRISPRi). CRISPRi can be enhanced by complexing dCas9 to repressors, for reversible gene knockdown, whereas dCas9-activator complexes can be used for reversible overexpression. In addition, dCas9 complexed to epigenetic modifiers can be used for methylation or histone modifications, and Cas9 with a fluorescent molecule can tag genomic loci.[4] The range of functional domains coupled to Cas9 is expanding, linking CRISPR to advances in our understanding of genetic processes and our ability to manipulate them. One area where CRISPR has been readily adopted is in modelling neurological disease with human induced pluripotent stem cells (hiPSCs).

Cell models: hiPSCs

hiPSCs are somatic cells reprogrammed to an embryonic stem cell-like state, which retain the donor's genetic identity and can make any cell type. hiPSCs from a donor with a neurological disease allow disease processes in cells usually inaccessible in a living patient to be studied in hiPSC-derived astrocytes, glia and neurons. CRISPR, ZFNs and TALENs can enhance hiPSC models by correcting or introducing genetic aberrations linked to a particular disorder, creating isogenic hiPSC lines, in which a specific genetic change can be studied without confounding genetic background effects. Isogenic hiPSC models have been made for multiple neurological disorders (see Table 1), including schizophrenia and Parkinson's disease,[5] and offer a platform for drug screening, as well as for mapping pathways affected by disease-causing mutations.

In addition to DNA mutations, epigenetic changes, which alter gene expression without affecting the DNA sequence, have been impli-

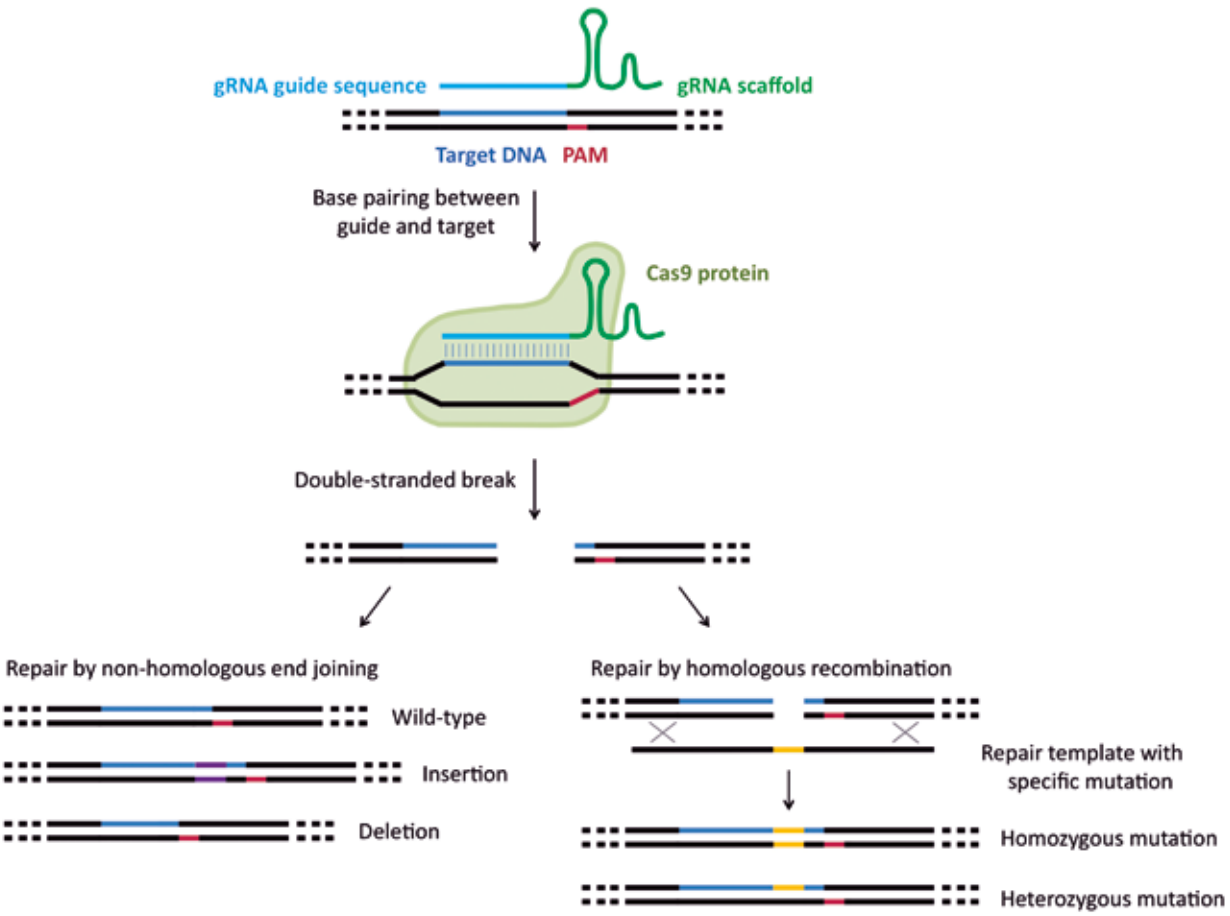

Figure 1. Using the Cas9 CRISPR system for gene editing.
Guide RNA (gRNA) is composed of a scaffold sequence (required for binding between Cas9 and the gRNA) and a 20 base pair sequence which is designed complementary to the DNA target. The DNA target must be upstream of a proto-spacer adjacent motif (PAM) sequence, which is required for DNA cleavage. Cas9 nuclease is directed to the target DNA by base pairing between the target DNA and guide RNA, resulting in a double-stranded DNA break. The double-stranded break can be repaired by non-homologous end-joining (NHEJ) or homologous recombination (HR). NHEJ results in either restoration of the wild-type sequence, insertions or deletions (indels). Indels vary in length and can cause frame-shift mutations, leading to premature stop codons and gene knockout. HR requires a DNA template with homologous regions up- and down-stream of the break. Therefore, a DNA repair template can be designed in order to introduce precise insertions, deletions or point mutations.

cated in neurological disorders including Alzheimer's disease and epilepsy, as well as in neurological processes such as memory and cognitive ageing.[6] Several groups have made CRISPR-induced epigenetic modifications in cell models: for example, dCas9 fused to a histone demethylase has been targeted to gene enhancers, where it reduced gene expression in human cells.[7] This proof of concept suggests that CRISPR could be used to study disease-linked epigenetic changes in cell models.

Animal models

Cell models are useful to study particular cell types in isolation, but animal models can give a more physiological representation of the human brain. The use of small animals, with relatively simple nervous systems, could be extended by using CRISPR to target multiple loci at once in a reverse genetic screen, in which indel mutations are made to identify genes with roles in a particular process. One group has used multiplexed guide RNAs to make indels at 48 loci thought to be involved in synapse formation in zebrafish, leading to the identification of two novel genes.[8]

CRISPR also facilitates the creation of larger animal models, which can otherwise be a lengthy and expensive process, particularly when multiple mutations are required. CRISPR has been used to make up to five mutations simultaneously in mouse embryonic stem cells, without apparent off-target effects.[9] Genes can be targeted with CRISPR in vivo in existing mouse models, which can be aged to study ageing-related neurological changes. Three

Table 1: Examples of CRISPR as a tool to model aspects of neurological disorders in iPSCs.

Neurological disorder or disorder group	Gene or chromosome target	Mutation induced with CRISPR	Reference
Major Mental Illness	DISC1	Frameshift mutation in exon 2 (homozygous), frameshift mutation in exon 8 (homozygous and heterozygous)	[16]
Autism	CHD8	Knock out (heterozygous)	[17]
Huntington's disease	HTT	Insertion of 97 CAG repeats into exon 1	[18]
Recurrent microdeletion and microduplication syndromes	16p11.2 and 15q13.3 copy number variants	575kb deletion, 740kb deletion, 740kb insertion	[19]
Epilepsy	SCN1A	Insertion of tdTomato into GAD67 to fluorescently label GABAergic neurons	[20]
Fragile X syndrome	FMR1	Deletion of CGG repeats at the 5'-UTR of FMR1	[21]

genes involved in learning and memory have been simultaneously knocked out using CRISPR in a live adult mouse brain,[10] showing that changes can be made in assembled neural circuits, which is an important step towards using CRISPR therapeutically in the brain.

Mouse models have provided valuable insights into neurological disorders, but their relevance to humans is limited by their relatively fast brain development, short lifespans and in some cases by gene expression under exogenous promotors. Larger mammalian models have brains closer in size and complexity to humans, and lifespans long enough to study ageing-associated neurological diseases: pig and non-human primate models have been made to study Alzheimer's, Huntington's, and Parkinson's diseases, amongst others.[11] These models used one causative mutation, but CRISPR can be used to make multiple mutations in the same animal, allowing the study of multifactorial diseases or subtle phenotypes: in transgenic pigs, simultaneous mutations have been made in Parkin, DJ-1 and PINK1 (genes linked to early-onset Parkinson's disease).[12] In one cell monkey embryos indels have been made in two endogenous genes, which (although they are not linked to a particular human disorder) indicate the potential to alter multiple endogenous genes related to neurological diseases.[13]

Limits of CRISPR in the brain

CRISPR is a flexible and widely available tool which has been used to induce multiple specific disease-relevant mutations in cell and animal models of neurological disease. It has the potential to extend the use of current models through reversible modulation of gene expression and through epigenetic modifications. However, several challenges must be overcome for CRISPR to be used in a living brain. For instance, off-target effects are undesirable in animal models, and would be a safety concern if CRISPR was used therapeutically. Additionally, in vivo delivery of CRISPR components to the brain is difficult. Viral delivery is limited by the virus's cloning capacity,[10] but other methods, such as liposomal delivery of Cas9 protein and gRNA, have been used for gene knockout in the mouse inner ear in vivo.[14] Finally, the correction of mutations or deletions by HR (following a CRISPR-induced DNA break) requires efficient DNA repair machinery, which may be less active in post-mitotic cells like neurons.[15] CRISPR-mediated changes which do not require DNA repair, such as epigenetic modifications or CRISPRi, may therefore be more easily induced in neurons in vivo. Alternatively, NHEJ, which does occur in neurons, could be used to make indels for therapeutic gene knockout in disorders caused by toxic gain of function, such as Huntington's disease.

Some of these problems may be overcome by utilising alternative CRISPR systems as gene editing tools. As more prokaryote genomes are sequenced, CRISPR or CRISPR-like systems with different effectors or DNA cleavage characteristics may come to light, which could further diversify CRISPR's gene editing potential. Even without new CRISPR systems, the growing family of CRISPR-based tools clearly indicates that CRISPR is yet to reach its full potential in neuroscience.

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Surgical Considerations in the Management of Epilepsy

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Abstract
There is class I evidence to support the use of surgery in the management of medically refractory epilepsy,[1] with better clinical outcomes and cost effectiveness. Despite this, surgery remains an underutilised resource. One reason is that epilepsy is a complex and heterogeneous condition, and individuals require comprehensive pre-operative evaluation to determine whether surgery is appropriate for them. Surgery may be curative, with the aims of achieving seizure freedom, or palliative, with the aim of reducing seizure frequency. Surgery may also be diagnostic, with intracranial EEG playing an important role in the presurgical evaluation. In this article, the process of presurgical evaluation is summarised, followed by an overview of current surgical treatments available.

Presurgical Evaluation

Cortical zones

Six cortical zones have been defined in the presurgical evaluation of patients for epilepsy surgery[2] (see Table 1, Figure 1). The epileptogenic zone (EZ) is defined as the area of cortex indispensible for the generation of clinical seizures. There is no single diagnostic test for the EZ, and it can only be identified retrospectively, with long-term seizure freedom following cortical resection. The aim of presurgical evaluation is to infer the localisation of the EZ, and ensure that this can be safely resected without causing significant deficits.

Patient selection

There are four general criteria necessary for patients to meet to be considered candidates for presurgical evaluation and resective surgery.

1) Drug resistant epilepsy
2) Clinical diagnosis of focal seizures
3) Absence of contra-indications for presurgical evaluation and epilepsy surgery
4) Declaration by the informed patient and/or carer that he/she wishes to undergo presurgical evaluation

General pathway for presurgical evaluation

The general pathway followed by most Epilepsy Surgery Units is described in Figure 2.[3] The initial clinical evaluation and clinical investigations are commonly referred to as Phase 1 in the process,[4] and are composed of clinical evaluation of seizure semiology, scalp EEG and video telemetry, structural imaging (MRI) and neuropsychological and psychiatric assessment. See Table 2.

If the outcome of Phase 1 is a clear hypothesis for the site of the EZ, in an area that is surgically accessible with concordant investigations, then the recommendation may be to proceed with resective surgery. If there is uncertainty on the localisation of the EZ, further investigations are often necessary. This is known as Phase 1.5, and includes advanced imaging techniques and intracranial EEG (see Table 3). There is great

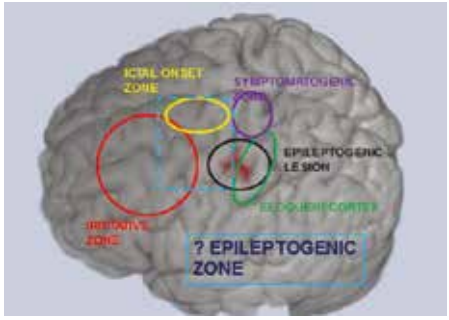

Figure 1: Illustration of discordant cortical zones and lesions

Table 1: Description of cortical zone and lesions (Rosenow and Luders, 2001).

Epileptogenic zone	Region of cortex that can generate epileptic seizures. By definition, total removal or disconnection is necessary for seizure freedom
Irritative zone	Region of cortex that generates interictal epileptiform discharges, evident in the EEG or magnetoencephalography (MEG)
Seizure onset zone	Region where the clinical seizures originate
Epileptogenic lesion	Structural lesion that is causally related to the epilepsy
Ictal symptomatogenic zone	Region of cortex that generates the initial seizure symptoms
Functional deficit zone	Region of cortex that in the interictal period is functionally abnormal, as indicated by neurological examination, neuropsychological testing and functional imaging or non-epileptiform EEG or MEG abnormalities
Eloquent cortex	Region of cortex that is indispensable for defined cortical functions

Table 2: Structural MRI protocol for epilepsy imaging	
Acquisition	Reason
Volumetric T1 (1mm isotropic)	Excellent grey-white matter contrast, can be reformatted in any plane for post-processing purposes
T2 (axial and coronal)	Assessment of hippocampus
Fluid attenuated inversion recovery (axial and coronal)	Sensitive to hippocampal sclerosis, focal cortical dysplasia, tumours, inflammation
T2 gradient echo or susceptibility weighted (axial)	Sensitive to calcified and vascular lesions

Table 3: Advanced imaging tools used in presurgical evaluation of epilepsy	
Localise epileptogenic zone	
Ictal-interictal subtraction single photon emission CT (SPECT)	Injection of a radiolabelled tracer (99mTc-hexamethyl-propylenamine oxime and 99mTc-ethyl cysteinate dimer) detected by CT and used to infer changes in cerebral blood flow (CBF).
Positron emission tomography (PET)	Use of tracer labelled with positron-emitting isotopes (18F-deoxyglucose (FDG)) to map cerebral glucose metabolism.
EEG-fMRI	Simultaneous recording of EEG and fMRI, to map cerebral blood oxygen level-dependent (BOLD) signal changes associated with interictal (IED) and ictal epileptic discharges
Magnetoencephalography	Direct recording of the magnetic brain activity associated with neuronal activity in the cerebral cortex
Protecting eloquent brain	
Functional MRI	Indirectly detects focal areas of increased neuronal activity by identifying increased BOLD signal changes when the patient performs specific tasks. It can be used to map language, motor function and memory.
Diffusion weighted imaging	Maps the diffusion of water in biological tissues, so that each voxel has an intensity that reflects the best measurement of the rate of water diffusion. Used to delineate the white matter pathways of the brain through a technique called tractography

benefit in integrating all available imaging data on 3D multimodality brain reconstructions to guide decision making and planning of surgery[5] (Figure 3). 3D multi-modality image integration is especially useful in more complex patients with extratemporal epilepsy who undergo advanced imaging and intracranial EEG implantation.

