

ACNR

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ADVANCES IN CLINICAL NEUROSCIENCE & REHABILITATION

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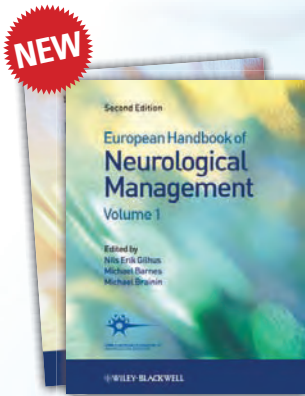
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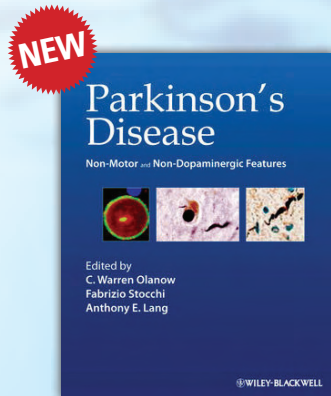
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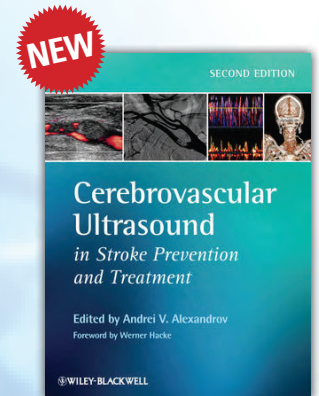
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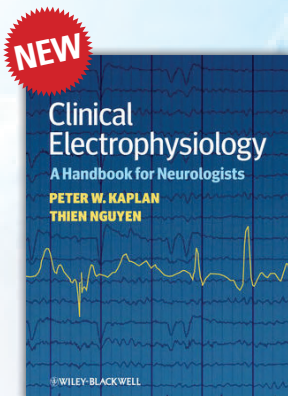
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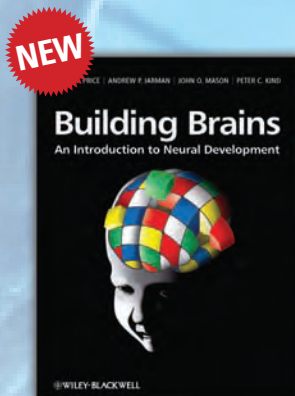
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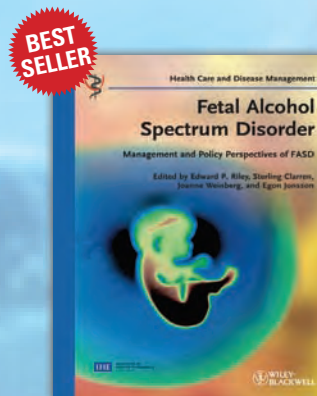
Edited by
Andrei V. Alexandrov



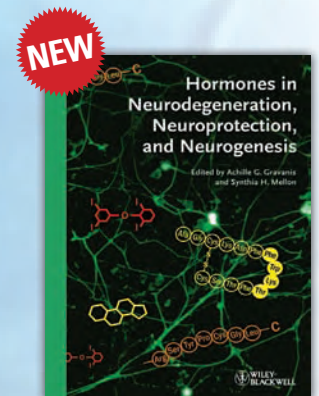
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Roger Barker is co-editor of ACNR, and is Honorary Consultant in Neurology at The Cambridge Centre for Brain Repair. His main area of research is into neurodegenerative and movement disorders, in particular parkinson's and Huntington's disease. He is also the university lecturer in Neurology at Cambridge where he continues to develop his clinical research into these diseases along with his basic research into brain repair using neural transplants.



Alasdair Coles is co-editor of ACNR. He is a University Lecturer in Neuroimmunology at Cambridge University. He works on experimental immunological therapies in multiple sclerosis.



Mike Zandi is co-editor of ACNR. He is a Specialist Registrar in Neurology at the National Hospital for Neurology and Neurosurgery, Queen Square, London. He is interested in clinical and experimental neuroimmunology.



Stephen Kirker is the editor of the Rehabilitation Section of ACNR and Consultant in Rehabilitation Medicine in Addenbrooke's NHS Trust, Cambridge. He trained in neurology in Dublin, London and Edinburgh before moving to rehabilitation in Cambridge and Norwich. His main research has been into postural responses after stroke. His particular interests are in prosthetics, orthotics, gait training and neurorehabilitation.



Boyd Ghosh is the Editor of our Conference News section. He is currently a Specialist Registrar in Southampton having completed a PhD in Cambridge in cognitive neuroscience. His special interests are cognition and movement disorders, with a particular interest in progressive supranuclear palsy. He is currently secretary for the ABN trainees committee.



Rhys Davies is the editor of our Book Review Section. He is a consultant neurologist at the Walton Centre for Neurology and Neurosurgery in Liverpool and at Ysbyty Gwynedd in Bangor, North Wales. He has a clinical and research interest in cognitive neurology.



Alastair Wilkins is our Case Report Co-ordinator. He is Senior Lecturer in Neurology and Consultant Neurologist, University of Bristol. He trained in Neurology in Cambridge, Norwich and London. His research interests are the basic science of axon degeneration and developing treatments for progressive multiple sclerosis.



Peter Whitfield is ACNR's Neurosurgery Editor. He is a Consultant Neurosurgeon at the South West Neurosurgery Centre, Plymouth. His clinical interests are wide including neurovascular conditions, head injury, stereotactic radiosurgery, image guided tumour surgery and lumbar microdiscectomy. He is an examiner for the MRCS and is a member of the SAC in neurosurgery.



Heather Angus-Leppan is ACNR's ABN representative on the Editorial Board. She is Head of the Neurology Department at Barnet Hospital and Consultant Neurologist, Honorary Senior Lecturer and Epilepsy Lead at the Royal Free Hospital, London, UK. She is the Honorary Assistant Secretary of the Association of British Neurologists, Honorary Secretary of the Neurosciences Section of the Royal Society of Medicine and current Chair of the Map of Medicine Epilepsy Group, UK.

International editorial liaison committee

Professor Riccardo Soffietti, Italy: Chairman of the Neuro-Oncology Service, Dept of Neuroscience and Oncology, University and S. Giovanni Battista Hospital.

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Professor Hermann Stefan, Germany: Professor of Neurology /Epileptology in the Department of Neurology, University Erlangen-Nürnberg.

Professor Nils Erik Gilhus, Norway: Professor of Neurology at the University of Bergen and Haukeland University Hospital.

Committee commitment for Glenside Hospital's Andrew Norman

Andrew Norman, CEO of The Glenside Hospital for Neuro Rehabilitation in Salisbury, has been appointed onto the committee of the South of England Acquired Brain Injury Forum (SEABIF). The forum acts as a vital resource for those with Acquired Brain Injury (ABI) and aims to connect those requiring information and services with organisations that are able to assist. As an active committee member, Mr Norman will use his experience of more than 15 years in neuro rehabilitation to assist those seeking information, advice and help from the forum. He said: "I was honoured to be asked to join such an important committee, which will be vital not only for people with acquired brain injuries but also for their family members and carers. The forum aims to help those from Hampshire and the Isle of Wight to Dorset, Wiltshire and Berkshire and I am delighted to be a part of it. "Not only will forum users be able to benefit from my personal experience in the area, but will also benefit from the expertise of all staff at Glenside Hospital."



The forum is a regional group of the United Kingdom Acquired Brain Injury Forum (UKABIF) which promotes national understanding of all aspects of ABI. For more information contact: T: 023 80 238001 E: laura@carswellgould.co.uk / lisa@carswellgould.co.uk

Award for Professor Roger Lemon

Congratulations to Professor Roger Lemon on being honoured by the Betty and David Koetser Foundation for Brain Research. The Betty and David Koetser Foundation supports clinical and basic research in the field of brain research with focus on the investigation of movement disorders and neuropsychology, and is based in Zurich. The Foundation awards research grants to support neuroscience projects. Additionally, outstanding achievements in Neuroscience are honoured annually with this award. Previous laureates include Pat Wall, Semir Zeki, Charles Weissmann, Alim Louis Benabid, Wolf Singer, Rodolfo Llinas, Martin Schwab and Karl Deisseroth. Professor Lemon said "Obviously I am delighted, because the Award is really a tribute to my research team, the Sobell Department, IoN and UCL."