Surgery

Intracranial EEG

Intracranial EEG monitoring (ic-EEG) is indicated in patients with medically intractable focal epilepsy, where non-invasive investigations have failed to find a focus.[6] Ic-EEG remains the gold standard for identifying the region of tissue that must be removed to ameliorate seizure activity. The decision to proceed to ic–EEG, and the precise location and configuration for surgery, arises from a multi-disciplinary case review with all the non-invasive investigations. Subdural grid electrodes are used to capture foci at the cortical surface (Figure 4). Depth electrodes placed percutaneously are used to capture activity in the deep cortical and subcortical structures, including the hippocampus, amygdala, insula, cingulate gyrus and areas of cortical dysplasia at the depth of a sulcus. The capture of foci in a three dimensional way is best achieved with stereoelectroencephalography (SEEG) (Figure 5).

SEEG requires precise imaging of the intracranial arteries and veins to avoid vascular injury during insertion, a planning station to design electrode arrangements and a robust method to accurately execute the trajectories. The most accurate techniques use frame-based stereotactic techniques (Leksell, Brown-Roberts-Wells, Cosman-Roberts-Wells systems) and robot implementation,[7-9] although there is increasing interest in frameless stereotactic techniques using custom-designed guidance tools.[10]

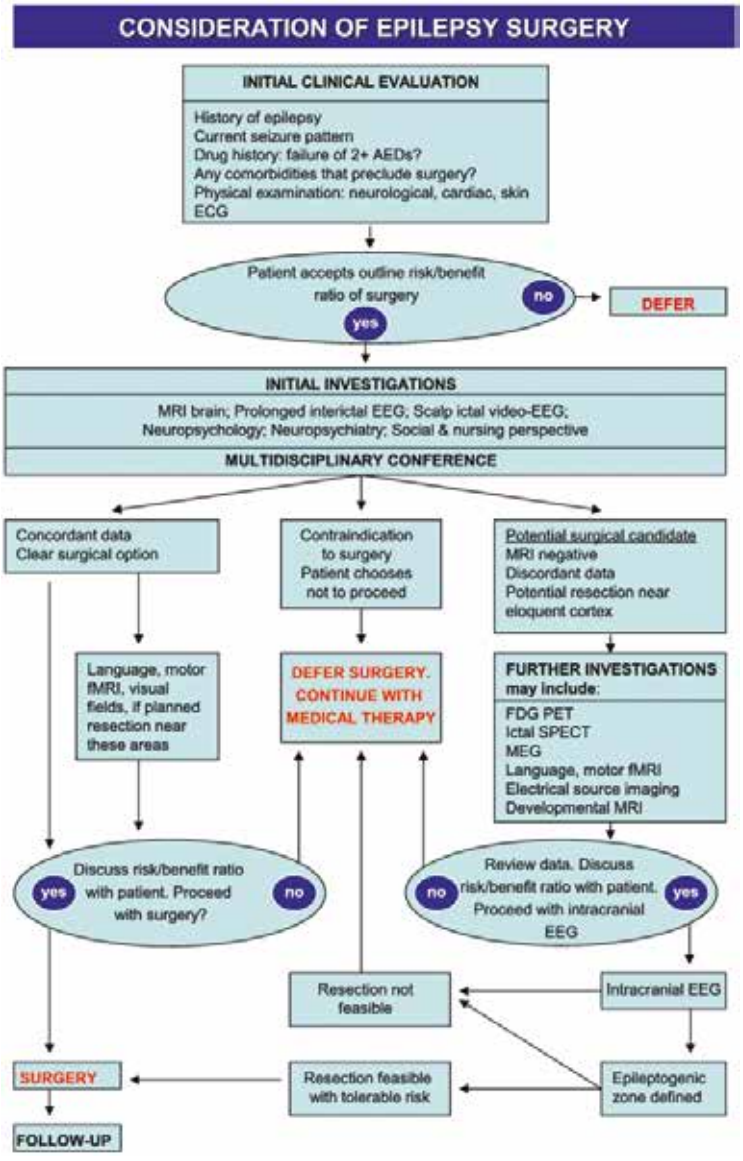

Figure 2: The common pathways for presurgical evaluation in epilepsy surgery (Duncan, 2011).

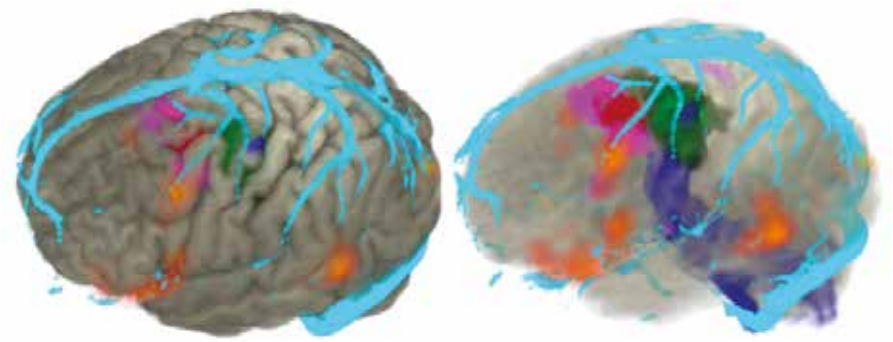

Figure 3: 3D multimodality imaging in AMIRA
Volume rendering of cortex (grey) displayed in AMIRA software with the following associated modalities: focal cortical dysplasia (red), FDG-PET hypometabolism (purple), hand motor fMRI (green), corticospinal tractography (blue), veins (cyan).

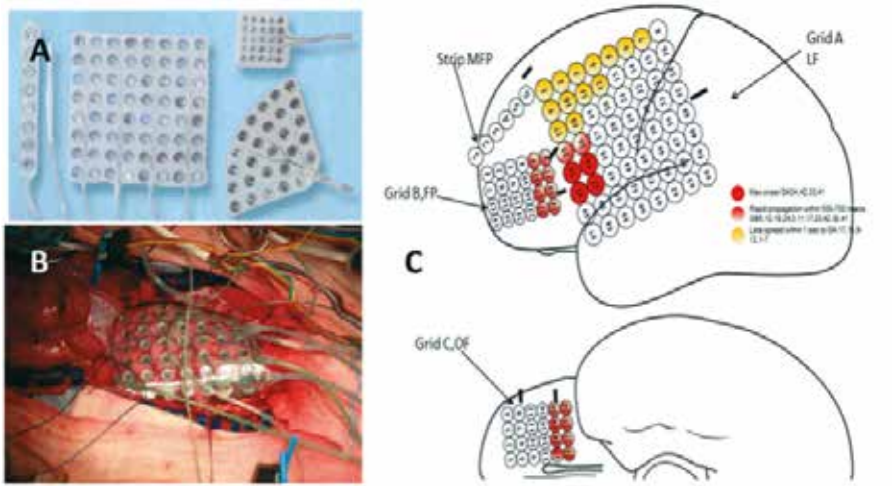

Figure 4: Intracranial EEG with subdural grids
A- Photograph demonstrating a selection of subdural grids, subdural strips and depth electrodes that are commercially available. Featured products are from PMT corporation.

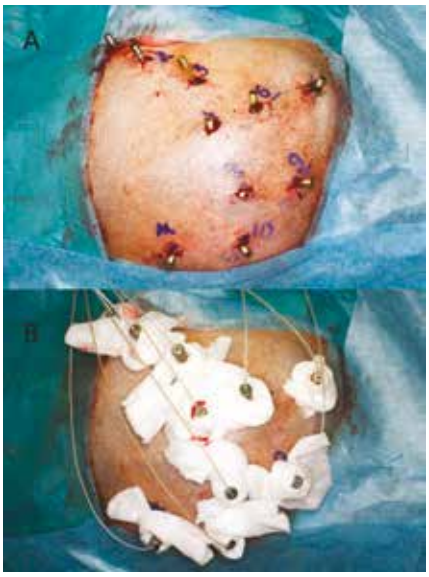

Figure 5: Post-operative appearance of bolts and electrodes
A) Percutaneous electrode bolts, B) Electrodes secured within percutaneous bolts

The ic-EEG implantation strategy should be tailored for individual patients, following discussion between the neurophysiologist and the neurosurgeon at the Multidisciplinary telemetry meeting. Patients with seizure onset at the cortical surface, close to eloquent areas, will be more suited to subdural grid implantation, whereas patients with seizure onset at the depths of a sulcus, or inaccessible areas of cortex, are more likely to benefit from SEEG.[11] Historically epilepsy surgery units tended to favour one technique over another, and preferentially accumulated experience in one approach. However there has been a recent trend towards the more widespread adoption of SEEG, which has the dual advantage of achieving improved coverage at depth, with lower complication rates.

Curative surgery

Patients with concordant phase 1 investigations, and patients with a robust hypothesis for localisation of EZ following phase 1.5 investigations, may proceed to resective surgery. The goals of resective surgery are to achieve seizure freedom whilst minimising any functional neurological deficit.

Temporal lobe surgery

The standard Anterior Temporal Lobe Resection (ATLR) was first described by Penfield in 1952, and is also known as 'The Montreal Procedure'[12] (Penfield et al, 1952.) This involves an en bloc anterolateral neocortical resection extending from the pole along the superior temporal gyrus to the level of the central sulcus in the non-dominant hemisphere or to the precentral sulcus on the dominant side, which corresponds to 5 or 4.5cm respectively, and across the temporal stem to the collateral sulcus separating the fusiform gyrus from the parahippocampal gyrus. The temporal horn of the lateral ventricle is then entered and the mesial temporal structures, including the hippocampus, parahippocampal gyrus,uncus and typically 4/5 of the amygdala, are resected.

Selective amygdalohippocampectomy

The selective amygdalohippocampectomy is a modification of the standard Montreal procedure, with a more selective removal of the mesial temporal structures, sparing much of the lateral neocortex. The procedure was first proposed by Niemeyer in 1958.[13] There have been several technical modifications, including Olivier with the trans-cortical or trans-middle temporal gyrus approach,[14] and Yasargil with the trans-Sylvian approach.[15] This operation is indicated when pathology is limited to the mesial structures. The difference lies in the approach to the temporal horn of the lateral ventricle. The intraventricular component of the operation, with resection of hippocampus, parahippocampal gyrus, uncus and amygdala, remains the same.

The theoretical advantage of a selective approach is that there is sparing of the lateral neocortex, which may preserve neurocognitive function. This has not been clearly demonstrated with studies that compare selective approaches to the standard ATLR.[14,16-18]

Extra-temporal Surgery

Lesionectomy

Lesions that can produce epilepsy include areas of cortical dysplasia, tumours (low grade, dysembryoplastic neuroepithelial tumours (DNET)),[19] areas of cerebral infarction or traumatic injury, and vascular malformations.[20] Complete removal of the structural lesion and some of the adjacent cortex yields excellent results. Peri-lesional resection can be guided by use of intra-operative EEG.

Surgery for focal cortical dysplasia and structural vascular abnormalities differs from other lesionectomies due to an indistinct border of the structural abnormality. A total resection is made difficult by horizontal encroachment into eloquent cortex, and vertical encroachment into white matter. For this reason ic-EEG is often performed prior to resection, to guide resection margins and protect eloquent cortex.[21]

Palliative Surgery

Palliative surgery is indicated in patients with medically refractory epilepsy where curative

surgery is not possible. This may be because presurgical evaluation has not generated a robust hypothesis for the localisation of a solitary EZ that is amenable to resection. Alternatively the EZ may be widespread or multifocal, or arising from eloquent brain.

Hemispherotomy

Hemispherotomy is indicated in patients with unilateral and widespread epilepsy. Common conditions include congenital hemiplegia from a prenatal vascular insult, Sturge-Weber syndrome, hemimegencephaly or diffuse hemispheric cortical dysplasia, Rasmussen encephalitis, hemiconvulsion-hemiplegia-epilepsy, or a sequel of trauma or infection.[22]

The goal is the disconnection of corpus callosum, internal capsule and corona radiata, mesial temporal structures and frontal horizontal fibres. This may be achieved by the vertical parasaggital approach[23] or by the lateral or peri-insular approach,[24] depending on surgeons' preference.

Corpus callosotomy

Corpus callosotomy is indicated in patients with intractable generalised epilepsy where one of the main seizures types are atonic seizures or drop attacks. The goal is the section of the corpus callosum. A standard craniotomy and interhemispheric approach is followed by sectioning of the corpus callosum. The optimal extent of sectioning is not fully understood.[25] A partial callosotomy involves sectioning of the anterior two thirds of the corpus callosum from the border of the anterior commissure up to the splenium. Sparing the splenium is thought to reduce the risk of disconnection syndromes. A complete callosotomy is carried through the splenium to the arachnoid of the quadrigeminal cistern.

Vagus nerve stimulation

Vagus nerve stimulation (VNS) is an adjunctive treatment in the management of medically refractory epilepsy in patients who are unsuitable candidates for resective surgery. The mechanism of action is not completely understood, although current evidence points towards a deactivation of the nucleus of the solitary tract, with widespread projections to the dorsal raphe nucleus, locus coeruleus, hypothalamus, thalamus, amygdala and hippocampus.[26]

Deep brain stimulation

There is a long history of interest in the use of Deep brain stimulation (DBS) for epilepsy control. The postulated mechanism of action is by interrupting the propagation of seizure activity or by increasing the overall seizure threshold. Multiple targets have been put forward, centred in and around the circuit of Papez.[27]

The current results with DBS for the treatment of epilepsy remain modest, even accounting for the difficult patient group with highly refractory epilepsy.[28] Stimulation-related side effects have been reported, most commonly with psychiatric disturbances and depression. There is also the possibility of habituation to long-term stimulation.

Non-invasive surgery

There is great interest in less invasive surgical treatments that can generate lesions at depth without requiring the opening of the head. These include MR-guided laser therapy, focused ultrasound, stereotactic radiosurgery and also radiofrequency ablation. A more detailed account of these is given elsewhere.[29] More work is needed to demonstrate the efficacy of these techniques.

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Addressing sleep-wake disturbances in patients with traumatic brain injury

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Abstract
Sleep disturbance is common following traumatic brain injury (TBI) and can affect recovery course and disrupt rehabilitation. Poor sleep affects neuropsychiatric, behavioural and physical symptoms as well as learning and memory, leading to suboptimal cognitive recovery and prolonged stay in the hospital. Sleep disturbance may also be a marker for more severe injury.

The data on the prevalence of sleep problems following TBI is relatively limited; various studies looking into this have reported overall prevalence rates of between 40 and 70%. Furthermore, TBI patients with sleep problems often have difficulty identifying their symptoms, making it more difficult to establish the true nature of these. Numerous factors contribute including the direct effect of trauma, neuropsychiatric consequences, psychotropic medication and increased risk of primary sleep disorders such as sleep apnoea if inactivity leads to increased weight gain. The relationship between the type or location of injury and sleep disturbance is not well established.

Sleep disturbances commonly identified post-TBI include insomnia, hypersomnia and alterations of the sleep-wake cycle or circadian rhythm. A detailed sleep history from patient and/or carer is vital. Sleep assessment scales including the Epworth Sleepiness Scale are useful alongside review of sleep charts for in-patients. One must consider neuropsychiatric comorbidities including depression, anxiety and pain. Referral to a sleep service for respiratory sleep studies or polysomnography can help to accurately diagnose sleep apnoea, parasomnia or causes of hypersomnia and many sleep disorders have effective therapies.

The key to management is establishing an accurate sleep disorder diagnosis. The treatment of insomnia and circadian rhythm disorder should initially be non-pharmacological, focusing on sleep hygiene and CBT and regulating exposure to natural light. Stimulants may be effective for persistent hypersomnia if respiratory causes have been excluded.

Background
Sleep-wake disturbances (SWDs) are commonly seen in patients who sustain a traumatic brain injury (TBI). For example, Gardani et al[1] recently found that 2/3 of their rehabilitation inpatients with severe TBI showed signs of a sleep cycle disturbance, and 50% met the criteria for a sleep disorder. This can occur in the immediate period after the injury and may persist for several years after the event.[2,3]

SWDs can affect the recovery course and exacerbate other problems commonly seen in the recovery period post-TBI including pain, fatigue, cognitive impairment and psychiatric problems such as anxiety and depression[4] – indeed, Rao et al[5] found that SWDs in the acute post-injury period were associated with neuropsychiatric symptoms for the next year. As such, it is important for the clinician managing patients with TBI to be aware of the possible sleep problems that may manifest themselves and how to appropriately investigate and manage them.

What should we be looking for?
Prevalence of sleep disorders varies significantly between studies due to differences in methodology, diagnostic criteria and patient populations; Table 1 highlights the most common disorders and selected prevalence figures. Despite these variations, reduced amount of sleep (insomnia), excessive daytime sleepiness (EDS), increased sleep need (pleiosomnia) and circadian rhythm disturbance are generally the most commonly seen SWDs in TBI patients. It is suggested that in the immediate post-injury phase patients have problems with initiating and maintaining sleep, whereas chronic brain injury patients experience excessive sleep.

Table 1 – sleep disturbances commonly identified in TBI patients[2,6,8]

Sleep Disorder	Prevalence (%)
Excessive daytime sleepiness (EDS)	67 (Imbach et al)
Insomnia	40 (Zeitzer et al)
Circadian rhythm disturbance	36 (Ayalon et al)

Insomnia is likely multifactorial, and may be related to the neural damage itself or neuropsychiatric/neuromuscular sequelae (e.g. depression, pain). Zeitzer et al highlight in their review[6] that there are broadly two types of patients in this area; those who report difficulty sleeping without necessarily having objective findings to correlate with this, and those with increased daytime sleepiness and reduced concentration with more investigative correlates.

Pleiosomnia, that is to say increased need for sleep, and EDS have also recently been found to be especially common in TBI patients, with patients requiring on average an extra hour of sleep per 24 hours compared to healthy controls.[2] Objectively measured EDS is seen in up to two-thirds of patients and for at least 18 months post-injury, although evidence suggests that patients themselves may not report this. As is seen in insomnia, there is often significant discrepancy between patient description and investigative findings.

Circadian rhythm disturbance can take the form a delayed sleep phase disorder (DSPD)[8] or less commonly an irregular sleep wake pattern or free running pattern and may be related to dysfunctional melatonin production. There is a relationship between DSPS and depressive symptoms; whether there is a causal relationship between the two is as yet uncertain.

Sleep apnoea, especially obstructive (OSA), is a common cause of daytime sleepiness in the general population and although it may not be caused directly by brain injury, it may slow down or complicate recovery.[10] Risk factors include weight secondary to decreased activity and some psychotropic medications alongside sedative or opioid medication. It is also significant for its implications on driving and long-term cardiovascular risk. It is important to remember this has a well tolerated and cost effective treatment with CPAP therapy.

Asking patients about restless legs as a common secondary cause of insomnia is also important, checking serum ferritin for such patients and replacing if below 45 may be of benefit.

In less common disorders such as parasomnias, the duration of sleep is typically unaffected but patients (or more likely, carers) may complain of sleep-walking or other unusual activities during sleep; however, there is debate regarding the true prevalence and clinical presentation of parasomnias after brain injury. Narcolepsy with cataplexy, another cause of excessive sleepiness, is also occasionally described but there is little evidence of a significantly increased risk following TBI. Interestingly, transient hypocretin deficiency is seen after TBI which provides one mechanism for hypersomnia.

How should we investigate?

The investigative process should be guided by clinical judgement based on the symptoms present and level of neuropsychiatric impairment in the patient; a standard approach often suffices. Simple self-report methods such as the Epworth Sleepiness Scale (ESS) and Pittsburgh Sleep Quality Index may be of use in less cognitively impaired patients but it should be considered that TBI patients tend to under-report excessive sleepiness and insomnia.[2,6] Added value can come from asking the bedpartner or spouse to complete the ESS where possible. Assessment of BMI, caffeine, nicotine and alcohol intake alongside regular medications should also be a standard part of the clinician's initial workup. As such, a sleep history and typical 24 hours from the patient and/or carer should be part of all TBI assessments.

Table 2 – recommended history, examination and investigations for TBI patients

• Comprehensive history including pre-morbid history of sleep problems, previous medical history and drug/alcohol history/BMI
• Epworth sleepiness score and consider the STOPbang screening tool for sleep apnoea
• Are there any comorbid neuropsychiatric disorders? E.g. mood disorder, anxiety disorder, pain, or substance abuse
• Mental state examination
• Neurological examination
• Current Medications
• Baseline blood tests including ferritin, vitamin B12, thyroid function test, folate and ESR
• Brain imaging (CT/MRI)
• Sleep service referral and consider sleep studies if possible sleep apnoea, injurious parasomnia, persistent hypersomnia or insomnia

Sleep charts, which can be completed by nursing staff for patients in inpatient facilities, are useful to quantify the amount and timing of sleep and thus can suggest a need for further investigation or management. Furthermore, sleep charts over time can be used to more objectively monitor response to treatment especially for disorders such as insomnia or hypersomnia.

There is widespread availability of domiciliary respiratory sleep studies to screen for sleep apnoea. Video-Polysomnography (PSG) and occasionally actigraphy are objective tests for assessing the amount and quality of a patient's sleep but are limited by availability in some settings. Where they are available these tests, along with Multiple Sleep Latency Testing (MSLT) are the gold standard for pathological hypersomnia and, have utility in investigating disorders where the aetiology is not elicited through simple measures or self-report questionnaires.[12] They can also help differentiate sleep disorders from fatigue, which is also common post-TBI and can confuse the picture.

It should be considered that such complaints as insomnia or excessive sleepiness may be symptoms of other underlying primary sleep disorders (such as OSA or restless syndrome), or part of psychiatric disorders such as depression and PTSD or other medical comorbidities. Screening or further investigation for these may therefore prove useful, as would referral on to appropriate clinicians for further assessment and management.

Once we've identified a problem – what next?

The key to management lies in integrating the sleep disorder itself with comorbidities and contributory factors, and tackling each of these appropriately. Mood disorders and pain may be difficult to manage but any improvement in these may yield direct benefits to sleep. Equally improving sleep is shown to improve mood and pain scores.

At a conservative level sleep hygiene focus is often a useful first step in management, particularly for patients presenting with insomnia, hypersomnia or circadian rhythm disturbances. This may consist of simple measures such as reinforcing a regular sleep schedule, avoiding stimulant drinks like tea/coffee and limiting night-time stimulation from electronic devices with bright screens. Non-pharmacological methods such as CBT should be considered first-line for insomnia (CBT-I) with evidence for benefit in primary and comorbid insomnia. For hypersomnia, reviewing sedative medication and maintaining simple sleep charts over a two week period should be considered initially to highlight any contributory lifestyle factors.

There are numerous pharmacological options available for insomnia and EDS (see Table 3) and medications may be useful in a range of underlying disorders, such as antidepressants for depression/anxiety disorders and low dose antipsychotics in aggressive patients. The literature surrounding the use

Table 3 – pharmacological options for insomnia and symptoms of excessive sleepiness. *not for long term use

Insomnia	Increased sleepiness
Zopiclone*, zolpidem*	Methylphenidate
Benzodiazepines* e.g. clonazepam/temazepam	Modafinil/armodafinil
Melatonin	Amantadine
Agomelatine	
Antidepressants e.g. amitriptyline, trazodone, Mirtazapine	
Antipsychotics – Risperidone/Quetiapine	

of these medications in TBI populations is however quite limited and their use should be evaluated in terms of the benefit they impart versus any side-effects they yield – particularly any cognitive or behavioural changes.

From our clinical experience, we have perceived more benefit from the use of low-doses of trazodone (e.g. 75mg) and mirtazapine (e.g. 15mg) for insomnia. However, mirtazapine can aggravate restless legs so this should be screened for first. Benzodiazepines should be used with caution and only for short periods of two weeks or less, they have very limited evidence base for chronic insomnia. They may contribute to symptoms of sleep apnoea as well as worsening daytime tiredness. Likewise, Z-drugs (zopiclone, zolpidem) should be avoided where possible.

Finally, if the standard measures to improve sleep disturbance fail, referral to a specialist sleep service is important as these clinicians may be able to elicit the true nature of the apparent disorder in order to guide further treatment. They may also provide other alternatives to medications such as continuous positive airway pressure (CPAP) for OSA.

Is there a need to screen?

Given that SWDs are so common in this population, we would argue that any patient presenting post-TBI should be screened for such a disturbance.[13] There are, however, currently several questions to address before this can be implemented as standard:

- Are there any risk factors within the TBI patient group that yield an even higher likelihood of SWD being present, such as TBI severity, area of injury, type of injury or presence/duration of unconsciousness?
- Is it logistically and economically viable to screen for SWDs in the context of their prevalence and importance in this population group?
- What are the most effective management methods for SWDs in these patients, and does effective management lead to better overall long-term outcomes? There is evidence suggesting that such measures do indeed improve cognitive and behavioural outcomes[14] but further work is needed.
- What are the biological mechanisms behind the high prevalence of SWDs in the TBI population? There are several hypotheses, such as the role of sleep in clearance of metabolic waste products,[15] further research into which may guide future management options (e.g. correcting a neurotransmitter imbalance) or allow better prediction of those more at risk of SWD.

If it is deemed to be viable, work in these areas may facilitate the development of a robust, evidence-based screening approach or set of guidelines for the assessment and management of post-TBI SWDs.

Key Messages

- Post-TBI sleep disturbance is common and impacts on both quality of life and effective neurorehabilitation.
- The most commonly seen of such SWDs include insomnia, increased sleep need, and excessive daytime sleepiness. Other disorders such as obstructive sleep apnoea may complicate recovery.
- Effective early investigations may include sleep charts and self-report questionnaires, but referral to sleep clinics for more robust workup should always be considered in cases of doubt.
- Conservative management such as sleep hygiene focus should not be overlooked and pharmacological management should be considered in the context of the patient's wider neurorehabilitation needs. Again, sleep clinicians are central for more specialist management.
- Future research may provide backing for a formal screening guideline for TBI patients, helping to earlier identify those most at risk and provide early management if needed.

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Journey to the South

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I was fortunate to be offered the Association of British Neurologists (ABN) Australasian Fellowship in 2015. The fellowship consists of a 12 month clinical neurology training period in Australia. It counts as a year in my neurology training accreditation towards CCT. I was given the opportunity to choose my preferred location out of the pre-selected hospitals, and I decided to go for Box Hill Hospital in Victoria, Australia.

The Move

With the fellowship in hand, along came the mammoth task of sorting out all the necessary visa applications, medical registrations, essential documents and moving! It took me a few weeks to get linked in with the HR department at Box Hill Hospital, who were very helpful in guiding me through the entire process.

The first step was to obtain verification of my medical degree by applying for Primary Source Verification via the Australian Medical Council (AMC). This is a compulsory process for all international medical graduates outside of Australia. Once approval was achieved, I was able to apply for provisional medical registration with the Australian Health Practitioner Regulation Agency (AHPRA). Visa application was not complicated, as everything was done via the Australian immigration website. The entire application process set me back a few hundred pounds.

I arrived in Melbourne just five days prior to my starting date. I was greeted by glorious warm sunshine as it was summer in January. I was fortunate that a family friend offered me his spare bedroom while I looked for a place to rent. Setting up a bank account was pretty straight forward. Jet lag was a major problem for me for the first two weeks there.

The Training Structure

The junior doctors changeover in Australia occurs in February, which was when I started. The first day of work was just similar like anywhere else really; completing different forms, applying for the ID badge, car parking permit, orientation and brief summaries of the ward/hospital policies.

Box Hill Hospital is one of the seven hospitals for Eastern Health that covers East Victoria. It is the tertiary referral centre for all other hospitals in Eastern Health and a university teaching hospital. The hospital underwent major refurbishment in 2014.

The neurosciences department is mainly based at Box Hill Hospital, with both inpatient and outpatient services. This hospital runs a 24 hour stroke thrombolysis service, neurodiagnostics, neuropsychology, neuroradiology and outpatient clinics. There are usually 20-25 inpatients at any one time. The clinics cover MS, stroke, general neurology, neurocognitive and epilepsy.

A neurology consultation service and outpatient clinics are provided at Maroondah Hospital, which is a district general hospital. The movement disorder outpatient clinic is delivered at Wantirna Health, which is a smaller hospital unit mainly for palliative care and medicine for the elderly. Neurosurgery services are undertaken in collaboration with Royal Melbourne Hospital, Austin Hospital or St Vincent's Hospital within Victoria.

My rotation consisted of four-monthly blocks. I started off with two blocks at Box Hill Hospital, which were the general neurology block, followed by stroke. My last four months were based at Maroondah Hospital and Wantirna Health. My role as a registrar was similar to the UK. There were daily morning ward rounds, with the charge nurse and allied health professionals. Consultant ward rounds were conducted twice weekly. I would go around with the junior doctors on the other occasions. The general neurology block includes inpatient consultations; either telephone advice or reviews, and general neurology clinics.

My stroke block was definitely the busiest as Box Hill Hospital is an active stroke thrombolysis unit. Ward rounds were constantly disrupted with acute stroke calls, which need to be attended urgently at the emergency department by the stroke team. All stroke cases were discussed with the stroke consultant on duty who was easily reachable with a phone call. I recall thrombolysing up to four patients within normal working hours on one occasion.

On calls were usually 1 in 3 to 4 depending on how many colleagues were on leave, and includes out of hours stroke thrombolysis. The on calls were generally busier. I was called back after midnight on numerous occasions, mainly for acute stroke calls. All registrars on the on call rota are entitled to a half day off once a week, which was helpful in catching up with rest.

There were many different teaching sessions, covering a wide range of neurology curriculum topics throughout the year. There were weekly neurology grand rounds and neuroradiology meetings. There was also monthly "Brain school" conducted via video conferencing. For trainees in Victoria only (like me), there were monthly early morning teaching sessions, starting at 7.45am, that ran at different locations in Victoria.

Differences and New Experiences

The Australian health care system differs from the UK because both government and private health care coexist. Medicare Australia provides universal health care and is partly funded by an income tax surcharge of a person's taxable income. Certain exemptions do apply, of course. An extra Medicare surcharge applies to individuals with higher incomes do not have the appropriate level of private health care insurance. My understanding was that this was to encourage individuals who can afford it to take up private health care insurance, and reduce demand on public hospitals. Medicare entitles residents to free treatment as a public patient in a public hospital. For outpatient services, residents could receive free or subsidised treatment from specialists, depending on the method in which the specialists charge for the services provided. Medicare will cover a certain percentage of the service provided by specialists. The patients would have to pay for the balance, unless they have private insurance that could help cover the charges incurred.

Interestingly, ambulance services, whether emergency or not, within Victoria are not covered by Medicare. Therefore, anyone who uses the ambulance service will need to pay for the service, except for

patients who have arranged for ambulance cover with a health insurance fund or hold certain exemption cards.

Just like in the UK, neurology registrar jobs are competitive. However, the training programme is shorter. It runs over three years, with two years spent in core training posts, and one year in a non-core training post, which may include research or subspecialty clinical work.

Time sheets. This was new to me. Salary in Australia was paid every two weeks. All doctors have to fill in a time sheet fortnightly to ensure the correct amount is paid. The time sheet records were particularly important for the out of hours on-call times as one is paid according to the hours that you are in the hospital.

For me, being actively involved in the stroke service was a valuable experience. I gained so much confidence in assessing acute stroke patients, carrying out thrombolysis and referring on for endovascular clot retrieval when indicated. The stroke block also helped sharpen my skill in interpreting acute CT brain imaging including vascular and perfusion scans.

On top of that, I continued to build on my general neurology knowledge and experience throughout the year.

Life Outside Work

Melbourne really does live up to its reputation of being one of the world's most liveable cities. There were many things to do and see. Everyone was friendly and upbeat. Despite the many late nights, early morning calls back to the hospital and sleep deprivation, I felt I had a good work and life balance. I suspect that the weather played a huge part in it. The milder winter months and hot sunny summer allowed me ample opportunities to engage in different outdoor activities.