European Guideline Audit Programme Grant

The EFNS invites applications for a European Guideline Audit Programme Grant. Its main focus is to enhance the delivery of treatment in accordance with EFNS guidelines. This grant should be used to perform an audit with scientific means to ensure the quality and quantity of implementation. This will fulfil the third EFNS mission, high quality of neurological health care, by strengthening the standard, availability, and uniformity of neurological services in Europe. An initial grant of 50,000 Euros will be made for one audit project in 2011 and further competitions may be held in 2012 if the first year applications are judged to be of a high standard.

More information is available at: www.efns.org/The-EFNS-Guideline-Audit-Programme.692.0.html

Professor Maguire awarded Kemali prize

Congratulations to Wellcome Trust Centre for Neuroimaging's Professor Eleanor Maguire who is the recipient of the Eighth International Prize of the Dargut and Milena Kemali Foundation for Basic and Clinical Neurosciences, for innovative contributions to understanding human memory.

The Kemali Prize (25,000 Euro) will be awarded at the Congress of the Federation of European Neuroscience Societies, FENS FORUM 2012, to be held in Barcelona, Spain (July 14 - 18, 2012).



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Relapse

Unchanged or
increased rate, or
ongoing severe
relapses



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- Patients with high disease activity despite treatment with a beta-interferon. These patients may be defined as: those who have failed to respond to a full and adequate course (normally at least one year of treatment) of beta-interferon. Patients should have had at least 1 relapse in the previous year while on therapy, and have at least 9 T2-hyperintense lesions in cranial MRI or at least 1 Gadolinium-enhancing lesion. A "non-responder" could also be defined as a patient with an unchanged or increased relapse rate or ongoing severe relapses, as compared to the previous year.

- Patients with rapidly evolving severe relapsing remitting multiple sclerosis defined by 2 or more disabling relapses in one year, and with 1 or more Gadolinium enhancing lesions on brain MRI or a significant increase in T2 lesion load as compared to a previous recent MRI. **Dosage: Adults:** Treatment should be initiated and supervised by a physician experienced in multiple sclerosis. One 0.5 mg capsule to be taken orally once daily. Patients can switch directly from beta-interferon or glatiramer acetate to Gilenya provided there are no signs of relevant treatment-related abnormalities, e.g. neutropenia. Use with caution in patients aged 65 years and over. Safety and efficacy of Gilenya in children up to 18 years has not been established. No dose adjustments required in patients with mild to severe renal impairment or mild to moderate hepatic impairment. Exercise caution in patients with mild to moderate hepatic impairment. Do not use in patients with severe hepatic impairment (Child-Pugh class C). Use with caution in patients with diabetes mellitus due to an increased risk of macular oedema. **Contraindications:** Known immunodeficiency syndrome, patients with increased risk for opportunistic infections, including immunocompromised patients (including those currently receiving immunosuppressive therapies or those immunocompromised by prior therapies), severe active infections, active chronic infections (hepatitis, tuberculosis), known active malignancies, except for patients with cutaneous basal cell carcinoma, severe liver impairment (Child-Pugh class C), hypersensitivity to the active substance or to any

of the excipients. **Warnings/Precautions: Bradycardia:** Initiation of treatment results in a transient decrease in heart rate which may be associated with atrioventricular conduction delays. Observe all patients for 6 hours for bradycardia. In the event of bradycardia-related symptoms, initiate appropriate clinical management and observe until symptoms resolve. The same precautions apply if Gilenya is discontinued for more than 2 weeks. Gilenya has not been studied in patients with sitting heart rate <55 beats per minute, second degree or higher AV block, sick-sinus syndrome, ischaemic cardiac disease, congestive heart failure, significant cardiovascular disease, a history of syncope or those taking beta blockers. Seek advice from a cardiologist before initiation of treatment in these patients. Gilenya should not be co-administered with class Ia (e.g. quinidine, disopyramide) or class III (e.g. amiodarone, sotalol) antiarrhythmic medicinal products. Exercise caution at treatment initiation in patients receiving beta blockers, or other substances which may decrease heart rate (e.g. verapamil, digoxin, anticholinesteratic agents or pilocarpine) due to possible additive effects. Avoid medicinal products that may prolong QTc interval. **Infections:** Reduction of the lymphocyte count to 20-30% of baseline values occurs with Gilenya. Perform a complete blood count (CBC) at baseline, and periodically during treatment, and in case of signs of infection, stop Gilenya until recovery if absolute lymphocyte count <0.2x10⁹/L is confirmed. Consider VZV vaccination of patients without a history of chickenpox or VZV antibody negative patients prior to commencing Gilenya. Gilenya may increase the risk of infections. Employ effective diagnostic and therapeutic strategies in patients with symptoms of infection while on Gilenya and for 2 months after discontinuation. **Macular oedema:** Macular oedema with or without visual symptoms has been reported in patients taking Gilenya. Perform an ophthalmological evaluation 3-4 months after Gilenya initiation. Evaluate the fundus, including the macula in patients reporting visual disturbances. Perform ophthalmological evaluation prior to initiating therapy and periodically thereafter in patients with diabetes mellitus or a history of uveitis. Discontinue Gilenya if a patient develops macular oedema. **Liver function:** Do not use Gilenya in patients with severe pre-existing hepatic injury (Child-Pugh class C). Delay Gilenya initiation in patients with active viral hepatitis until resolution. Recent transaminase and bilirubin levels should be available before initiation of Gilenya. Monitor liver transaminases at months 1, 3 and 6 and periodically thereafter. Institute more frequent monitoring if transaminases rise above 5 times the ULN, including serum



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A new perspective in MS

bilirubin and alkaline phosphatase (ALP) measurement. Stop Gilenya treatment with repeated confirmation of liver transaminases above 5 times the ULN and only re-commence once liver transaminase values have normalised. Patients with symptoms of hepatic dysfunction should have liver enzymes checked and discontinue Gilenya if significant liver injury is confirmed. Resume Gilenya only if another cause of liver injury is determined and if the benefits of therapy outweigh the risks. Exercise caution with Gilenya use in patients with a history of significant liver disease. **Serological testing:** Peripheral blood lymphocyte counts cannot be utilised to evaluate the lymphocyte subset status of a patient treated with Gilenya. Laboratory tests involving the use of circulating mononuclear cells require larger blood volumes due to reduction in the number of circulating lymphocytes. **Blood pressure effects:** Gilenya can cause a mild increase in blood pressure. Monitor blood pressure regularly during Gilenya treatment. **Respiratory effects:** Use Gilenya with caution in patients with severe respiratory disease, pulmonary fibrosis and chronic obstructive pulmonary disease due to minor reductions in values for forced expiratory volume (FEV₁) and diffusion capacity for carbon monoxide (DLCO). **Prior immunosuppressant treatment:** No washout is necessary when switching patients from interferon or glatiramer acetate to Gilenya assuming any immune effects (e.g. neutropenia) have resolved. Exercise caution when switching patients from natalizumab to Gilenya owing to the long half life of natalizumab and concomitant immune effects. **Stopping therapy:** Gilenya is cleared from the circulation in 6 weeks. Caution is indicated with the use of immunosuppressants soon after the discontinuation of Gilenya due to possible additive effects on the immune system. **Interactions:** Anti-neoplastic, immunosuppressive or immune-modulating therapies should not be co-administered due to the risk of additive immune system effects. Exercise caution when switching patients from long-acting therapies with immune effects, e.g. natalizumab or mitoxantrone. No increased rate of infection was seen with concomitant treatment of relapses with a short course of corticosteroids. Vaccination may be less effective during and for up to 2 months after Gilenya treatment. Avoid use of live attenuated vaccines due to infection risk. Due to additive effects on heart rate, exercise caution when initiating Gilenya in patients receiving beta blockers, or class Ia and III antiarrhythmics, calcium channel blockers like verapamil or diltiazem, digoxin, anticholinesteratic agents or pilocarpine. Caution is indicated with substances that may