I am a huge foodie. The food and coffee culture in Melbourne was amazing. The food was interesting, as it comprised of inventive fusion cuisines. There were endless cafés along the Melbourne laneways and food markets to tempt any appetite. Seafood was extremely fresh and affordable there. Imagine freshly shucked oysters for AUD 1 each at the fish market daily!

Food culture aside, Melbourne also has multiple art and design markets held over the year. It was great fun visiting these markets and getting myself immersed in all the creativity.

Conclusion

I thoroughly enjoyed my experience in Melbourne. I would recommend anyone who is keen to work in Australia to not hesitate. Yes, the application and moving process might be tedious…but the entire experience was unforgettable, eye opening and absolutely worth it.

Dementia Academy launches Interactive Pathway Toolkit to support clinical practice

There are around 800,000 people with dementia in the UK and the number of people affected is expected to double by 2040 with economic costs likely to treble from the current estimated costs of £23 billion per year (Alzheimer's Disease Society). The need for integrated care planning has never been more needed as society struggles to cope with the increasing numbers of people living with dementia.

Based on an initial idea from Faculty member Dr Iracema Leroi, February has seen the Dementia Academy launch a new multi-level Dementia interactive care pathway toolkit that we hope will be a useful resource for everyone working in dementia care. The work is a partnership resource between the Dementia Academy, The University of Manchester/Manchester Mental Health and Social Care Trust Institute of Brain, Behaviour and Mental Health, and NHS Greater Manchester and Eastern Cheshire Strategic Clinical Networks, as well as other local organisations.

It had been identified that there was a significant gap in the joined-up knowledge of how professionals can support people living with dementia and their caregivers. Professionals require easily accessible, pragmatic, and dynamic information about dementia which can be tailored to the specific needs of their local populations to assist in supporting people with dementia at all stages of the condition and in various settings.

Based on other pathway models developed by the Parkinson's Academy, an Expert Reference Group was estasblished led by Dr Iracema Leroi, Sue Thomas and Dr Tony Burch, a London GP now working in GP education with Health Education London. Via the setting of two consecutive day-long Dementia MasterClasses which were supported by the NHS England National Clinical Director for Dementia Prof Alistair Burn, an overall framework outline was developed to elicit the knowledge, expertise and opinions required to develop draft versions of the interactive care pathway. The format of the pathway was based on previous successfully implemented care pathways for other conditions like Parkinson's.

Using a modified Delphi technique the contents were elicited using various methods at the Dementia MasterClass including: (1) didactic lectures from experts in the field; (2) small break-out group consensus discussions prompted by prototype clinical cases drawn from various care settings; (3) a facilitated panel discussion of multi-disciplinary experts regarding 'crisis points' in community setting; and (4) small group workshops regarding key psychosocial support issues, each led by a relevant expert. In the first MasterClass, the basic content was agreed upon by group consensus.

The information was captured by field notes and video recording and transcribed into the interactive format by the pathway lead Sue Thomas, and fed back to the group for approval of content. In the second MasterClass, two months later, and with a different group of expert professionals, the first draft of the pathway was presented, the content sharing activities repeated, and specific feedback on the draft pathway requested from the professionals before eliciting the input from patient and caregiver stakeholders in an informal focus group setting. This led to a second and third iteration of the pathway.

Content identified as essential has been obtained by working in partnership with the NHS Greater Manchester and Eastern Cheshire Strategic Clinical Networks and also includes contributions on aspects of care for example around delirium, anticholinergic burden and end of life care. Experts in each MasterClass were drawn from the following care disciplines: geriatric psychiatry, mental health nursing, primary care (GPs), geriatric medicine, neurology, occupational therapy, social work, third sector, emergency services (police and ambulance), commissioning and policy leaders.

The output is an Dementia interactive care pathway toolkit based on what participants felt would be of most use to them in both providing and commissioning dementia services. The toolkit uses the England Dementia Pathway Transformation Framework 'Well Pathway for dementia' including care pathway guidance for GPs and clinicians on:

- **Preventing Well** – Prevention and pre-diagnosis
- **Diagnosing Well** – Accurate, timely diagnosis and treatment and case finding
- **Living Well** – Immediate post-diagnosis period and ongoing post-diagnostic support
- **Supporting Well** – Health and social care, advocacy, hospital treatment etc.
- **Dying Well** - Palliative and end of life care, preferred place of death

The development process has included consultation and participation with patients and carers, ambulance, police and social services and we hope the overall pathway will be useful to other localities and professionals.

The pathway is highly adaptable to incorporate local care needs and guidelines as well as to capture updates in care practices. In the growing field of dementia care, an Interactive Dementia Pathway Toolkit that this adaptable and dynamic will improve the care of people with dementia and their families, particularly in primary care settings and we would welcome feedback on its usefulness in clinical practice.

The Dementia Academy's next expert training MasterClass will be held in October 2017. To find out more visit: www.dementiaacademy.co

The Neuroethics of Biomarkers

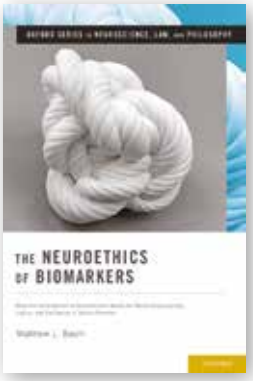
What the development of bioprediction means for moral responsibility, justice, and the nature of mental disorder

Biomarkers have become an integral part of clinical practice in some spheres of neurology, such as dementia where they are enshrined in diagnostic criteria for Alzheimer's disease as part of a clinico-biological (as opposed to an older clinico-pathological) definition of disease. The hope is that identification of disease in preclinical phases using predictive biomarkers may facilitate preventative treatment. But objections may be raised, for example to medicalising those who are currently well. The ethics of biomarker use in neurological and psychiatric disorders is explored in this volume by Matthew Baum, a Harvard MD-PhD trainee.

Addressing the bioprediction of brain disorder, the author argues for a reorientation of the medical concept of "disorder", rejecting the old binary or categorical formulation (disorder/normalcy) in favour of a probabilistic model based on present and future risks of harm. This is justified in part by the belief, undoubtedly true, that "There is no a priori justification for believing that biomarkers will map cleanly onto diagnostic categories arrived at by historical accident" (p. 46). The result is a proposal for a "probability dysfunction" model in which disorders are conceptualised as graphs of probability over time, the area under which would help to separate out self-limiting disorders from those with low probabilities of harm over longer time periods.

"Risk banding", based on the shape of the probability function, is the strategy advocated to determine the necessity or otherwise for response. This is illustrated with respect to bioprediction of future psychotic episodes and dementia (Chapter 5). This "risk of harm" approach is not seen as a fracture with past practice, since "Diagnosis is application of heuristic categories that capture a risk of harm associated with biological variation" (p. 125). The probabilistic claims of biomarkers may be used as a form of Bayesian updating. But will patients accept this reformulation?

This thought-provoking book will particularly appeal to those of a philosophical bent, rather than those who just want to know about biomarkers. It is not a book for dipping into during the interstices of the outpatient clinic, although the author must be commended for making the material accessible, his text is highly readable (and sometimes funny). Some clinicians will perhaps have little interest in the ramifications of predictive biomarkers for legal practice and societal distributive justice (when is biopredicted risk morally significant?), although even here there are interesting learning points: the discussion of prediction of seizures and driving is particularly pertinent. Furthermore, I was amazed to learn that in law the appeal to the "reasonable man" is regarded as an "objective" test, although the author rightly points out that this is almost always subjective in that it relies "almost exclusively on common sense and the persuasion of skilled law professionals to do this Bayesian updating" (p. 138). Whatever deficiencies there may be in medical (neurological) practice, at least we are attempting to put it on a research-based evidential footing.



Author: Matthew L Baum
ISBN: 978-0190236267
Published by: Oxford University Press
Price: £38.99
Pages: 206

Reviewed by: AJ Larner, Cognitive Function Clinic, WCNN, Liverpool, UK.

The Brain: A Student's Self-test Colouring Book

I had two motives for reviewing 'The Brain: A Student's Self-test Colouring Book'.

Firstly, seeing well-learnt knowledge presented in a new way is useful preparation for teaching and it so happens that I have recently had to take responsibility for pre-clinical Neuroscience teaching. And secondly, I have always taken (childish) pleasure in reading encyclopaedias designed for children. The latter is generally manifested as taking a few minutes longer than strictly necessary in leafing through such volumes in bookshops when deciding on a purchase to offer as a gift to some unsuspecting young relative.

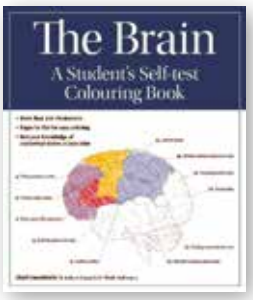
For the mature clinician or scientist of the nervous system, this book may be the literary equivalent of Lucozade. But few of us have such stamina or such sophistication of the palate that we can't get some refreshment, or even pleasure, from an occasional sip of fizzy pop.

Unsurprisingly, there were moments when the need for a more sophisticated beverage was felt. In discussing the conduction of the action potential, the term 'saltatory' was said to derive from the Latin for 'to dance', which got me 'jumping'. At one point, the dorsal root was mislabelled as the dorsal horn. The medial lemniscus was omitted from the section of text concerning somatosensory pathways.

For me, the biggest missed trick in terms of providing depth to the reader's learning was the failure to distinguish either in the drawings or accompanying texts those areas that are juxtaposed largely for reasons of parallel development, from neighbouring regions that are intimately linked in function. The basal ganglia provide a good example: the caudate and putamen are both functionally part of the neostriatum but separated by the anterior limb of the internal capsule, whose constituent fibres must traverse the deep grey matter of the forebrain from the origin in the cortex to their destination in the pons and elsewhere. I understand that one has to draw a line on descriptions of function in a book about structure; I just think they drew it too soon.

For the medical neurologist, coronal and axial sections through the diencephalon and basal ganglia are perhaps less like the backs of our hands than for surgeons and radiologists. I found those pages the most useful.

All in all, this is a modest book – modestly priced and quick to leaf through. I can recommend it to by peers, especially those wishing to consolidate their Anatomy before teaching.



Consultant Editors: Dr Joshua Gowin and Dr Wade Kothman
Published by: Quad Books
ISBN: 978-0857624635
Price: £14.99
Pages: 192

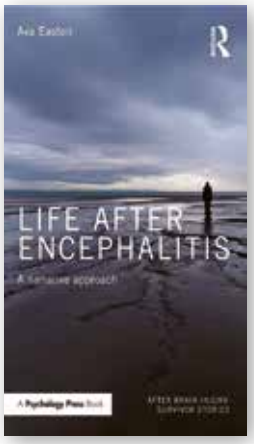
Reviewed by: Rhys Davies, Consultant Neurologist, Liverpool, UK.

Life After Encephalitis: A Narrative Approach

Ava Easton has been Chief Executive of the Encephalitis Society since 2011, having worked for the charity since the year 2000. She and her team have made the charity highly visible and successful, with fundraising efforts including initiating World Encephalitis Day (22nd February), and other innovations including neuropsychological support for patients with encephalitis who cannot access services locally. Here she delivers a necessary and timely book on encephalitis for people (not only the patients) affected by viral or autoimmune encephalitis. The book opens with a foreword by the journalist Simon Hattenstone, who describes his own childhood illness and puts it best, "I always thought I was a one-off; unique. Ava Easton makes it clear that there is nothing unique about encephalitis". This book is among other titles in a series – *After Brain Injury: Survivor Stories*, edited by Barbara Wilson – that explores in turn: life after encephalitis, survivors' stories after brain injury, loss of identity, and surviving brain damage after assault.

The book delivers the meaning of what it is to have had encephalitis through the tales of patients and their relatives. There is medical and scientific commentary to fill in some gaps and support the stories, and chapter 2 is a clear stand-alone primer on encephalitis, but this is not a dry textbook. We hear accounts from and chapters devoted each to, and named: 'the survivors themselves – see Ross's story below, the spouse, the parents and the children'. Though this is a book as part of a series devoted to survivors and surviving brain injury, the book doesn't shy away from tackling the stories of those who have lost a loved one due to encephalitis in chapter 7, in Johnny's story. What follows then are a couple of chapters on Ava's central thesis: the power of the narrative to communicate and affect therapeutic change after an illness such as encephalitis. This is a balanced view and tackles some of the pitfalls, including lost stories, lost memories, consent, bias and potential harms in practice. I read the book while also reading the similarly powerful *Refugee Tales* (ed David Herd and Anna Pincus, Comma Press, 2016), and, this being the centenary of Constantin von Economo's description of encephalitis lethargica in 1917, Joel Vilensky's historical account (OUP 2011), with a chapter on self-reports of people with encephalitis lethargica from the last century.

This is an essential book, not only for those recovering from encephalitis, those relatives or friends or professionals involved in the care of people with encephalitis, neurology wards and clinic areas, but also the general reader interested in knowing more about the impact of sudden acquired brain disease on people through patient narratives.



Author: Ava Easton
ISBN: 978-1138847200
Published by: Psychology Press
Price: £19.99
Pages: 200

Reviewed by: Michael Zandi, ACNR co-editor, Honorary Consultant Neurologist National Hospital for Neurology and Neurosurgery, Queen Square, London.

This is an edited excerpt from Ross's Story in *Life After Encephalitis* by Dr Ava Easton (pages 55-61). Published in 2016 by Psychology Press. Copies can be purchased from The Encephalitis Society (www.encephalitis.info) or from Amazon, among other suppliers.

Ross's Story

Ross has been feeling unwell for some weeks now, and is being treated for depression and anxiety…

"My dad asked me to go and see his GP. It was probably the tenth visit to a GP in the space of six weeks, but I agreed. This GP prescribed beta-blockers and another anti-depressant. This would be the third anti-depressant drug I had been prescribed in six weeks. I had seen four different GP's all of whom had different ideas about how to treat me. How did I know who to believe?

The 10th of July was a very bad day…I kept telling my family there was something wrong with me; that it couldn't just be depression. I started hitting my head against walls to try and knock the burning out of it...I was screaming. I was crying. I was in agony. I was convinced that I was about to die. My parents called 999 and I was taken to hospital for chest x-rays and CT scans of my head. I spent the night terrified that the lumbar puncture that they were planning to do would go wrong and I would end up disabled after it. That next morning a doctor told me that there was nothing wrong with me physically, they weren't going to do the lumbar puncture, and that I had a mental problem. I was discharged.

I returned to my parent's home…the tingling started… it was going to happen again. I lost all sense of what was right in the world. The screaming started again…I couldn't think, and worse, now I couldn't remember. I couldn't picture people's faces in my mind. I started shouting out friends and family names as I thought that if I didn't I was going to forget them. It literally felt as if memories were draining out of my brain. I was taken back to hospital for the second time in 24 hours…I was discharged for a second time, and the local crisis team visited daily.

Things began to feel a little more under control. I was referred to a psychologist, and I was prescribed an anti-psychotic medication. This made me very dozy but at least it controlled things.

By now I had spent months convinced that it couldn't be a mental health problem. I had tried everything I could to make myself happy: I had reduced work, taken breaks away, but nothing was helping. Every morning I started the day questioning what the point of the day was; what the point of existing was.

I made it through the next few weeks, then something happened. Life was turning very dark. On the 26th August I was at home on my own. I took a belt, wrapped it around my neck and wedged the end in the top of a closed door. I let the belt take the weight and I was happy that it would soon be over. Fortunately the belt snapped. That night my girlfriend found out what had happened. She rang the crisis team who were close to taking me away with them, but, they didn't.

On the 30th we were due to fly to Crete. The crisis team said even thinking about going was a bad idea. However, I was determined to try, just to keep some normality in my life. We got in the car but didn't get far before the panic started. I was trying to get out of a moving car, and my girlfriend turned the car round and headed home. The crisis team were called again – I was placed under section two of the mental health act, and taken to hospital.