inhibit CYP3A4. Co-administration of fingolimod with ketoconazole increases fingolimod exposure. No interaction has been observed with oral contraceptives when co-administered with fingolimod. **Fertility, pregnancy and lactation:** There is potential for serious risk to the fetus with Gilenya. A negative pregnancy test is required before initiation of Gilenya. Female patients must use effective contraception during treatment with Gilenya and for 2 months after discontinuation. Discontinue Gilenya if a patient becomes pregnant. Fingolimod is excreted into breast milk. Women receiving Gilenya should not breast feed. Fingolimod is not associated with a risk of reduced fertility. **Undesirable effects:** *Very common* ($\geq 1/10$): Influenza viral infections, headache, cough, diarrhoea, increased alanine transaminase (ALT), back pain. *Common* ($\leq 1/100$ to $< 1/10$): herpes viral infections, bronchitis, sinusitis, gastroenteritis, tinea infections, lymphopenia, leucopenia, depression, dizziness, paraesthesia, migraine, blurred vision, eye pain, bradycardia, atrioventricular block, hypertension, dyspnoea, eczema, alopecia, pruritus, asthenia, increased gamma-glutamyl transferase (GGT), increased hepatic enzymes, abnormal liver function test, increased blood triglycerides, decreased weight. *Uncommon* ($\geq 1/1,000$ to $< 1/100$): pneumonia, macular oedema, decreased neutrophil count. **Packs and price:** Perforated unit dose blister packs containing 7 x 0.5 mg hard capsules: £367.50. Blister packs containing 28 x 0.5 mg hard capsules: £1470. **Legal classification:** POM. **Marketing Authorisation Holder:** Novartis Europharm Ltd, Wimblehurst Rd, Horsham, W Sussex, RH12 5AB, UK. **Marketing Authorisation Numbers:** 7 x 0.5 mg hard capsules: EU/1/11/677/001, 28 x 0.5 mg hard capsules: EU/1/11/677/005 **Date of last revision of prescribing information:** March 2011. **Full Prescribing Information available from:** Novartis Pharmaceuticals UK LTD, Frimley Business Park, Frimley, Surrey, GU16 7SR. Tel: (01276) 692255 Fax: (01276) 692508.

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Date of preparation: March 2011 Code: FIN11-102

Roger Barker is currently out of the country and not e-contactable. So, after a decade of helping him run this fine journal, finally I have been entrusted to write the editorial. (A thought immediately comes to mind: does anyone ever read the editorials?)

The article which I most enjoyed this month was written by the engineering-imaging-museum sociology collaboration of Quiroga, Dudley and Binnie. They compared the eye tracking behaviour of people viewing a famous painting (Ophelia by Millais) when seeing the original in the Tate Britain or when looking at a digital reproduction on a screen. The subtext is: is there any point to museums? Or could they all be replaced by large screens at home and the internet...read on to find the answer.

Required reading for anyone wishing to understand the emerging field of the synaptopathies is the review by Bayés and Grant (who – in the conference review section – is quoted as saying the brain “could break in so many ways”!). Pedersen and Larsen review the surprisingly few long-term cohorts of people with Parkinson’s disease, in which the CamPaign study (run by Roger Barker!) receives commendations for being the only one of five years’ duration. I am shocked; in my world of multiple sclerosis, there are at least three well-defined cohorts of patients going back to the early 1980s...what has the PD research community been doing? The ABNT contributions to the ACNR get better and better: this issue, Alty and Stanton review the potential implications of NHS reforms on training.

In the rehabilitation article, Sara Ajina and Geraint Rees revisit the area of blindsight, what this tells about the routes of visual processing and how this can be exploited for helping patients with hemianopia following strokes. This article illustrates how basic neuroscientific discoveries can filter down into clinical practice.

Simon Hickman, a long-time contributor to ACNR, has kindly pulled together a new series on neuro-ophthalmology. The opening salvo is from Haak, Clatworthy and Morland, with an account of fMRI in neuro-ophthalmology. Amazingly, they suggest that fMRI could be used to detect or monitor retinal lesions.

Finally, we have our usual sections of journal and book reviews. As TS Eliot said: “Some editors are failed writers, but so are most writers.” ♦



Alasdair Coles, Co-Editor.

*Alasdair Coles, Co-Editor,
Email. Rachael@acnr.co.uk*

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in post-marketing experience. Atrial fibrillation or flutter have been reported in open-label trials and in post-marketing experience. Patients should be made aware of the symptoms of second-degree or higher AV block and of the symptoms of atrial fibrillation and flutter. Patients should be counseled to seek medical advice should any of these symptoms occur. Excipients in the syrup may cause allergic reactions (possibly delayed), should not be taken by those with fructose intolerance and may be harmful to patients with phenylketonuria. Monitor patients for signs of suicidal ideation and behaviours. Advise patients and carers to seek medical advice should such signs emerge. **Interactions:** Prolongations in PR interval with lacosamide have been observed in clinical studies. Use with caution in patients treated with products associated with PR prolongation and those treated with class I antiarrhythmic drugs. Strong enzyme inducers such as rifampicin or St John's Wort may moderately reduce the systemic exposure of lacosamide. No significant effect on plasma concentrations of carbamazepine and valproic acid. Lacosamide plasma concentrations were not affected by carbamazepine and valproic acid. No clinically relevant interaction with ethinylestradiol and levonorgestrel. No effect on pharmacokinetics of digoxin. **Pregnancy and Lactation:** Should not be used during pregnancy. For precautionary measures, breast feeding should be discontinued during treatment with lacosamide. **Driving etc.:** Patients are advised not to drive a car or operate other potentially hazardous machinery until they are familiar with the effects of Vimpat on their ability to perform such activities. **Adverse Effects:** Very common (≥10%): Dizziness, headache, diplopia, nausea. Common (between 1%-10%): Depression, confusional state, insomnia, balance disorder, abnormal coordination, memory impairment, cognitive disorder, somnolence, tremor, nystagmus, hypoesthesia, dysarthria, disturbance in attention, blurred vision, vertigo, tinnitus, vomiting, constipation, flatulence, dyspepsia, dry mouth, pruritus, rash, muscle spasms, gait disturbance, asthenia, fatigue, irritability, injection

site pain or discomfort, irritation, fall, skin laceration. The use of lacosamide is associated with dose-related increase in the PR interval. Adverse reactions associated with PR prolongation may occur. Please consult SPC in relation to other side effects. **Pharmaceutical Precautions:** Tablets: None. Syrup: Do not store above 30°C. Use within 4 weeks of first opening. Solution for infusion: Do not store above 25°C. Use immediately. **Legal Category:** POM. **Marketing Authorisation Number(s):** 50 mg x 14 tabs: EU/1/08/470/001; 100 mg x 14 tabs: EU/1/08/470/004; 100 mg x 56 tabs: EU/1/08/470/005; 150 mg x 14 tabs: EU/1/08/470/007; 150 mg x 56 tabs: EU/1/08/470/008; 200 mg x 56 tabs: EU/1/08/470/011; Syrup (15 mg/ml) x 200 ml: EU/1/08/470/014; Solution for Infusion (10 mg/ml) x 20 ml: EU/1/08/470/016. **NHS Cost:** 50 mg x 14 tabs: £10.81; 100 mg x 14 tabs: £21.62; 100 mg x 56 tabs: £86.50; 150 mg x 14 tabs: £32.44; 150 mg x 56 tabs: £129.74; 200 mg x 56 tabs: £144.16; Syrup (15 mg/ml) x 200 ml: £38.61; Solution for Infusion (10 mg/ml) x 20 ml: £29.70. **Marketing Authorisation Holder:** UCB Pharma SA, Allée de la Recherche 60, B-1070 Brussels, Belgium. **Further information is available from:** UCB Pharma Ltd, 208 Bath Road, Slough, Berkshire, SL1 3WE. Tel: 01753 534655. Fax: 01753 536632. Email: medicalinformationuk@ucb.com. **Date of Revision:** 05/2011 (UK/11VPE0072). Vimpat is a registered trademark.