I was transferred to a higher security hospital where I remained for seven weeks. My medication was increased to keep me stable and in the October I was transferred to a general hospital, where I was scheduled to see a sleep specialist since my sleep was getting more bizarre.

The sleep specialist looked at me in a new way – in a way other doctors hadn't. I owe him a lot, probably my life. After being with him for hours, he wrote to the mental health hospital saying I should be reassessed and probably taken off all of the drugs I was on. I was referred to a neurologist, and spent a month in the neurology ward with the consultants searching for an answer. Finally, the test for anti-NMDA receptor encephalitis returned positive. My brain was seriously unwell, and I was immediately started on Intravenous Immunoglobulin (IVIg) treatment.

The 8th of November 2014 is the first day that I remember since the middle of August. I remember lying in a bed thinking where on earth am I? In front of me was a notepad with a note from my mum saying I was in hospital and that it was the middle of November.

Looking back, the biggest clue to there being something wrong were my memory issues. With the depression and anxiety we kept finding possible reasons for them, but the memory loss? That was unexplainable. I started to forget pin numbers, passwords, directions, how to use maps, how to put up a tent, I couldn't remember names or faces. The only explanation anyone provided was I was so stressed that I was just shutting down.

I don't hold a grudge about what I went through, I just wish they had thought about, and looked for, a cause outside of their own discipline earlier on. Mental Health and Neurology both work with the brain – stronger links between the two may have saved me months of misdiagnosis."

The Encephalitis Society

The Encephalitis Society began life in 1994 when it became clear there was little to no information or support for people affected by encephalitis and their families. Today The Society has the vision:

To live in a world where Encephalitis is as rare as it possibly can be given its eradication is unlikely, and that those affected and their families, have access to early diagnosis, excellent management of their condition, timely access to rehabilitation and other forms of social support.

Its primary aim is to 'Improve the quality of life of all people affected by encephalitis', and The Society achieves this in three primary ways:

- Supporting adults and children affected by Encephalitis, their families and carers by providing advice and evidence-based information and working at a national and international level to improve services.
- Raising awareness about the condition and its subsequent problems among relevant professionals, statutory agencies and the general public.
- Conducting research and work in partnership with other researchers and their establishments.

The Illness

Encephalitis is inflammation of the brain. The inflammation is caused either by an infection invading the brain (infectious); or through the immune system attacking the brain in error (post-infectious or autoimmune encephalitis).

Encephalitis is a thief, one that has quietly been at work for hundreds of years, robbing families of their loved ones, and even in those families where the person survives, it often robs them of the person they once knew. Encephalitis steals their capacity to remember as well as their personalities and the types of abilities we all generally take for granted: concentration, attention, thinking, judgement, inhibition. For many there are additional outcomes such as epilepsy and levels of fatigue so great that returning to work or education are mere pipe dreams. This is of course, where the person survives, many don't.

For many years statistics around incidence were scarce to non-existent and encephalitis was side-lined into the silo of 'rare disease'. However due to great work conducted by many committed researchers and their institutions over the last decade we now know there are around 6000 people diagnosed with encephalitis in the United Kingdom alone each year.[1] That's 16 people every day. The authors suggest this may be an underestimate. Not only that but it is thought that, and again this is an underestimate, that encephalitis is costing the NHS around £40 million a year. A figure that does not include the costs of rehabilitation, long-term care, and the loss to the economy from those of working-age unable to return to work.

Therefore encephalitis has a higher incidence than motor neurone disease and certain forms of meningitis.[2] Yet, despite encephalitis being more common, these conditions continue to receive a much higher clinical and public profile. Invariably people have not heard of Encephalitis unless it has happened to them or they are caring for a survivor.

Support and Information

Support and information for survivors and family members is critical. Encephalitis is a complex condition to diagnose and manage. Therefore a lot of the information surrounding it is often complex for the uninitiated. The Society takes this information and restructures it in ways that are meaningful for those new to the condition. Information consists of factsheets, newsletters, and guides for adults and families. All the information provided is evidence-based, peer-reviewed and accredited by NHS England. Therefore patients and professionals alike can be assured about the reliability of the material. The Society also provides direct support via phone, email, skype, and chat online. Other services include connecting people in a similar situation, and a burgeoning global network of volunteers. There are also moves afoot to provide more long-term and social support to patients in evolving encephalitis clinics in Oxford and London.

More recently The Society has launched The Encephalitis Society Neuropsychology Service. This operates in the knowledge that neuropsychology is perhaps the primary intervention that, if a person survives, can help support The Society's primary aim of improving people's quality of life. The service is operated by a consultant Neuropsychologist and is not established to duplicate the work of the many excellent services around the country. The service is there primarily to pick up people in areas where a neuropsychology service does not exist, and also in areas where waiting lists are detrimental to maximising a person's potential recovery and rehabilitation (www.encephalitis.info/support/neuropsychology-service).

Awareness

The Society's primary awareness drive is World Encephalitis Day on 22nd February each year (www.worldencephalitisday.org). This global day was launched in 2014 and to date has reached more than 20 million people since its inception. 2017 sees landmark buildings and businesses around the world illuminating in red, in order to drive awareness about the condition, through digital and social media channels. There are lots of other ways each year for people to get involved by engaging with their #RED4WED and #ShowYouKnow campaigns as part of the day's activities.

Research

The Society is involved with a plethora of research studies including two randomised control trials in Oxford and Liverpool. The Society provides a substantial amount of information for professionals each year including an 'Advances in Research' guide which acts as an annual archive of the year's most prominent research into the condition. In addition there are a range of initiatives engaging with junior doctors and early years' researchers such as essay prizes and travel bursaries. The Society also contributes to research financially and has just launch a co-funded PhD fellowship with The University Liverpool. There is also a popular annual conference held in December in London each year and which brings interested professionals up to speed with the latest in the condition.

The Society strives hard to meet its aims and objectives. They achieve a huge amount with few resources, a small team, and with the voluntary contributions of its Board of Trustees and Scientific Advisory Panel.

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1. Granerod J, Cousens S, Davies NW, Crowcroft NS, Thomas SL. *New estimates of incidence of encephalitis in England.* Emerging Infectious Disease 2013;19(9).
2. Easton, A. *Life After Encephalitis: A narrative approach* (2016). Routledge. Oxon

To find out more or get involved visit www.encephalitis.info

...6000 people are diagnosed with encephalitis in the United Kingdom alone each year. That's 16 people every day...Not only that but it is thought that encephalitis is costing the NHS around £40 million a year. A figure that does not include the costs of rehabilitation, long-term care, and the loss to the economy from those of working-age unable to return to work

Royal College of Psychiatrists Faculty of Neuropsychiatry Annual Conference

Conference details: 15th-16th September 2016, London, UK. ***Report by:*** Dr George El-Nimr, Consultant Neuropsychiatrist and Academic Secretary to the Faculty of Neuropsychiatry at the Royal College of Psychiatrists. ***Conflict of interest statement:*** None declared.

On the 15th and 16th September 2016 the Headquarters of the Royal College of Psychiatrists in London witnessed an exceptionally successful annual conference for the Faculty of Neuropsychiatry. The event was oversubscribed, with speakers and delegates from many countries around the world.

International perspectives and a number of advanced research initiatives were presented. The conference also explored how medical humanities and modern science can work together to inform day-to-day practice and future thinking.

The conference opened with an introduction from Professor Eileen Joyce, Chair of the Faculty of Neuropsychiatry before Dr Wendy Burn presented an overview of the Gatsby/Welcome Neuroscience Project. This two year initiative by the Royal College of Psychiatrists aims at introducing a modern neuroscience perspective into psychiatrists' clinical work. This involves reshaping psychiatric training to incorporate recent progress in basic and clinical neuroscience.

The following session addressed the topic of alcoholic brain damage and was chaired by Dr El-Nimr, the Faculty's Academic Secretary. The first talk was on Neuro-psychopharmacology of Alcoholism and was presented by Professor Anne Lingford-Hughes, Professor of Addiction Biology at Imperial College London and Chair of the Academic Faculty of the Royal College of Psychiatrists. Professor Lingford-Hughes' research has focused on using PET and fMRI neuro-imagining and neuro-pharmacological challenges to characterise the neurobiology of addiction. This talk was followed by Professor David Nutt's presentation on "stopping alcohol from damaging our brains; a national perspective". Professor Nutt emphasised that alcohol is actually the leading cause of death in men under 50 years in the UK today. He explained how we have got to this unwelcome position and proposed proven approaches, such as minimum unit pricing and restricted sales, to rectify it.

Professor Kenneth Wilson then talked about how services for patients with alcohol related brain damage can be established. Professor Wilson, a retired Professor of Old Age Psychiatry at the University of Liverpool, gave an overview of service provision for people with alcohol related brain damage, providing a financially viable case for provision and generalisation of the service.

The second plenary session covered important issues related to neuroscience and humanities. Professor Michael Kopelman, Emeritus Professor of Neuropsychiatry, King's College London considered how brain and culture can influence both neurological and psychogenic forms of amnesia. Dr Ken Barrett, retired Consultant Neuropsychiatrist then gave an inspiring talk on the changing views on the adaptability of the brain. Dr Barrett considered how in the last 30 years the mainstream view of the brain has shifted from the hard-wired, immutable, inflexible and functionally localised position to something more dynamic, adaptable and functionally complex.

Professor Andrea Cavanna of Birmingham University gave a neuro-philosophy perspective on consciousness in neuroscience and culture. The increasing appreciation of neuroscientists of the conscious experiences and also the increasing interest of philosophers in neuro-scientific data to refine theoretical positions were highlighted.

The afternoon session included a number of clinical and medico-legal seminars. Seminars covered Management challenges in functional neurological disorders, facilitated by Dr Niruj Agrawal, talking to the Court of Protection about the brain, that was jointly delivered by Dr Janet Grace and Mr Joe O'Brien. A seminar on sleep classification was led by Dr Irshaad Ebrahim.

Following on from the seminar sessions, Professor Alasdair Coles (Professor of Neuroimmunology at the University of Cambridge) talked about behaviour and neuro-immunology. Professor Coles addressed the relationship between the brain and immune system and how they interact at multiple levels. The potential impact of this on therapeutic strategies was also highlighted. The role of anti-neuronal membrane antibodies in psychosis was discussed.

Professor Josef Priller, Professor and Chair of the Department of Neuropsychiatry at Charité, Germany presented advances in Huntington's disease research and how this can be translated into practice. Recent developments in the treatment of Huntington's disease were presented, with particular focus on the neuropsychiatric symptoms. Dr Valerie Voon of the University of Cambridge then talked about new advances in understanding and managing neuropsychiatric symptoms of Parkinson's disease. Recent studies were focused on dopaminergic, serotonergic and noradrenergic systems and interventional studies relevant to psychosis, apathy, impassivity and impulse control disorders.

On Friday, Mr James Piercy gave an inspiring talk about his journey with brain injury, being on the receiving end of care both in the acute and chronic phases.

The plenary covered the latest developments in neuropsychiatry services in a session entitled "Neuropsychiatry from around the Globe". Dr Esan talked about Neuropsychiatry in Anglophone countries of West Africa. Dr Wong followed with an interesting talk entitled "The budding Neuropsychiatry service: Sharing of experience from Hong Kong and the East Asian region". The impressive British Columbia Neuropsychiatric programme, based in Vancouver, Canada was presented by Professor Hurwitz and Dr Hassan. Building on this insight into what happens in different parts of the world in terms of neuropsychiatry services, Dr Faruqui, immediate past Chair of our Faculty gave a presentation on how our Faculty developed international collaboration in delivering clinical neuropsychiatry training.

Later in the morning, a number of trainees presented their research work in the context of "trainee award presentations" session. This covered specific clinical areas including autistic spectrum disorder, the use of transcranial direct current stimulation in Lewy Body dementia, the retrospective implications of NMDA receptor-antibody encephalitis, neuropsychiatric symptoms in multiple sclerosis and the neuropsychiatric outcomes in phenylketonuria.

A collection of seminars were then delivered by a number of eminent clinicians. Hurdles in establishing services for brain injury was presented by Drs Raymont, Mueller and Brooks. Professor Turk and Drs Garg and Mukjerjee held a seminar on behavioural phenotypes. Conference delegates also appreciated a seminar delivered by Dr Mueller on EEG in neuropsychiatry clinic, particularly addressing questions that clinicians are "too embarrassed to ask!". The day concluded with a lively debate on whether sleep disorders should be managed by psychiatrists. Professor Shapiro supported the motion which was opposed by Professor Williams. Professor Williams has extensive experience in establishing sleep services and getting involved in various national and international sleep related initiatives. Professor Shapiro argued passionately that psychiatrists are best placed to manage sleep disorders. The day was closed by announcing the oral presentation and poster winners. In addition to a financial reward, winning trainees were able to publish their work in the Faculty of Neuropsychiatry official newsletter.

Excellent feedback was received from delegates, sponsors and speakers from different countries and disciplines. This year's conference will also be held at the Royal College of Psychiatrists headquarters on 14 and 15 September 2017.

70th Annual meeting of the American Epilepsy Society

Conference details: 2nd-6th December, 2016, Houston, Texas. ***Report by:*** Dr Seán J Slaght, Consultant Neurologist, Wessex Neurological Centre, Southampton. ***Conflict of interest statement:*** Dr Slaght's attendance at this Conference was organised and paid for by Bial. ***First published online:*** 6/1/17.

Americans always do things bigger and certainly the 70th Annual meeting of the American Epilepsy Society rose to the challenge. Almost 5000 delegates came together in Houston, Texas to share in the latest developments in Epilepsy, both clinically and from the research point of view.

Houston is the 4th largest city in the United States and like many American cities spread out over a vast area. The conference was held in The George R. Brown Convention Centre, in Downtown Houston, amongst the skyscrapers of banks, offices and hotels. As part of a delegation of British Epileptologists, it was with mixed feelings that we landed in Texas to find four days of rain and temperatures around 12°C in the daytime. We had all hoped for the usual Texan Autumn weather of 20-25°C and gentle sunshine, but a good bit of British weather certainly helped to keep us focused on the conference. The sun did come out on the final day to see us off.

Any conference this size has numerous parallel sessions. The highlights of the first day included the Epilepsy Specialist Symposium, this year focused on Epilepsy surgery and how to choose the right option for your patient. The Judith Hoyer Lecture delivered by Dr So was a summary of the history of research

into SUDEP, the current state of knowledge and where we need to go next, the contribution to this field by many British clinicians and investigators was highlighted. Among the many Special Interest Group (SIG) sessions the Global Health SIG was an insight into how American Neurologists are reaching out to help those in low-income countries, nearby and afar to improve their health systems.

The Presidential symposium on day two was titled Epilepsy Care: A Futurist View. Five experts in the fields of Genetics, imaging, anti-epileptic medications, bioinformatics and surgery were tasked with reflecting the current, state of the art in epilepsy care and where we might (or should) be in 15-25 years time. The Epilepsy therapies symposium followed with an update on new therapies for hard to treat epilepsy. The day was rounded off with the North American Commission Symposium Treatment of Epilepsy in Pregnancy.

The third day of the Conference centred on the Annual Course, a well thought out and planed all-day pedagogic course. This year it was centred on refractory epilepsy. Illustrated by four cases (infancy, childhood, early adult and elderly), the day explored the diagnosis (structural/genetic/etc), medical and surgical treatment and palliation in this hard to treat group of patients. In parallel to the annual course were investigator workshops and poster sessions.

Running throughout the conference were parallel investigator workshops and poster sessions, giving the opportunity to catch up on the latest research and network with like-minded clinicians and scientists. One of the highlights for me was the Lennox and Lombroso Lecture delivered by Dr Jean Gotman, a fascinating insight into how we may be able to combine EEG and fMRI to help better localise the focus of seizures to improve outcomes in Epilepsy surgery.

This was certainly a big conference, and it delivered in terms of excellent teaching and opportunities for networking. Despite the large size there was a friendly atmosphere, a feeling of collaboration and a buzz of new possibilities on the near horizon for our patients with Epilepsy.

PREVIEW: Pain Therapeutics 2017

Conference details: 17th Annual Conference: 22nd & 23rd, 2017. Interactive Workshop: 24th May, 2017. www.pain-therapeutics.co.uk

Created with an expert scientific advisory board, SMi's 17th annual Pain Therapeutics conference will hone in on the latest innovations and novel approaches to pain therapy and analgesic drugs as well as look at the practicalities of using animal models and translational biomarkers in pain research.

Aimed at an audience of scientific leaders and senior specialists in neuroscience, CNS, clinical operations and pharmacology, Pain Therapeutics 2017 will keep attendees at the forefront of medical breakthroughs to adapt to the growing need towards minimising opioid dependency and new drug discovery.

Presentations from a selection of hand-picked pharmaceutical companies currently developing novel treatments in pain, will provide delegates with an understanding on key topics such as product formulation; opioid addiction; translational pain research; and breakthroughs in drug discovery.

Interactive workshops and exclusive new findings from phase II clinical trials will be just some of the highlights at the 17th annual show when it returns to London this spring.

KEYNOTE SPEAKERS INCLUDE:

- Prof Anthony Jones, Professor of Neuro-Rheumatology, University of Manchester
- Dr Steven Kamerling, Therapeutic Area Head for Pain, Inflammation and Oncology, Zoetis
- Dr Joseph W. Stauffer, Chief Medical Officer, Cara Therapeutics Inc
- Dr Stephen Doberstein, Senior Vice President and Chief Scientific Officer, Nektar Pharmaceuticals
- Dr Iain Chessell, Head of Neuroscience, AstraZeneca
- Dr Randall Stevens, Chief Medical Officer, Centrexion Therapeutics Corp
- Dr Richard Butt, Chief Executive Officer, Apollo Therapeutics
- Prof Theo Meert, Head of Global Government Grant Office, Janssen Pharmaceutica NV
- Dr Narender Gavva, Scientific Director, Amgen
- Dr Thomas Christoph, Head of Pharmacology and Biomarker Development, Grunenthal GmbH
- Dr Ian Bell, Principal Scientist, MSD, USA

The packed agenda also features talks from Lilly UK, Novartis, Pharmaleads, Mundipharma Research and more!

REASONS TO ATTEND IN 2017

- Awareness of new guideline on the clinical development of medicinal products intended for the treatment of pain
- Strategies and real case studies to minimise risk of opioid dependence
- Evaluate the translation gap with case studies from a pre-clinical and clinical perspective
- Explore the latest in the area of Neuropathic pain for 2017 with the latest case studies from top pharma companies
- Examine the use of animal models to study pain pathways

Visit the website for further details at www.pain-therapeutics.co.uk or contact the team on +44 (0)20 7827 6000 email: events@smi-online.co.uk

RMSANZ ASM 2016

Conference details: 16th-19th October, 2016, Melbourne, Australia. ***Report by:*** Damien Daniel B.Com MBBS FAFRM (RACP), Consultant Rehabilitation Medicine Physician, Geelong, Australia. ***Conflict of interest statement:*** None declared.

I'm sure I'm not shocking you when I say not all scientific conferences fulfil the promises of their themes/slogans. The inaugural Annual Scientific Meeting (ASM) of the Rehabilitation Medicine Society of Australian and New Zealand (RMSANZ), however, truly lived up to its theme. It was "Change. Challenge. Opportunity".

The RMSANZ ASM was held from October 16-19, 2016 in Melbourne, Australia. Delegates came from all over Australia, New Zealand, the Pacific Islands, South-East Asia, India and Sri Lanka, and even from as far away as Saudi Arabia. One of the wonderful benefits of the ASM was the opportunity to meet rehabilitation physicians from around the world, compare the systems we work in and the challenges we face, and to provide ideas from our different environments and perspectives.

The list of invited speakers was an impressive ensemble of rehabilitation physicians, medical specialists from other disciplines, and scientists from all over the world. A cast of eminent local RMSANZ members and allied health professionals supported them.

Dr David (DJ) Kennedy from Stanford University (USA) opened the meeting with a fascinating talk on how even the most basic statistics and analyses we use in our research might be flawed. This is despite conventional wisdom and wide acceptance. It was a great start to the conference, and reflected the theme beautifully. And it was an absolute paradigm shift for me.

For me suddenly the ASM was not just about the future – the changes that are coming, the challenges we will face and the opportunities that we may need to adopt. It also became about the changes we should be making now to our current practice, the challenges we should pose to the current status quo, and the opportunities we can create now, by changing our traditional way of thinking. Therefore the theme became active, not just passive.

The next day Professor Jianan Li from Nanjing Medical University (China) presented the George Burniston Oration to open the plenary, Rehabilitation in the Era of New Global Health: Challenges and Opportunities. He gave a fascinating insight into the development of rehabilitation medicine as a speciality in China. It is often too easy for current trainees and recent Fellows (myself included) to forget that the speciality of Rehabilitation Medicine was also only recently developed in Australia and New Zealand. Like China, we owe a great debt of gratitude to those who have gone before us and championed the speciality. Again the message coming through was "be active, not passive".

One of the most popular talks came next in the plenary Opportunity Knocks: Rehabilitation Physicians as Entrepreneurs. Dr Gaetan Tardif of the University of Toronto presented his experience of service development in Canada. He also introduced his team's latest innovation, a device for diagnosing obstructive sleep apnoea (OSA) that patients can use at home, with data downloaded to a central lab. OSA is not a traditional rehab area, which again perfectly reflected the theme of the ASM. The talk was inspirational and practical in equal measure. The device is yet to receive funding for market launch, but watch this space closely.

Research was, as it should be, a major feature of the conference. To our benefit it included a great deal of research presented by our allied health colleagues. At times this was done in partnership with rehabilitation physicians, but not always, revealing an opportunity gap. Based on the presentations I saw, we should definitely team up with our allied health colleagues more often in research projects. It will be to everyone's benefit.

A huge part of the programme for Australian delegates was discussion around the changing national funding model for disability support. The federal government's National Disability Insurance Scheme (NDIS) is the only scheme of its kind in the world. Its aim is to put the control into the hands of the disabled by providing them the funds for their needs (equipment etc.) to procure from providers of their choice. It's a paradigm shift for Australian disability services. We were fortunate to have the CEO of the NDIA (the agency that oversees the NDIS), Mr David Bowen, speak about the vision and the experience so far (in the test centres). He was followed by local Fellows, who talked about their experiences dealing with the NDIS system in these test centres. The juxtaposition was fascinating.

RMSANZ Special Interest Groups (SIGs) also met at the ASM. The RMSANZ SIGs cover a broad range of interests including MSK, neurological, amputee, care of the older person, and paediatric rehabilitation medicine. A new SIG, Pain, was formed at this ASM. In Australia and New Zealand, anaesthetists have traditionally dominated pain medicine, but more rehabilitation physicians are now actively getting involved.

In addition to the ASM proper, there were two full days of challenging pre-conference courses. These ranged from a Work Based Learning and Assessment workshop, a Neuroimaging examination workshop, to a full day on Strategic Thinking – Making Your Vision a Reality. Another innovative addition to the pre-conference courses was the Botulinium Toxin Certification Level 1 Injection Training, which ventured from the traditional "demonstration" model. It added hands on injections by participants under expert guidance. This was an innovation of the Society's Botulinium Toxin Expert Working Party.

The inaugural RMSANZ ASM was a great success. It lived up to its ambitious theme, "Change. Challenge. Opportunity". I trust it inspired many people, as it did me, to approach our current working lives in rehabilitation medicine with an attitude of actively seeking to change, challenge, and find opportunities.

PREVIEW: Dizziness: A multidisciplinary approach

Conference details: 6th-9th June, 2017, 33 Queen Square Lecture theatre, London WC1N 3BG.

This four day course will include instructional sessions, practical workshops, and case study analysis.

It is aimed at physicians, surgeons, scientists, physiotherapists and allied health professionals who evaluate, diagnose and manage patients with dizziness and/or imbalance. The course is run by an international, multidisciplinary faculty, which includes both highly experienced clinicians and researchers.

Teaching level is intermediate to advanced. The course will be best suited to those with an initial understanding of the vestibular field and will serve as an update and refresher course to those with an advanced knowledge of the vestibular field. The attendance fees are as follows: consultants (medical/non medical): 4 days £750. All others: 4 days £500. Single day: £200

Keynote speakers include: Profs Michael Halmagyi, Linda Luxon, Jeffrey Staab, Sue Whitney and FlorisWuyts.

For more information see the course website at https://queensquaredizzycourse.com
Email: thedizzinesscourse@uclh.nhs.uk
T. +44 20 3456 5025

The Encephalitis Society Professional Seminar 2016

Conference details: 5th December 2016, London, UK; ***Report by:*** Dr Ester Coutinho, Neurologist and DPhil candidate, University of Oxford, UK. ***Edited by:*** Dr Ava Easton, The Encephalitis Society. ***Conflicts of interest:*** None declared.

I was among the many attendees of The Encephalitis Society Professional Seminar and I am very pleased to report the tremendous success of the event. The seminar, organised under the theme "New frontiers - Neurology & Patient experiences", was the perfect platform for national and international experts to share their most recent and exciting research. The event was marked by the attendance of many newcomers (myself included!), from a variety of backgrounds: scientists, healthcare professionals, lawyers and charity members. Undeniably, this was a testimony to the efforts of The Encephalitis Society in promoting a multi-disciplinary network, working together for the common goal of improving the life of patients affected by encephalitis.

The afternoon started with a warm welcome from Dr Ava Easton, CEO of the Encephalitis Society and Professor Tom Solomon, Chair of the Encephalitis Society Professional Advisory Panel and leading expert in the field.

The first keynote address was by Professor Jean Paul Stahl, Head of the Infectious Diseases Department at the University Hospital in Grenoble, France, who presented the work developed by the French Encephalitis group. Professor Stahl shared data from a French national prospective study describing the French experience of encephalitis, and the results of an extensive aetiological investigation, and an assessment of risk factors associated with poorer outcomes. The study not only identified Herpes Simplex Virus and Varicella Zoster Virus as the major causes of encephalitis, but also highlighted the importance of lesser-known culprits, mainly tuberculosis and listeriosis, as causes of encephalitis in France, particularly among those with worse outcomes. In addition, the very high percentage of patients (over 90%) experiencing persistent memory, speech, cognitive or other problems, highlighted the need to optimise treatment strategies. Questions such as the optimal length of acyclovir treatment, the use of adjuvant steroid treatment and the management of sequelae were among those asked and will be pursued in the future by the group.

The next speaker, Dr Rachel Kneen, from the Liverpool Brain Infections Group, presented preliminary findings from the UK ChiMES (childhood meningitis and encephalitis) study, aiming to improve outcomes of children with encephalitis and meningitis and over 2900 patients recruited to date. Dr Kneen pointed out that management is still sub-optimal among children suffering from a CNS infection, many of whom have long-term consequences, such as behavioural, motor or feeding difficulties. To address these, the study group aims to create a clinical predictor tool to assist in early diagnosis and treatment. Concluding the presentation, we also heard about two ongoing randomised placebo controlled trials, the DexEnceph and the IgNiTE study, assessing the role of dexamethasone in herpes simplex encephalitis in adults and early treatment with human immunoglobulin (IVIG) in children with encephalitis of all causes.

Dr Ava Easton presenting award to Professor Barbara Wilson.

Professor Arun Venkatesan, from the Johns Hopkins Hospital, Baltimore, then presented data on a retrospective study using fluorodeoxyglucose-positron emission tomography/computed tomography (FDG-PET/CT) in autoimmune encephalitis. He highlighted the importance of finding a method to aid the early diagnosis of autoimmune encephalitis, given the implications for therapy and the heterogeneity of CSF and MRI findings. A retrospective review of 61 patients with autoimmune encephalitis revealed that most (85%) had abnormalities in their FDG-PET/CT imaging, the majority showing hypometabolism. In addition, this preliminary study pointed specifically to occipital hypometabolism as a potential biomarker for NMDAR encephalitis and even as a marker of severity in this disease.

Next, Dr Catriona McIntosh from the Brain Injury Rehabilitation Trust, Leeds, took us through a very complex and interesting clinical case. Dr McIntosh spoke of the complexities of neuropsychological assessment and rehabilitation in a Colombian patient with a right temporal lobe lesion due to encephalitis, who had a personal history of feral childhood and subsequent physical and emotional abuse. Despite the difficulties of such an exceptional case, it was reassuring to hear that targeted cognitive therapy was beneficial.

After a short break and light refreshments, the second keynote address of the afternoon was delivered by Dr Jim Morrow, a recently retired neurologist and a survivor of VGKC-complex antibody encephalitis. This was an extraordinary personal recount of the events that led to Dr Morrow's diagnosis, treatment and recovery.

Next, Dr Mark Ellul, from the University of Liverpool, spoke about the emerging mosquito-borne Zika virus infection and its implications for the nervous system. The Zika virus outbreak reached the news due to a recently established association with congenital microcephaly, but Dr Ellul further explored the spectrum of the infection that has been associated with an acute polyradiculoneuropathy, as well as myelitis, encephalitis or meningoencephalitis. Dr Ellul told us about an ongoing collaboration with Brazil that will lead to a full characterisation of the infection and its neurological manifestations and to a prospective case-control study to examine the role of Zika virus in Guillain-Barré syndrome.

Dr Sarosh Irani, from the University of Oxford, focused on antibody-mediated epilepsies. He spoke about a specific form of epilepsy associated with LGI1 antibodies, named faciobrachial dystonic seizures. The clinical description, treatment and outcome of a large cohort was presented. Importantly, we heard how early treatment with steroids or IvIg, but not antiepileptic drugs, appeared to effectively terminate the seizures and appeared to prevent cognitive impairment in the many patients that presented with FBDS prior to the onset of a more global encephalopathy.

Next, Nicola Wainwright, a specialist clinical negligence lawyer with Leigh Day, spoke on the role of lawyers in improving patient experiences. On the background of cases of medical negligence, Ms Wainwright spoke of learning lessons and strategies for preventing future adverse events.

Finally Dr Mildred Iro, from the University of Oxford, presented the results of an observational study on hospital admission trends of childhood encephalitis in England. This register-based, retrospective study analysed the epidemiology, time trends and incidence, of paediatric encephalitis in England over the past 33 years.

Concluding the day, Dr Ava Easton and Professor Solomon gave a joint talk entitled "Lessons from every side: learning from doctor and lay patient narratives".

Dr Easton reflected on the importance of bridging doctor and patient narratives. Perhaps a reflection of our modern times, medical literature is dominated by either research reports on large cohorts, where individual stories are lost, or clinical cases providing an objective recount of patient's symptoms and physical findings. Dr Easton reminded us how much health professionals learn from listening to patients' narratives, as well as how much patients benefit from that improvement in communication. Patients' concerns often go beyond the disability caused

Drs Domingo Escudero and Dr Jim Morrow, both Neurologists and encephalitis survivors.

by medical illness; this "hidden disability" can stem from lack of understanding or recognition of the disease by others, the absence of obvious risk factors and the impact of the disease on family life, among others factors. This introduction to the science of narrative medicine pre-empted the presentation of her book "Life after encephalitis: a narrative approach" which shares unique narratives of encephalitis survivors and their relatives.

Professor Solomon also had published a book "Roald Dahl's Marvellous Medicine", which introduces aspects of Dahl's life unknown to the many fans of the beloved author. Professor Solomon recalled his relationship with the author while working as a junior doctor in Oxford and caring for Dahl during his final weeks of life, and spoke about Dahl's fascination with medicine, reflecting many unfortunate personal and family events. Not only did Dahl himself suffer a head injury when his fighter plane crashed during World War II, but his son also suffered a severe brain injury leading to hydrocephalus, his daughter died of measles encephalitis and his wife suffered a stroke at a young age. We heard how, driven by these misfortunes and a rare intellect, Roald Dahl invented a valve for the treatment of hydrocephalus, was an active supporter of the implementation of measles immunisation and pioneered many stroke rehabilitation techniques, among many other contributions in several medical areas. Not only is this a fascinating story to read, proceedings from this book will support charities in areas of interest to Dahl, including the hosts of the seminar, The Encephalitis Society.