References:

1. Vimpat Summary of Product Characteristics.
 2. Beyreuther BK et al. CNS Drug Rev 2007; 13(1): 21-42.
 3. Chung S et al. CNS Drugs 2010; 24(12): 1041-1054.
- Date of preparation:** June 2011. UK/11VPE0083a

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ACNR

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Publisher: Rachael Hansford
E. rachael@acnr.co.uk

ADVERTISING

Rachael Hansford
T. 01747 860168 M. 07989 470278
E. rachael@acnr.co.uk

COURSE ADVERTISING

Rachael Hansford E. rachael@acnr.co.uk

EDITORIAL

John Gustar E. editorial@acnr.co.uk

DESIGN & PRODUCTION DEPARTMENT

E. design.dept@sky.com

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Parkinson's Disease; What Can We Learn from Long-term Cohort Studies?



Kenn Freddy Pedersen,

is consultant neurologist and researcher at the Norwegian Centre for Movement Disorders, Stavanger University Hospital, Norway. His scientific and medical interests focus on cognitive and neuropsychiatric disturbances in patients with Parkinson's disease.



Prof Jan Petter Larsen

is the director of research at the Norwegian Centre for Movement Disorders at the Stavanger University Hospital. The research group has for several years had a focus on non-motor problems in Parkinson's disease and is working with both clinical epidemiology, and translational and basic research.

Correspondence to:

Prof. Jan Petter Larsen
Stavanger University Hospital,
Box 8100,
N-4068 Stavanger, Norway
E-mail: jpl@sus.no

Information on the progression or development over time of the signs and symptoms, impairments and need for care in patients with Parkinson's disease (PD) are important in the management of these patients. Also, the study of risk factors for the progression and clinical heterogeneity of the disease are important research issues related to PD. In addition, the development of the Braak hypothesis on the disease progression in the brain has increased the interest in long-term information on the clinical development of PD. Such information is also essential for defining and measuring disease progression in studies of potential neuromodulatory therapies for the disease. Large longitudinal prospective cohort studies of unselected patients with incident PD and a comparable control group are the optimal research design to obtain this information.

Long-term cohort studies

A cohort study is a form of longitudinal study used in medicine to describe the development, risk factors, or aetiology of present or future diseases or symptoms in a group of people. Long-term cohort studies are usually defined as lasting at least five years when studying specific diseases and should preferably include a control group to compare for the general effect of health events related to aging.

Long-term cohort studies in PD

We will in this review discuss both available and lacking information from long-term longitudinal cohort studies on the clinical progression of PD. Although few studies fulfil the desired optimal study design to investigate the progression of PD, we have identified several long-term cohort studies that may bring important information on this issue. In addition, several studies are in progress and hopefully they will further improve this knowledge. We have chosen not to include therapeutic studies and instead focused on cohort studies that have examined the broad spectre of the symptoms in PD. A PubMed search using the terms "Parkinson" and "cohort study" was performed, in addition to examining review papers on the issue for references to relevant studies.

We identified four long-term studies in PD that fulfilled our search requirements,¹⁴ but only the CamPaIGN study has been following an unselected cohort of patients with incident PD for at least five years (Table 1). In addition, we found three on-going potentially long-term cohort

studies⁵⁷ that had published at least one-year follow-up results (Table 2). Also, several studies are planned but are still in a recruitment phase or have not yet published longitudinal data. Among these, the Michael J. Fox Foundation has initiated and financed the Parkinson's Progression Markers Initiative (PPMI).

The progression of motor symptoms and disability in PD

To study and describe the progression of symptoms associated with motor function in PD is indeed difficult to perform. This is caused by the heterogeneity of the clinical picture and disease development among individual patients, different temporal changes of key motor symptoms in PD (ie. tremor, bradykinesia, rigidity, and postural abnormalities), and the impact of different symptomatic treatment strategies that influence the apparent level of motor impairment. In addition, there is so far not available any longitudinal cohort study of unselected patients with incident PD that includes detailed information on the motor symptoms. Based on the abovementioned cohort studies and other relevant studies it is, however, possible to draw some conclusions.

Results from studies in the pre-levodopa era indicated that the progression was fast with the majority of patients reaching a bedridden state within 10-14 years.⁸ This was supported also by short-term evaluations of patients in the placebo arms of treatment studies. The more recent prospective cohort studies do indicate a much slower progression.^{9,10} These studies have, however, included patients with more advanced parkinsonism. Taken together, it seems that there are different rates of decline in different phases of the disease with faster decline in the early stages.¹¹ This different rate of decline can be either driven by the disease biology or by factors related to the scales that are applied to measure progression. Moreover, features like older age, cognitive impairment, and lack of tremor seem to be associated with a more severe motor decline in PD.¹²

The development of the different key motor symptoms of the disease is also important to address as the presence of a motor pattern dominated by postural instability gait disorder (PIGD) is a risk factor for both increased cognitive and motor decline. The evaluation of PiGD is based on the relative presence of different motor symptoms and it has been shown that early PD is usually found to be tremor dominant, while during the development of the disease the PiGD pattern becomes evident in nearly all patients.¹³ This

Table 1: Long-term (5 years or more) cohort studies in PD

Study	Study population	Duration of study	Focus of studied features	Study of biological markers	Control group
The Sydney Multicenter Study ²	Selected early PD	From 1984	Non-motor problems	No	No
Washington Heights, New York study ¹	Unselected cohort from PD prevalence study	From 1989	Motor and non-motor problems	No	No
The Stavanger Parkinson Project ⁴	Unselected cohort from PD prevalence study	From 1993	Motor and non-motor problems	No	No
The CamPaIGN study ³	Unselected cohort of incident PD	From 2000-2002	Motor and non-motor problems	Yes	No

Table 2: On-going long-term cohort studies of incident PD with published data from at least one year follow-up

Study	Study population	Number of patients (recruitment period)	Focus of studied features	Study of biological markers	Control group
The Amsterdam study ⁷	Selected incidence cohort	126 (2002 – 2005)	Motor and non-motor problems	No	No
The Norwegian ParkWest study ⁵	Unselected incidence cohort	212 (2004 – 2006)	Motor and non-motor problems	Yes	Yes
The Umeaa study ⁶	Unselected incidence cohort	112 (2004 – 2007)	Motor and non-motor problems	Yes	Yes (partly)

implies that the PIGD form of parkinsonism is not a specific type of PD, but in most patients represent a more advanced stage of the disease process. Reaching this stage of disease development could therefore represent a milestone along the trajectory of disease progression.

The apparently established facts regarding development of motor complications in PD is that 50 % of the patients have such problems after five years with the disease. Results from available epidemiological studies indicate that this is a marked overestimation.^{14,15} Both motor fluctuations and dyskinesia seem to develop in less than 30% after about six years with medication. These studies have, however, examined and followed groups of patients from cross-sectional studies. Also motor complications are potential markers or milestones to be used in the evaluation of disease progression.

The progression of non-motor symptoms in PD

While PD has traditionally been considered a motor system disorder, it is now widely recognised that non-motor symptoms are not only common but also a key determinant of reduced functioning and quality of life.¹⁶ Non-motor symptoms such as olfactory loss, constipation, depression, and rapid eye movement (REM) sleep behaviour disorder (RBD) might even precede the onset of motor symptoms by

several years.¹⁷ A combination of some of these non-motor symptoms may therefore potentially be used to identify a population “at risk of PD”, perhaps together with functional imaging and future biological markers, which will be particularly important if neuroprotective therapies become available.

Although non-motor symptoms can present at any stage of the disease, they tend to become more prominent in late or advanced PD. For example, non-motor symptoms such as falls, hallucinations, and dementia have consistently been reported as strong predictors of nursing home placement and mortality in advanced cases. Also, two recent longitudinal studies found that more than 80% of PD patients ultimately develop dementia.^{2,18} However, cognitive impairment is also a frequent finding in patients with early PD, as shown in the CamPaIGN study where 17% of an incident PD cohort developed dementia during the first five years.³ In one of the few long-term prospective studies that have addressed non-motor symptoms in PD, the Sydney multicentre study, non-levodopa-responsive problems such as hallucinations, falls, symptomatic orthostatic hypotension and urinary dysfunction were reported to be more disabling than levodopa-induced dyskinesias in patients who were still alive 15 years from diagnosis.¹⁹ Other long-term studies have reported that excessive daytime sleepi-

ness²⁰ and fatigue²¹ become more frequent with disease progression, although the latter seems to have a more non-persistent course in individual patients. In contrast, the frequency of RBD seems to vary over time and existing longitudinal data on depression in PD suggest that some patients might have a persistent or variable course with repeated remissions and relapses of depression, and that the more severe cases often seem to become chronic.