The Outstanding Achievement Awards for Excellence in Encephalitis Healthcare were awarded at the end of the day. These awards were created to recognise those individuals and organisations within medical health and research establishments, whose contribution made a difference to patients affected by encephalitis. Nominations had been made by healthcare professionals or researchers judged by The Encephalitis Society. The prizes were given in six different categories: Researcher to Assoc. Professor Sarosh Irani, University of Oxford; Rehabilitation Team to Ms Sue Brentall (Occupational Therapist), Mr James Pamment (Clinical Psychologist) and Dr Jessica Fish (Clinical Psychologist), The Oliver Zangwill Centre for Neurological Rehabilitation; Professional Allied Medicine to Ms. Alison Gummery (Neuropsychologist), University of Liverpool; and the Lifetime Achievement awarded, very deservedly, to Professor Barbara Wilson, Consultant Clinical Neuropsychologist, The Oliver Zangwill Centre, Cambridgeshire.

The afternoon ended with a Cheese and Wine Reception and a book signing session by Dr Ava Easton and Professor Tom Solomon, thus providing a relaxed and friendly environment for all attendees to meet and share ideas.

The 2017 conference to be held in London on the 4th December will be accepting abstracts in the Spring of 2017. For more information, visit www.encephalitis.info/research/conferences-and-events or email mail@encephalitis.info
Professional members (membership is free and takes two minutes to complete online) receive free places www.encephalitis.info/research/professionals/professional-membership/

To list your event in this diary email Rachael@acnr.co.uk by 6th April, 2017

FEBRUARY

Dementia Masterclass – The Neurology Academy
25 February, 2017; Dubai, UAE globalhealthtraining@pill.org.pk.
Book at http://bit.ly/2d03uQd

MARCH

ILAE British Chapter Epilepsy Neuroimaging Teaching Course
10-11 March, 2017; Chalfont St Peter, UK
https://billetto.co.uk/en/events/ukilae-epilepsy-neuroimaging-teaching-course
Contact Hannah E. members@ilaebritish.org.uk

Mild traumatic brain injury: Diagnostic, clinical and legal controversies
14 March, 2017; RSM, London, UK – www.rsm.ac.uk/events/pyh05

End of Life in Disorders of Consciousness Conference
March 24 2017; Royal Hospital for Neuro-disability – institute@rhn.org.uk – www.rhn.org.uk/eol

Neurology 2017 – Leading edge neurology for the practicing clinician
30-31 March, 2017; London, UK – http://www.ucl.ac.uk/ion/education/courses/other/neurology/ – T. 020 344 84139

17th Annual Course: Neuroradiology & Functional Neuroanatomy
27-30th March 2017; London, UK – E. skaaro3@ucl.ac.uk

APRIL

National brain injury conference: Out of the Comfort Zone – Difficult decisions following a brain injury
25 April, 2017; Hilton Newcastle Gateshead, UK – www.casemanagement.co.uk/events/jsp-conference-2017 – T. Steph or Millie on 0114 229 0100, E. conference@jspsh.co.uk

President's prize meeting and Neurology in Africa – guest lecture by Dr Hadi Manji
27 April, 2017; RSM, London, UK – Evening meeting. www.rsm.ac.uk/events/cnh05

MAY

MRCP PACES Course in Neurology & Ophthalmology Queen Square
13 May, 2017; London, UK – T. 020 344 84139

Pain Therapeutics
22-23 May, 2017; London, UK – http://bit.ly/2kuabLG

JUNE

Trigeminal Neuralgia Study Day for Healthcare Professionals
3 June, 2017; London, UK – www.tna.org.uk – T. 01883 370214

Non Specialist Multiple Sclerosis Masterclass – MS Academy
7-9 June, 2017; Sheffield, UK – info@neurologyacademy.org – T. 0845 338 1726
Module 2: 12 January 2018

Overcoming Personality Disorders in Brain Injury Rehabilitation
16 June, 2017; Ely, Cambridge, UK – Rachel Everett, E. courses@ozc.nhs.uk – T. 01353 652165.

JULY

Alzheimer's Association International Conference
14-15 July, 2017; London, UK – www.aaic2017.com

Functional symptoms in neurology & psychiatry
20–21 July, 2017; Royal Society of Medicine, London, UK
2 day meeting. www.rsm.ac.uk/events/cnh06

Alzheimer's Association International Conference
16-20, July 2017; London, UK – https://www.alz.org/aaic/

SEPTEMBER

Community Brain Injury – Developing a treatment plan for cognitive, communication and emotional changes
22 September, 2017; Ely, Cambridge, UK – Rachel Everett, E. courses@ozc.nhs.uk
T. 01353 652165.

NOVEMBER

Brain Injury and Alcohol
10 November, 2017; Ely, Cambridge, UK – Rachel Everett, E. courses@ozc.nhs.uk
T. 01353 652165.

Specialist Multiple Sclerosis Masterclass – MS Academy
22-24 November, 2017; Sheffield, UK – info@neurologyacademy.org – T. 0845 338 1726
Module 2: 15 June 2018

2018

FEBRUARY

10th World Congress for NeuroRehabilitation – WCNR2018
7-10 February, 2018; Mumbai, India – E: traceymole@wfnr.co.uk – W: www.wcnr2018.com

PREVIEW: 5th TNA UK conference June 2017

Report by: Joanna Zakrzewska, Chair of Medical Advisory Board of TNA UK and Adrian Hale, Chairman of Trigeminal Neuralgia Association UK.

Patients and healthcare providers' perspectives on the diagnosis and management of trigeminal neuralgia.

A recent article in the BMJ by Chu et al (BMJ 2016;354:i3883 doi: 10.1136/bmj.i3883) highlights the need for more medical conferences to actively involve patients using the old slogan – nothing about us without us.

This fifth one day joint conference between sufferers of trigeminal neuralgia (TN), their carers and health care providers (HCP) aims to improve our understanding of diagnosis and management of TN as a result of sharing information.

A panel of HCPs from different specialities will provide their diagnosis based on four different histories presented by patients. We will then discuss the varying presentation of this condition followed by Prof Nurmikko's talk on how modern imaging may help in diagnosis and prognosis. Working in groups, patients will discuss how they have been managed medically and HCPs will decide on the ideal medical management. Feedback from the groups will determine how much of a mismatch there is between recommendations and actual treatments. Prof Zakrzewska will provide some insight on how patients with TN are managed in their first three years in the US based on insurance claims.

HCP's suggest that a 50% reduction in pain after drug therapy and 100% pain relief after surgery are considered good outcomes. Sufferers working in groups will discuss outcomes that are important to them including views on the recently developed Penn Facial measure. Dr Riodrain will discuss how core outcome measures in effectiveness trials could be developed using the COMET methodology http://www.comet-initiative.org/. This is of especial importance given upcoming drug trials for a new drug for TN.

One patient's journey from diagnosis to surgery will be portrayed through the use of photographic images created as part of a project on visualisation of pain. Mr Owen Sparrow will speak about his 20 years' experience of surgical management. The criteria for referral for Gamma Knife surgery to one of the two UK designated Trusts for this procedure will be provided by Prof Loescher.

The final session will explore ways in which patients can be supported through patient support groups, clinical nurse specialists and clinical psychology.

Previous conferences have been highly evaluated and have all had CPD accreditation from the Royal College of Physicians. We need to change the way TN is managed in the UK and such a joint meeting will be a stepping stone in the right direction. Come and get involved!

CONFERENCE PREVIEW ABN annual conference 2017 A port to the world

Liverpool, the home of the Beatles and the Mersey Beat is the location for the ABN annual conference 3-5 May. So what better place (with apologies to the Fab 4 and their lyrics), than the ACC Liverpool, to "Come Together" and enjoy 3 days of cutting-edge clinical neurology…rather than flogging yourself "Eight Days a Week"?

"We can work it out"

Liverpool is also famous as a Port City and the theme of the meeting is 'A Port to the World', reflecting not only its nautical history, but also how our meeting will take us on a neurological journey, covering themes such as:

- Setting a Precise Treatment Course: Personalised Medicine in Neurology with talks from Patrick Chinnery (Cambridge), Kevin Talbot (Oxford) and Munir Pirmohamed (Liverpool)
- Global challenges in neuroinfection (Tom Solomon (Liverpool), Hadi Manji (London), and Onn Min Kon (London)
- Navigating new mechanisms & treatments in neurodegeneration – John Collinge (London), Cath Mummery (London) and Anne Rosser (Cardiff)
- "To boldly go…" innovative developments in neuroscience – Phil White (Newcastle), Roger Barker (Cambridge), Anthony Macquillan (London)

"From us to you"

We were pleased with the success of our 2016 abstract bursary for junior researchers which supported an increase of 20% in abstract numbers and the award of almost 100 bursaries. We have had a record number of abstracts submitted for Liverpool, another 15% increase on 2016, and will be awarding another 100 abstract bursaries. Our poster exhibition this year will include a separate section featuring the work of ABN fellows and our pre-meeting training and development day on Tuesday 2nd May will again offer specific sessions for foundation doctors, specialist registrars and junior researchers. We will also be holding our regular 'Need to Know Neurology' session for GPs.

"With a little help from my friends"

The success of the ABN conference depends on the contributions of many different men and women. We are delighted to announce that our invited speakers include Prof Eric Hoffman, Associate Dean for Research, Binghamton University, State University of New York, who will deliver the 23rd Gordon Holmes lecture: 'Duchenne's Muscular dystrophy - from gene discovery to treatment' and Prof Andy Schwartz, Dept of Neurobiology, University of Pittsburgh who will deliver the Practical Neurology lecture 'Recent progress towards high performance neural prosthetics". His labs are currently developing prostheses capable of restoring reaching, grasping and manipulation to immobilised individuals.

The Special Interest Groups will once again run their own meetings over three different sessions during the conference, allowing delegates to choose from 15 different areas of interest. As mentioned above the plenary sessions will address topics on wide ranging themes - a port to the world of neurology.

So "Don't let me down" and get yourself a "Ticket to Ride" and enjoy the ABN annual meeting in the vibrant setting of Liverpool.

David Nicholl
Honorary Assistant Secretary
Association of British Neurologists

Programme of the Annual Meeting 3-5 May 2017 ACC Liverpool – Annual Sponsors for 2017: Biogen Idec, Roche, Novartis, Teva UK, Merck

	Wednesday 3 May
07:45	Committee meetings, **ABNT Forum**
09:00	**Opening and Welcome**
09:15	Plenary session 1 **Setting a precise treatment course: Personalised medicine in neurology** Personalised medicine- the contribution of genetics and genomics: Patrick Chinnery, Cambridge How close are we to personalised medicine for neurological disease? Kevin Talbot, Oxford Pharmacogenetics - its relevant to the neurologist: Munir Pirmohamed, Liverpool
10:45	Coffee & Exhibition 1
11:15	Parallel session 1 | Parallel session 2
12:30	Lunch, Exhibition Symposia 1 | Symposia 2
14:00	**Gordon Holmes Lecture**: Eric Hoffman, Binghampton University,USA Title:
14:45	Poster session with discussants 1
15:45	Coffee & Exhibition 2
16:15	**Practical Neurology lecture**: Andrew Schwartz, USA Title: 'Recent progress toward high-performance neural prosthetics'
17:00	Parallel session 3 | Parallel session 4
18:15	Late breaking news
18:35	**Drinks reception and posters**

	Thursday 4 May				
07:45	SIG 1:Epilepsy 1C	SIG 2: Movement Disorders 1B	SIG 3: Peripheral Nerve 1C	SIG 4: Autonomic 7	SIG 5: Myology 10
09:00	Plenary session 2 **Navigating new mechanisms & treatments in neurodegeneration**: Prion disease beyond prion disease: John Collinge, London Immunotherapy for neurodegenerative diseases: Cath Mummery, London New approaches in Huntington's disease- what have we learnt: Anne Rosser, Cardiff				
10:30	Coffee and Exhibition 3				
11:00	AGM				
12:00	Poster session with discussants 2				
13:00	Lunch, Exhibition Symposium 3 | Symposium 4				
14:30	**ABN Medallist lecture**: Martin Rossor				
15:15	Coffee and Exhibition 4				
15:45	**Business Session** | Parallel session 6				
17:00	SIG 6: MS and Neuroinflammation 1A	SIG 7: Functional Disorders 1B	SIG 8: Neuroinfection 1C	SIG 9: Neurocritical care 7	SIG 10: British Neurotoxin Network 10
18:00					
19:00	**Gala Dinner**: Liverpool Anglican Cathedral				

	Friday 5 May				
07:45	SIG 11: Neuro-ophthalmology 1A	SIG 12: Cognitive disorders 1B	SIG 13: Myasthenia Gravis 1C	SIG 14: Motor Neurone Disease 7	Traumatic Brain Injury 10
09:00	Case presentation competition				
10:15	**President's lecture** Life at the Periphery: Mary Reilly				
11:00	Coffee and Exhibition 5				
11:30	Plenary session 3 **Global challenges in neuroinfection** Encephalitis- a global issue: Tom Solomon, Liverpool CNS Tuberculosis in 2017 & the challenge of drug resistance: Onnmin Kon, London PUO & neurology in the returning traveller: Hadi Manji, London				
13:00	Lunch, Exhibition Symposium 5 | top 6 posters				
14:30	Plenary session 4 **"To boldly go..." innovative developments in neuroscience** Clot retrieval for stroke: Phil White, Newcastle Stem cells as treatment: Roger Barker, Cambridge Innovative approaches to peripheral nerve and plexus damage: Anthony MacQuillan, RNOH				
16:00	CPC/Hot Topics				
16:45	Prize presentations and close				
17:15					

The inaugural 'Neurorehabilitation in Movement Disorders' conference

Conference details: 6th October, 2016; London, UK. ***Report by:*** Dr Wei Jia Zhang, Specialty Registrar in Neurology, Royal Free Hospital.

Neurology has an undeserving reputation as a specialty that places great emphasis on diagnosis with little in the way of intervention. However, despite great advances in management options, many chronic neurological conditions are still limited with regard to disease-modifying treatments. After the initial diagnosis, follow-up clinics can focus primarily on symptom control and rehabilitation. The latter invariably will involve the multi-disciplinary team. Therefore, it is fitting that the inaugural conference on 'Neurorehabilitation in movement disorders' has the tag line 'a multi-disciplinary approach to the future'.

The recurrent theme running throughout the day was the use of technology in clinical care. Rising numbers of smart-phone users means we are increasingly using technology to maximise wellbeing. One only has to look at the vast number of apps driving the self-monitoring culture to appreciate the digital medicine revolution. Technology in healthcare is also particularly topical given some of the controversial comments regarding how technology may eventually replace the role of clinicians. Not many would agree with this view, and certainly one speaker at the conference, Suma Surendranath, was keen to stress that technology is merely aiding and not replacing clinical acumen. She presented interesting findings from a study by Parkinson UK on 'wearable technology'. This involved a device worn around the wrist that automated the assessment of bradykinesia and dyskinesia in patients with Parkinson's disease.

The take-home message is that big-data will not replace clinicians (indeed, we are not merely 'data-collecting sensors') but those receptive to technology may be able to perform their job better.

The theme of assistive technology continued with a presentation from Dr Martijin Beudel on his work developing an adaptive deep brain stimulation (DBS) system that can synergise with dopaminergic medication. He proposed that this was a smarter way of delivering treatment with fewer side-effects and less energy consumption, compared to the conventional (continuous) DBS.

It would be impossible to review all of the excellent talks given throughout the day, with diverse range of topics from functional movement disorders to rehabilitation in cerebellar dysfunction. Two particular talks stood out. One is that from Professor Monica Busse on the potential of functional and potentially disease-modifying effects of physical exercise in neurodegenerative conditions such as Huntington's disease. Dr Anna Sadnicka's talk on task specific dystonia gave a comprehensive overview of the pathophysiology and current therapeutic options. Her talk was brought to life with illustrative videos of musicians with this condition, and her involvement with this 'at-risk' group with regards to raising awareness of this condition, and educating the potential environmental risk factors that may act as triggers for disruption of fine motor control. The results from her clinical trial assessing the feasibility of delivering a tailored rehabilitative programme gives hope for novel therapeutic avenues.