Compared to the motor symptoms of PD, little is known about the natural history of non-motor symptoms. As non-motor symptoms seem to have a greater impact on functioning and quality of life than motor problems during the course of PD, future studies should assess these symptoms in a cohort of newly diagnosed PD with sufficient long-term follow-up evaluations for a better understanding of these issues. For this purpose, validated scales that broadly cover the non-motor symptom complex as well as symptom-specific features should be applied. Such longitudinal studies are important to gain information about the temporal changes of non-motor symptoms and the effect of therapeutic interventions.

What can we learn?

Information from long-term cohort studies of patients with PD may have several important implications for the management of the

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disease. Primarily, they will provide more reliable data on the progression of PD. This information is important for education of patient and caregiver and can also be used to establish milestones or clinical markers that may be used to examine possible therapeutic interventions that aim to modulate or halt disease progression. In addition, such long-term studies may be used to identify clinical or biological markers that are risk factors for a more severe disease development either in terms of motor progression or non-motor complications such as cognitive decline. Interventions that aim to modulate disease progression should select these subgroups of patients with a high risk for a faster decline as this will provide a study population with a higher probability to detect effects of the intervention within a reasonable time frame.

It is, however, important that long-term cohort studies examine the disease progression in patients with incident PD and preferably with a control group. The available data today from such studies are scarce. Only the CamPaIGN study has followed incident patients for more than five years, but without a control group. However, several large studies are planned or started and they will therefore within a few years give us a lot more information on these important issues in PD. ♦

REFERENCES

1. Mayeux R, Chen J, Mirabella E et al. *An estimate of the incidence of dementia in idiopathic Parkinson's disease.* Neurology. 1990;40:1513-1517.
2. Hely MA, Reid WG, Adena MA et al. *The Sydney multicenter study of Parkinson's disease: the inevitability of dementia at 20 years.* Mov Disord. 2008;23:837-844.
3. Williams-Gray CH, Evans JR, Goris A et al. *The distinct cognitive syndromes of Parkinson's disease: 5 year follow-up of the CamPaIGN cohort.* Brain. 2009;132:2958-2969.
4. Forsaas EB, Larsen JP, Wentzel-Larsen T, Alves G. *What predicts mortality in Parkinson disease?: a prospective population-based long-term study.* Neurology 2010;75:1270-1276.
5. Alves G, Muller B, Herlofson K et al. *Incidence of Parkinson's disease in Norway: the Norwegian ParkWest study.* J Neurol Neurosurg Psychiatry. 2009;80:851-857.
6. Linder J, Stenlund H, Forsgren L. *Incidence of Parkinson's disease and parkinsonism in northern Sweden: a population-based study.* Mov Disord. 2010;25:341-348.
7. Post B, Muslimovic D, van Geloven N et al. *Progression and prognostic factors of motor impairment, disability and quality of life in newly diagnosed Parkinson's disease.* Mov Disord. 2010;26:449-456.
8. Hoehn MM, Yahr MD. *Parkinsonism: onset, progression and mortality.* Neurology. 1967;17:427-442.
9. Jankovic J, Kapadia AS. *Functional decline in Parkinson disease.* Arch Neurol. 2001;58:1611-1615.
10. Alves G, Wentzel-Larsen T, Aarsland D, Larsen JP. *Progression of motor impairment and disability in Parkinson disease: a population-based study.* Neurology. 2005;65:1436-1441.
11. Maetzler W, Liepelt I, Berg D. *Progression of Parkinson's disease in the clinical phase: potential markers.* Lancet Neurol. 2009;8:1158-1171.
12. Marras C, Rochon P, Lang AE. *Predicting motor decline and disability in Parkinson disease: a systematic review.* Arch Neurol. 2002;59:1724-1728.
13. Alves G, Larsen JP, Emre M et al. *Changes in motor subtype and risk for incident dementia in Parkinson's disease.* Mov Disord. 2006;21:1123-1130.
14. Larsen JP, Karlsen K, Tandberg E. *Clinical problems in non-fluctuating patients with Parkinson's disease: a community-based study.* Mov Disord. 2000;15:826-829.
15. Schrag A, Quinn N. *Dyskinesias and motor fluctuations in Parkinson's disease. A community-based study.* Brain. 2000;123 (Pt 11):2297-2305.
16. Chaudhuri KR, Schapira AH. *Non-motor symptoms of Parkinson's disease: dopaminergic pathophysiology and treatment.* Lancet Neurol. 2009;8:464-474.
17. Chaudhuri KR, Healy DG, Schapira AH. *Non-motor symptoms of Parkinson's disease: diagnosis and management.* Lancet Neurol. 2006;5:235-245.
18. Buter TC, van den Hout A, Matthews FE et al. *Dementia and survival in Parkinson disease: a 12-year population study.* Neurology. 2008;70:1017-1022.
19. Hely MA, Morris JG, Reid WG, Trafficante R. *Sydney Multicenter Study of Parkinson's disease: non-L-dopa-responsive problems dominate at 15 years.* Mov Disord. 2005;20:190-199.
20. Gjerstad MD, Alves G, Wentzel-Larsen T et al. *Excessive daytime sleepiness in Parkinson disease: is it the drugs or the disease?* Neurology. 2006;67:853-858.
21. Alves G, Wentzel-Larsen T, Larsen JP. *Is fatigue an independent and persistent symptom in patients with Parkinson disease?* Neurology. 2004;63:1908-1911.



Seth Grant

currently heads the Genes to Cognition Programme and is Professor of Molecular Neuroscience at Edinburgh and Cambridge Universities and the Wellcome Trust Sanger Institute. His work addresses the molecular basis of behavior and the role of synapse evolution. Recent interest focuses on the molecular complexity of the human postsynaptic proteome and its disruption in brain disease.



Àlex Bayés

is a Postdoctoral Fellow in the Genes to Cognition Program at the Wellcome Trust Sanger Institute in Cambridge, UK. He obtained a PhD in biochemistry working on the structural basis of insect adaptation to plant defences. At the postdoctoral stage he is studying the molecular biology and pathology of the human synapse.

Correspondence to:

Prof SGN Grant,
Wellcome Trust Sanger Institute,
Genome Campus, Hinxton,
Cambridgeshire, CB10 1SA, UK.
Tel: +44 (0)1223 495380, 494908
Fax: +44 (0)1223 494919
Email: sg3@sanger.ac.uk

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Postsynaptic Proteins Play a Major Role in Neurological and Psychiatric Disease

At the turn of the 20th century¹ Sir Charles Sherrington coined the term synapse to describe the specialised junction between nerve cells. While it has been known for decades that synapses show abnormal structure and function in diseases, the awareness that many important neurological and psychiatric diseases can be caused by synapse dysfunction has only recently been appreciated. The term 'synaptopathy'² is now used to describe pathology of the synapse. Recent advances in our understanding of the protein composition of human synapses together with genetics has provided the first systematic view of the genetic basis of human synaptopathies.³ Mutations of postsynaptic proteins cause a striking number and range of diseases, and through the use of systems biology approaches it is now possible to understand the relationships between these diseases. In addition, molecular network diagrams of the proteins and diseases can be used to explore new therapeutic strategies. In this review, we will highlight some of the insights from this recent study on the proteome of neocortical synapse disease.³

Synapses are formed by the contact between the axonal presynaptic terminal on one neuron and the postsynaptic terminal on dendrites of another neuron and information is transmitted between neurons by the release of neurotransmitters. Thus, the postsynaptic terminal is the point on the surface of a neuron where information is received. In the late 1950s⁴ electron microscopy showed that the postsynaptic terminals of excitatory synapses had an electron-dense zone beneath the postsynaptic membrane (Figure 1a,b) which was named the Post-Synaptic Density (PSD). This electron density is caused by the high concentration of proteins, which allows for it to be isolated using biochemical fractionation.⁵ While it has been possible to isolate PSDs for several decades we have had to wait until recent improvements in proteomic methods to have a detailed identification of the individual proteins and the genes that encode them. PSD proteins can be systematically identified using sensitive mass spectrometry and DNA sequence information which form the basis of much modern proteomic technology.

The uses of proteomics for identification of large numbers of synapse proteins began a decade ago with studies in the mouse and we now know that the PSD of rodents comprises over 1000 proteins.^{6,7} A recent paper by the present authors used synapse

proteomic methods on the PSD isolated from human neocortex (hPSD) and discovered 1461 different proteins. It is worth noting that this is a high number compared to the proteomes of other subcellular structures (e.g. 917 proteins have been identified in human mitochondria⁸). The mammalian PSD is a highly complex structure, comprised of subsets of proteins assembled into multiprotein complexes, which together form a supramolecular structure with an overall mass estimated to be a thousand times larger than a ribosome.⁹

This remarkable complexity poses novel analytical problems and opportunities, which require bioinformatic methods such as those employed in the field of systems biology. Systems Biology is a rather new and still evolving area of biological research that essentially addresses the study of cells and organisms from a holistic point of view.^{10,11} For example, it is possible to use knowledge on the interactions between pairs of proteins to construct network maps of hPSD proteins. These networks were used to show how 'hub' proteins (highly connected proteins) organise subsets of PSD proteins; and allow to explore the relationships of proteins involved in particular diseases or disease phenotypes.

To understand the hPSD 'system', the 1461 different proteins were analysed individually and collectively. The first approach aimed at having an overview of the number and classes of diseases caused by mutations in hPSD genes, while the second aimed at identifying those diseases most relevant to the PSD compared to other neuronal or brain proteins. To perform the first analysis, the genes encoding human PSD proteins were searched against the database of inherited monogenic diseases (Online Mendelian Inheritance in Man, OMIM¹²). Genes in the hPSD caused a total of 269 monogenic diseases, but more importantly approximately half (133) were primary nervous system disorders. 114 hPSD proteins caused these nervous system diseases, a figure that will certainly grow as new mutations are discovered in large-scale genomic sequencing projects currently underway on patients.

Of all nervous system diseases identified, ~80% were central nervous system (CNS) pathologies. Using the International Classification of Disease (ICD-10) CNS diseases caused by hPSD genes could be classified into 4 of the 22 ICD-10 chapters (Figure 2a): Endocrine, Nutritional and Metabolic Diseases; Mental and Behavioural Disorders;

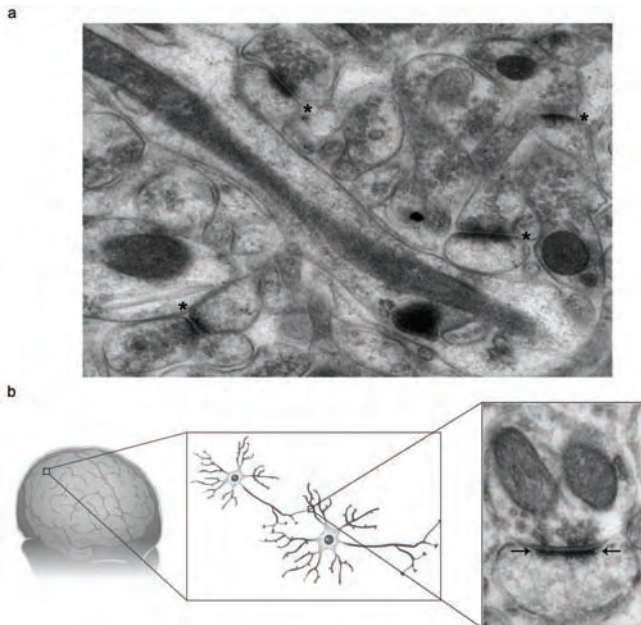


Figure 1: Electron microscopy images of synaptic and postsynaptic structures. a. Field electron micrograph of hippocampal CA1 region from mouse brain. Several excitatory synapses can be identified (marked with asterisks). b. Excitatory synapses mediate neuronal signal transmission in the brain. Nerve cells, represented in the middle panel, have very long branches and contact one another at synapses. Excitatory synapses (right image) are characterised by an electron-dense structure beneath the postsynaptic membrane known as the postsynaptic density (PSD), here shown between arrows.

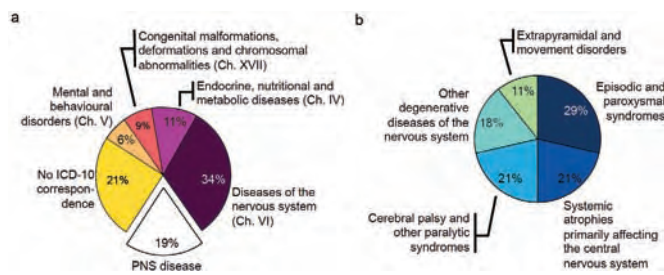


Figure 2: Classification of Nervous System diseases caused by hPSD proteins. a. Distribution and relative abundance of monogenic Nervous System diseases caused by hPSD proteins. Central nervous system diseases were classified using the International Classification of Disease (ICD-10) from the World Health Organisation (WHO) and are shown in coloured sections. The proportion of Peripheral Nervous System (PNS) diseases is also shown. b. Distribution and relative abundance of CNS diseases caused by hPSD proteins within Diseases of the Nervous System (Chapter VI, ICD-10). Figure adapted from Bayés et al.²

Congenital, malformations, deformations and chromosomal abnormalities; and Diseases of the Nervous System. Interestingly, within the 'Diseases of the Nervous System' chapter, the range of disease types caused by hPSD genes was quite wide and included neurodegenerative diseases, movement disorders, epilepsies or atrophies and paralytic syndromes (Figure 2b).

Diseases are characterised by their constellation of symptoms and signs, and often, different diseases share some symptoms, but not others. For example, cognitive impairments or motor dysfunction, such as ataxia, can result from mutations in many different genes and are found in different diseases. The symptoms and signs of diseases caused by mutations are called phenotypes, and those found in genetic diseases have been catalogued in databases of gene-to-phenotype relationships.¹³ These databases make it possible to ask: which symptoms and signs are more common in diseases caused by hPSD mutations? It is also possible to link these phenotypes to specific proteins and identify the subsets of hPSD proteins that are involved with cognition, ataxia and other phenotypes. These analyses provided a 'functional' understanding of the human synapse and led to a new model of disease where subsets of hPSD proteins work together to control human phenotypes. These molecular maps should be useful for identifying biochemical pathways

underlying the particular disease symptoms as well as suggesting new drug targets or genetic susceptibility genes.

These phenotypic analyses produce large amounts of data, therefore, statistical methods can be applied to address another question: to which diseases and phenotypes is the hPSD most important, particularly when compared to other neuronal or glial proteins? Two main conclusions arose from approaching this problem: firstly general nervous system disease phenotypes (i.e. Neurological Abnormality or Abnormality of the Central Nervous System) were overrepresented by hPSD genes revealing that the hPSD has a higher burden of these diseases than other brain structures. The second conclusion was that the hPSD is most relevant to cognitive disorders (particularly mental retardation) and motor diseases.

A systems biology study of the hPSD in psychiatric diseases with complex genetics, such as schizophrenia or autism, has not yet been done. Nevertheless, amongst the rapidly growing lists of genes associated with these devastating diseases there are many well known postsynaptic molecules¹⁴ and a preeminent role of synaptic dysfunction in schizophrenia,^{15,16} autism¹⁷ or mood disorders (bipolar disorder and major depression¹⁸) is becoming conceivable.