To conclude, the conference brought together world experts in neurorehabilitation and delivered an educational day in an informal setting where there was good engagement and debate between the speakers and the audience. Many thanks to the organisers for this excellent meeting.

PREVIEW: Attend the Global Forum to Advance Dementia Science

Conference details: 14-15 July, 2017; London, UK.

The Alzheimer's Association International Conference® (AAIC®) is the largest international meeting dedicated to advancing dementia science. Each year, AAIC unites the world's leading basic science and clinical researchers, next generation investigators, clinicians and the care research community to share research discoveries that will lead to methods of prevention and treatment and improvements in diagnosis for Alzheimer's disease and other dementias.

Join leaders from more than 70 countries at AAIC 2017 in London, England, from July 16-20, with preconferences on July 14-15.

AAIC features a strong scientific program with over 2,000 poster and oral presentations on the latest dementia research, as well as over 100 sessions and 500 presentations focusing on basic science, emerging research, innovative practice techniques, imaging, technology and more. The breadth of information shared at AAIC makes this the dementia conference you will not want to miss.

Whether attending a reception or preconference meeting, presenting a poster or talking to a colleague between sessions, AAIC is the go-to place to make connections with researchers from around the world. Do not miss the opportunity to elevate your career by sharing your research results and ideas, networking with colleagues and building collaborative relationships.

When registering for AAIC, select Membership +PLUS as your registration type to add a one-year membership to the Alzheimer's Association International Society to Advance Alzheimer's Research and Treatment (ISTAART), the professional society for individuals interested in Alzheimer's and dementia science. As an ISTAART member, you will have access to exclusive AAIC scientific sessions and preconferences and career-enhancing educational and networking events. ISTAART members also receive discounted registration and ongoing benefits, including a subscription to Alzheimer's & Dementia: The Journal of the Alzheimer's Association, monthly e-newsletters and networking forums.

To learn more and register for AAIC 2017, visit alz.org/AAIC-ACNR.

COPAXONE® no longer contraindicated during pregnancy in the UK

Teva Pharmaceutical Industries Ltd have announced that the label for COPAXONE® (glatiramer acetate) injection 20mg/mL, used for treatment in patients with relapsing forms of multiple sclerosis (RMS), has been updated in the UK to remove the pregnancy contraindication.

The label update followed an extensive analysis by regulatory authorities of available pregnancy cases among women who were already taking COPAXONE® when they learned they were pregnant. A supporting analysis was also provided comparing data from Teva's Glatiramer Acetate (GA) Pharmacovigilance Database which captured more than 8,000 pregnancies over a period of more than 20 years.

Staying on an MS treatment like COPAXONE® 20 mg/mL is now an option women can discuss with their doctor because COPAXONE® is no longer contraindicated during pregnancy. As a precautionary measure, it is preferable to avoid the use of COPAXONE® during pregnancy unless the benefit to the mother outweighs the risk to the foetus.

Professor Gavin Giovannoni, Chair of Neurology – Blizard Institute, Barts and The London, said: "People with multiple sclerosis want to live normal lives, but, for many women with relapsing MS, having to decide between planning a family and staying on their treatment to manage relapses is a reality they have to face. This label update provides specialists and their patients with MS, who are considering starting or extending their family, an important option in relation to their treatment of MS during pregnancy."

For more information, visit www.tevapharm.com

European Commission grants Marketing Authorisation for Zebinix® (eslicarbazepine acetate) for the treatment of partial-onset seizures in children

The European Commission has extended the Marketing Authorisation for Zebinix® (eslicarbazepine acetate) as a once-daily adjunctive treatment for patients aged above six years with partial-onset (focal) seizures with or without secondary generalisation.[i]

Eslicarbazepine acetate was previously indicated only for the adjunctive treatment of adults aged over 18 with partial-onset seizures with or without secondary generalisation.[ii]

The variation to the license is based on data from one Phase III study (305), one Phase II study (208) and from population PK modelling and exposure-efficacy analyses. The Commission considered the efficacy results from the mentioned studies to be acceptable for an extension of the Marketing Authorisation. The safety analyses show no new or unexpected safety findings and eslicarbazepine acetate does not appear to have negative neurocognitive consequences (power of attention, information processing and working memory).[iii]

References
[i] European Commission: Community register of medicinal products for human use. Product Information – Zebinix. Available at: http://ec.europa.eu/health/documents/community-register/html/h514.htm Last updated December 2016
[ii] Zebinix SMPC, Available at http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000988/WC500047225.pdf Last updated: May 2016
[iii] Moreira J, et al. J Neurol Sci 2015;357:e432–456 (abstract 1513; WFN15-1735; e439)

A UCLH neurologist has been named European Health Professional of the Year

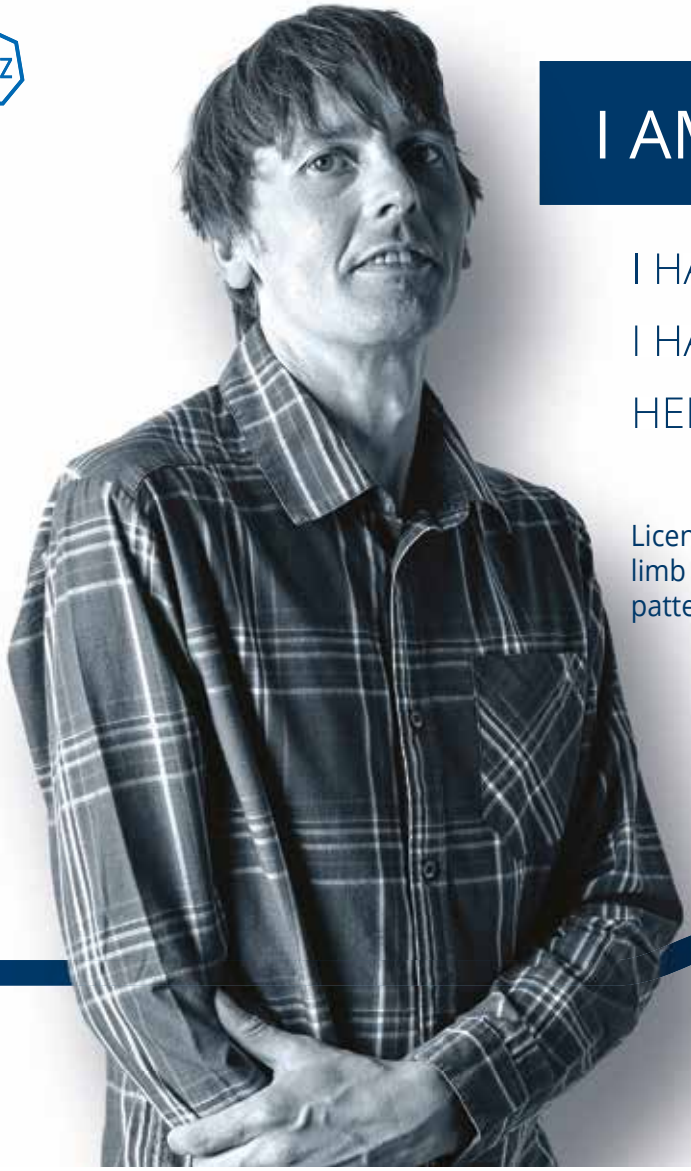
Paola Giunti has been honoured for her groundbreaking work on ataxia – a group of incurable conditions that affect co-ordination and balance. The complex nature of the condition means that few doctors have the expertise to treat patients. Dr Giunti responded to this gap in care by opening the UK's first specialist centre for ataxia 11 years ago. Based at the National Hospital for Neurology and Neurosurgery at Queen Square, it takes a holistic approach to care, providing diagnosis and access to research, as well as physiotherapy, occupational therapy and emotional and practical support. The patient base has expanded from 64 in 2005 to more than 800 a year today.

Naming its European Health Professional of the Year, the European Federation of Neurological Associations said: "Dr Giunti was nominated for her work in the field - including the establishment of the specialist ataxia centre, which we really see as a best practice example of a bespoke health service made in partnership with patients" The judging panel was also particularly impressed by her voluntary work with patient organisations and the wider patient community.

New Multiple Sclerosis treatment wins 1m funding

Cambridge-based LIFNano Therapeutics has created a possible new treatment for multiple sclerosis – and potentially other disease areas – and been awarded 1 million funding by Innovate UK. Its LIFNanoRx solution promises a new generation of treatments for currently untreatable diseases using simple and clean technology. Founded by Dr Su Metcalfe in 2013 as a spin-out from the University of Cambridge, the LIFNanoRx product exploits the body's own repair pathways by precise targeting of LIF to the treatment site. Moreover, since the LIF nanoparticles can be manufactured in bulk and stored until required, global access to therapy becomes possible, in marked contrast to the relatively expensive, globally restricted and specialised cell-based therapies currently being developed to treat MS. LIFNanoRx is designed to protect the brain. Using tiny soluble nanoparticles, LIF is slowly released precisely where it is needed. The released LIF then taps into the body[1]s own mechanisms for brain repair, with the potential not only to prevent disease progression but also to enhance current treatments of MS.

For more information, visit http:///lifnano.com



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HELPING PATIENTS ACHIEVE THEIR GOALS

Xeomin® (incobotulinumtoxinA) 50/100/200 unit vials. Prescribing Information: M-XEO-UKI-0050. Please refer to the Summary of Product Characteristics (SmPC) before prescribing. **Presentation:** 50/100/200 units of Clostridium Botulinum Neurotoxin type A (150 kD), free from complexing proteins as a powder for solution for injection. **Indications:** Treatment of blepharospasm, cervical dystonia of a predominantly rotational form (spasmodic torticollis) and of post-stroke spasticity of the upper limb presenting with flexed wrist and clenched fist in adults. **Dosage and Administration:** Due to unit differences in the potency assay, unit doses for Xeomin are not interchangeable with those for other preparations of Botulinum toxin. Reconstitute with 0.9% sodium chloride. ***Blepharospasm:*** Intramuscular injection, The initial recommended dose is 1.25-2.5 U per injection site, injected into the medial and lateral orbicularis oculi of the upper lid and the lateral orbicularis oculi of the lower lid. The initial dose should not exceed 25 U per eye but this can be subsequently increased. The total dose should not exceed 100 U every 12 weeks. Additional sites in the brow area, the lateral orbicularis oculi muscle and in the upper facial area may also be injected if spasms here interfere with vision. ***Spasmodic torticollis:*** Intramuscular injection, Xeomin is usually injected into the sternocleidomastoid, levator scapulae, scalenus, splenius capitis and / or the trapezius muscle(s) or any of the muscles responsible for controlling head position that may be involved. Up to 200 units can be injected for the first course of therapy with adjustments made for up to 300 units in subsequent courses. No more than 50 units should be given at any one injection site. ***Post-stroke spasticity of the upper limb:*** Intramuscular injection, dosage and number of injection sites should be tailored to the individual patient based on the size, number and location of muscles involved, the severity of spasticity, and the presence of local muscle weakness. The maximum total recommended dose is up to 400 units per treatment session. Repeated treatment should generally be no more frequent than every 12 weeks. ***Contraindications:*** Known hypersensitivity to Botulinum neurotoxin type A or to any of the excipients, generalised disorders of muscle activity (e.g. myasthenia gravis, Lambert-Eaton syndrome) and presence of infection or inflammation at the proposed injection site. ***Special warnings and precautions:*** Care should be taken not to inject into blood vessels, especially when injecting at sites close to sensitive structures such as oesophagus and carotid artery lung apices. Should be used with caution in patients with any bleeding disorder or receiving anticoagulant therapy or taking any substance with anticoagulant effect. Caution in patients with pre-existing neuromuscular disorders such as patients suffering from amyotrophic lateral sclerosis, other diseases which result in peripheral neuromuscular dysfunction or where the targeted muscles display pronounced weakness or atrophy. Patients with a history of dysphagia and aspiration should be treated with extreme caution. Spread of Botulinum toxin to sites far from injection site has been reported. Some of these can be life threatening and there have been reports of death, some associated with dysphagia, pneumonia and/or significant debility. Patients or caregivers should be advised to seek immediate medical care if swallowing, speech or respiratory disorders arise. Too frequent doses may increase the risk of antibody formation, and possible treatment failure. Should not be used during pregnancy unless clearly necessary. Should not be used during breast-feeding. ***Blepharospasm:*** Careful testing of corneal sensation should be performed in patients with previous eye operations. Due to its anticholinergic effects, it should be used with caution in patients at risk of developing narrow angle glaucoma. ***Spasmodic Torticollis:*** Patients should be informed that injections of Xeomin for the management of spasmodic torticollis may cause mild to severe dysphagia with the risk of aspiration and dyspnoea. Limiting the dose injected into the sternocleidomastoid muscle to less than 100 units may decrease the occurrence of dysphagia. Patients with smaller neck muscle mass, or patients who require bilateral injections into the sternocleidomastoid muscles are at greater risk. ***Post stroke Spasticity:*** Xeomin is not likely to be effective in improving range of motion at a joint affected by a fixed contracture. **Interactions:** No interaction studies have been performed. Concomitant use with aminoglycosides or spectinomycin requires special care. Peripheral muscle relaxants should be used with caution. 4-aminoquiniolones may reduce the effect. **Undesirable effects:** Usually, undesirable effects are observed within the first week after treatment and are temporary in nature. Undesirable effects independent of indication include; application related undesirable effects (localised pain, inflammation, swelling), class related undesirable effects (localised muscle weakness), and toxin spread (very rare - exaggerated muscle weakness, dysphagia, aspiration pneumonia). Frequency by indication defined as: *very common* (≥ 1/10); *common* (≥ 1/100 to < 1/10); *uncommon* (≥ 1/1,000 to < 1/100); *rare* (≥ 1/10,000 to < 1/1,000); *very rare* (< 1/10,000); *not known* (cannot be estimated from the available data). ***Blepharospasm:*** *Very Common:* Eyelid Ptosis, dry eyes. *Common:* Headache, facial paresis, blurred vision, visual impairment, diplopia, increased lacrimation, dry mouth, dysphagia, rash, injection site pain, fatigue, muscular weakness. ***Spasmodic torticollis:*** *Very common:* Dysphagia. *Common:* Headache, presyncope, dizziness, dry mouth, nausea, hyperhidrosis, neck pain, muscular weakness, myalgia, muscle spasm, musculoskeletal stiffness, injection site pain, asthenia, upper respiratory tract infection. ***Post-stroke spasticity:*** *Common:* Headache, dysaesthesia, hypoaesthesia, dysphagia, muscular weakness, pain in extremity, feeling hot, and injection site pain. Flu-Like symptoms and hypersensitivity reactions also have been reported. *For a full list of adverse reactions, please consult the SmPC.* **Overdose:** May result in pronounced neuromuscular paralysis distant from the injection site. *Xeomin® may only be used by physicians with suitable qualifications and proven experience in the application of Botulinum toxin.* **Legal Category:** POM. **List Price:** 50U/vial £72.00/€110.00, 100U/vial £129.90/€195.00, 200U/Vial £259.80/€390.0 **Product Licence Number:** PL 29978/0003, PL 29978/0001, PL 29978/0004; PA1907/001/001, PA1907/001/002, PA 1907/001/003 **Marketing Authorisation Holder:** Merz Pharmaceuticals GmbH, Eckenheimer Landstraße 100,60318 Frankfurt/Main, Germany **Date of Preparation:** August 2016 **Further Information Available from:** Merz Pharma UK Ltd., 260 Centennial Park, Elstree Hill South, Elstree, Hertfordshire WD6 3SR. Tel: **+44 (0) 333 200 4141**

Adverse events should be reported. Reporting forms and information for United Kingdom can be found at www.mhra.gov.uk/yellowcard. Reporting forms and information for Republic of Ireland can be found at http://www.medicines.ie/yellowcardreporting.aspx. Adverse events should also be reported to Merz Pharma UK Ltd at the address above or by email to UKdrugsafety@merz.com or on +44 (0) 333 200 4143.

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