Nowadays it is widely accepted that proteins do not function on their own but as parts of supramolecular complexes operating in a structurally organised fashion. The postsynaptic density might be one of the most sophisticated of these structures found in nature and as bewildering as its complexity might seem today, its study could have a transformative impact on neurology and psychiatry. The methods of synapse proteomics with neuroinformatics are now primed for studies of brain disease in living and post-mortem material and together with genetic approaches provide new strategies for disease diagnosis, categorisation and drug development. ♦

REFERENCES

- Sherrington, CS: The integrative action of the nervous system.: Charles Scribner's Sons: New York; 1906.
- Brose N, O'Connor V & Skehel P. *Synaptopathy: dysfunction of synaptic function?* Biochem Soc Trans 2010;38(2):443-4.
- Bayes A, van de Lagemaat LN, Collins MO, Croning MD, Whittle IR, Choudhary JS & Grant SG. *Characterization of the proteome, diseases and evolution of the human postsynaptic density.* Nat Neurosci 2011;14(1):19-21.
- Gray EG. *Electron microscopy of synaptic contacts on dendrite spines of the cerebral cortex.* Nature 1959;183(4675):1592-3.
- Carlin RK, Grab DJ, Cohen RS & Siekevitz P. *Isolation and characterization of postsynaptic densities from various brain regions: enrichment of different types of postsynaptic densities.* J Cell Biol 1980;86(3):831-45.
- Collins MO, Husi H, Yu L, Brandon JM, Anderson CN, Blackstock WP, Choudhary JS & Grant SG. *Molecular characterization and comparison of the components and multiprotein complexes in the postsynaptic proteome.* J Neurochem 2006;97 Suppl 1:16-23.
- Trinidad JC, Thalhammer A, Specht CG, Lynn AJ, Baker PR, Schoepfer R & Burlingame AL. *Quantitative analysis of synaptic phosphorylation and protein expression.* Mol Cell Proteomics 2008;7(4):684-96.
- Elstner M, Andreoli C, Klopstock T, Meitinger T & Prokisch H. *The mitochondrial proteome database: MitoP2.* Methods Enzymol 2009;457:3-20.
- Chen X, Vinade L, Leapman RD, Petersen JD, Nakagawa T, Phillips TM, Sheng M & Reese TS. *Mass of the postsynaptic density and enumeration of three key molecules.* Proc Natl Acad Sci USA 2005;102(32):11551-6.
- Chuang HY, Hofree M & Ideker T. *A decade of systems biology.* Annu Rev Cell Dev Biol 2010;26:721-44.
- Ideker T, Galitski T & Hood L. *A new approach to decoding life: systems biology.* Annu Rev Genomics Hum Genet 2001;2:343-72.
- McKusick VA. *Mendelian Inheritance in Man and its online version, OMIM.* Am J Hum Genet 2007;80(4):588-604.
- Robinson PN, Kohler S, Bauer S, Seelow D, Horn D & Mundlos S. *The Human Phenotype Ontology: a tool for annotating and analyzing human hereditary disease.* Am J Hum Genet 2008;83(5):610-5.
- Fernandez E et al. *Targeted tandem affinity purification of PSD-95 recovers core postsynaptic complexes and schizophrenia susceptibility proteins.* Mol Syst Biol 2009;5:269.
- Hashimoto R, Tankou S, Takeda M & Sawa A. *Postsynaptic density: a key convergent site for schizophrenia susceptibility factors and possible target for drug development.* Drugs Today (Barc) 2007;43(9):645-54.
- Walsh T et al. *Rare structural variants disrupt multiple genes in neurodevelopmental pathways in schizophrenia.* Science 2008;320(5875):539-43.
- Bourgeron T. *A synaptic trek to autism.* Curr Opin Neurobiol 2009;19(2):231-4.
- Machado-Vieira R, Manji HK & Zarate CA. *The role of the tripartite glutamatergic synapse in the pathophysiology and therapeutics of mood disorders.* Neuroscientist 2009;15(5):525-39.



Rodrigo Quian Quiroga

is a Professor of Bioengineering and the head of the Bioengineering Research Group at the University of Leicester. He graduated in Physics at the University of Buenos Aires, Argentina and obtained his PhD in Applied Mathematics at the University of Luebeck, Germany. Before joining the University of Leicester as a lecturer in 2004, he was a post-doctoral fellow at the Research Center Juelich, Germany, and a Sloan fellow at the California Institute of Technology, USA. In 2010 he obtained the Royal Society Wolfson Research Merit Award. His main research interest is on the study of the principles of neural coding, especially for visual perception and memory.



Sandra Dudley

is Senior Lecturer in the University of Leicester's School of Museum Studies. She is a social anthropologist with interests reflected in wide-ranging publications on material culture, museums, exile and Southeast Asia, including *Materialising Exile* (Bergahn, 2010), *Museum Materialities* (Routledge, 2010) and *The Thing about Museums* (Routledge, 2011).



Jennifer Binnie

is a PhD student at University of Leicester within the School of Museum Studies and the NeuroEngineering Lab. Her PhD, funded by AHRC and The Art Fund, is looking at the impact which art within museums and galleries may have upon wellbeing.

Correspondence to:

Rodrigo Quian Quiroga,
Department of Engineering,
University of Leicester,
LE1 7RH Leicester, UK.
Tel: +44 116 252 2314
Fax: +44 116 252 2619
Email: rqqg@le.ac.uk

Looking at Ophelia: A comparison of viewing art in the gallery and in the lab

Art could be thought of as a uniquely human trait, as an act of making something special.⁹ Those who have the skill to create accurate representations of the world around them, and imbue their chosen media with beauty, have been revered for centuries and their abilities to use or ignore the rules of physics within their work has led to insight into how the brain works⁴ such as through the exploration of visual illusions.⁷ As we can clearly differentiate between a work of art and the external world, the perception of art may differ from that of everyday experience. Although the understanding of the processes involved in visual perception has progressed over recent decades,^{17,11} we know relatively little of this inherently human act of viewing art.

The subjective qualities involved in the experience of art have hindered extensive scientific study in this area. The great variability involved in personal experience and the natural environment presents difficulties for researchers attempting to unpick the web of interacting factors involved, as a traditional approach of controlling the variables so that only one is altered can be impractical. At the same time, those coming from an arts and humanities perspective may be wary of such a reductionistic approach, thus the foundations of our understanding the perception of art has been built slowly. Notably, research conducted by the likes of Ramachandran & Hirstein (1999),²¹ Livingston (2002),¹⁵ and Leder et al (2004)¹⁴ has progressed what we do understand of the perception of art. Perhaps the most well known work is that of Zeki (1999),²⁶ who has also investigated the connection between neural activity and visual stimuli using fMRI to see areas of brain activation when participants viewed beautiful, neutral or ugly images.¹³ Eye tracking – i.e. identifying the point in space at which subjects look at each time – has also become a useful tool within visual perception research. The earliest eye tracking studies in art, by Buswell³ and Yarbus,²⁵ showed that the areas of an artwork which hold the most salient information are attended the most, aiding the viewer in completing their tasks, such as being able to answer questions, or gaining the general idea of what is represented within the artwork. Berlyne² proposed that the pattern for viewing images was not only based on gathering information but could be also separated into two types. These were global exploration, involving looking at the whole image to get the gist of the image, and exploration of specific areas in search for more particular information. Other influences such as the individual differences of the viewer, the familiarity of image and any alterations from what was expected can

also change the gaze patterns.^{12,20} As eye movements are related to the information provided within the artwork, it can be extrapolated that they are also related to perceptual processing and cognition.^{25,6}

While we know that task influences how we look at artwork, it is difficult to assess what is the particular 'task' or purpose of a viewer when none has been set explicitly, as is typically the case in the natural settings of museums and art galleries. Indeed the definition of what is considered art has changed many times and is often a very individual concept; thus the experience of art is also very subjective.

So far, the majority of eye tracking studies looking at art have used photographic images displayed in a lab or space other than a museum or gallery, but does this make a difference to how we view art? From a museum's point of view the authenticity of an original artwork is key to creating that specific 'kind of experience'.¹ With increasingly higher resolution images of artworks being made available to us through the internet, it could however be argued that the details seen within an original can be captured more accurately and in some cases be seen more clearly within their digital counterparts. Museums and art galleries document their collections for posterity but some within that field would argue that these are completely different objects rather than facsimiles (for different perspectives see 22,18,8). Previous research has suggested that while there is not a significant difference between the cognitive responses made to an original artwork and a digital representation, there is a difference in the affective responses made towards each of these.^{23,16} If these responses differ, could it be that the viewing strategies also differ? Or more simply put, do we look at originals and digital images differently?

After conducting an eye tracking study within Tate Britain using Ophelia by Millais, we decided to compare the eye movements of participants viewing the original painting to those looking at a digital image of the same artwork, to investigate whether these different presentation formats would influence eye movements, and in turn people's experience. Millais was one of the founding Pre-Raphaelite artists and painted this iconic image of Ophelia in 1851-1852. Depicting the death of the Shakespearean character, this painting holds much symbolism within the details, with each flower representing a different virtue or message, such as the daisies for innocence and the poppy for death, with which the depth of meaning is expanded.⁵



Figure 1: Digital reproduction of Millais' Ophelia.

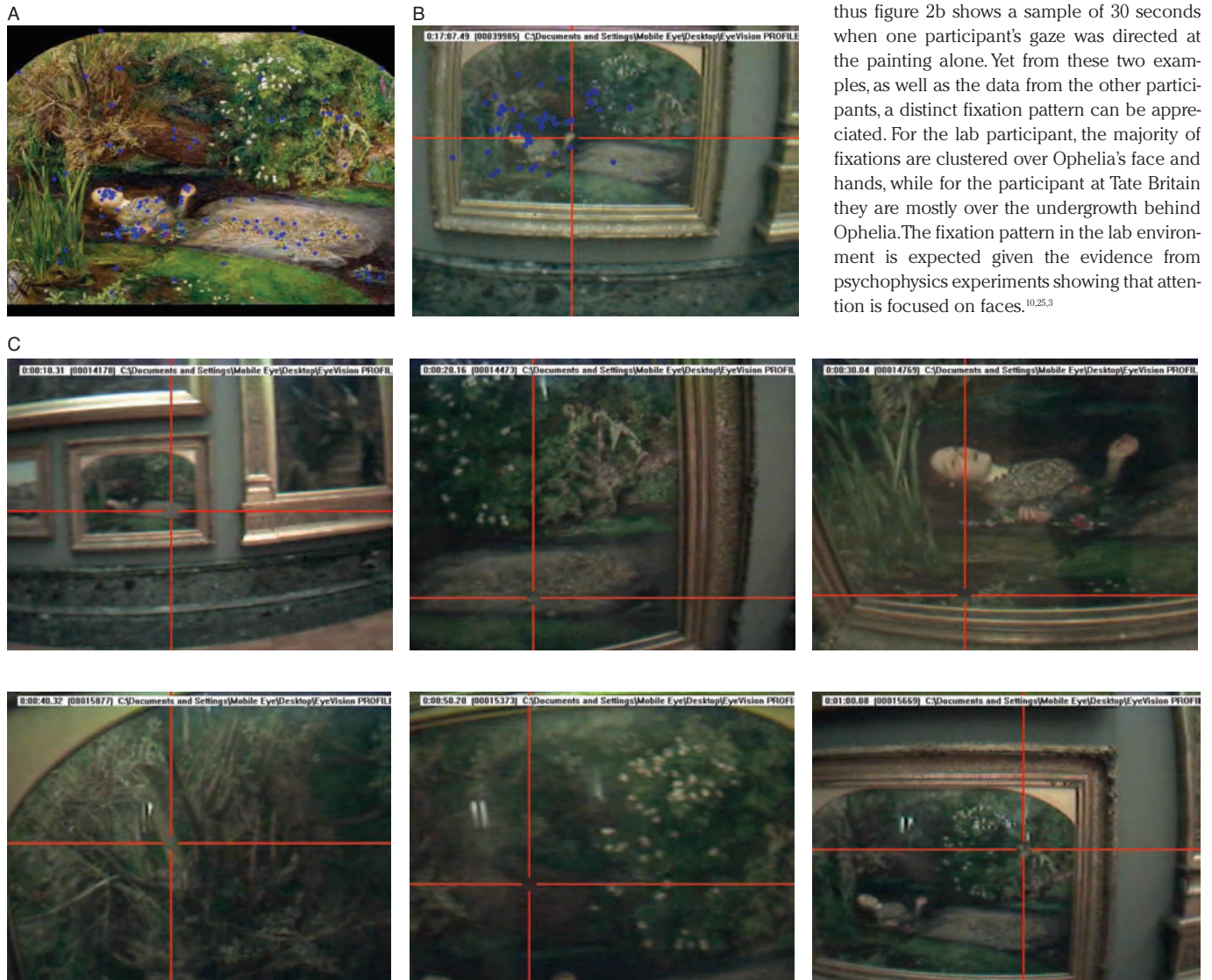


Figure 2. a: Typical pattern of fixations in the lab experiment. Each fixation is marked with a blue circle. b: Typical pattern of fixations in the gallery. c: Progression of movement while visually exploring Ophelia at Tate Britain. In each panel, the red cross marks the center of fixation.

In the study at Tate Britain six participants were guided around the galleries and were asked to look at Millais' Ophelia for a few minutes, while wearing a mobile eye tracker (ASL MobileEye). In the Lab study eight participants took part and viewed a digital image of Millais' Ophelia painting (see Figure 1) on a monitor within a booth. The digital reproduction was scaled to fit within 1024 x 768 pixels without cropping or stretching and was shown on a black background. Participants were asked to view the image for 1 minute without any particular task. The participants' eye movements were recorded using an EyeLink II in remote setting.

Figure 2 shows the typical fixation patterns for participants within the lab and within the art gallery. While figure 2a shows all fixations in the whole 60-second trial, figure 2b only shows the first 30 seconds of this participant's trial. Due to participants' freedom to constantly move within the art gallery, to approach the artwork and adjust their viewing angle and distance (illustrated with the series of snapshots in figure 2c), showing all fixations in a static image is difficult to represent accurately, thus figure 2b shows a sample of 30 seconds when one participant's gaze was directed at the painting alone. Yet from these two examples, as well as the data from the other participants, a distinct fixation pattern can be appreciated. For the lab participant, the majority of fixations are clustered over Ophelia's face and hands, while for the participant at Tate Britain they are mostly over the undergrowth behind Ophelia. The fixation pattern in the lab environment is expected given the evidence from psychophysics experiments showing that attention is focused on faces.^{10,25,3}

To inspect whether the abovementioned difference was significant across all subjects, two regions of interest were defined for both sets of data; the first around the whole figure of Ophelia and the second being the rest of the painting. Fixations made out of the image/painting were discarded. For both the data collected in the lab and at Tate Britain, we analyzed the number of fixations in each region in the first 60 seconds of viewing, comparing those on the figure of Ophelia to those on the rest of the painting. As can be seen in Figure 3, overall participants in the lab did fixate more upon the figure of Ophelia, whereas at Tate Britain more fixations were made with in the area of the painting surrounding her. In fact, both for the Tate and lab studies there was a significant difference between the number of fixations made to the two areas of the painting but showing exactly the opposite effect: in the recordings at Tate Britain, subjects tended to look significantly less to Ophelia than the rest of the painting $p < 10^{-3}$ (T-test), whereas in the lab subjects tended to fixate significantly more at Ophelia $p < 10^{-5}$ (T-test). To further explore this different pattern of viewing the painting in the lab and the museum, we calculated the difference of the number of fixations in the two regions for both groups of subjects and compared them with a T-test. This analysis showed that the differences between looking at Ophelia and the rest of the painting obtained for the subjects in the museum and in the lab was highly significant $p < 10^{-8}$ (T-test).

These contrary viewing patterns show that while the participants in the lab study focused on the smaller area of Ophelia, those in the Tate study explored more thoroughly the original artwork, exploring the larger area surrounding Ophelia. It could in principle be expected that a typical psychophysics effect of being attracted to the face, as the most salient feature (see 19 among many others) would be seen in participants in both studies. While in the lab this effect was prominent, in the museum subjects tended to explore the surrounding area of the painting, which contributes to the context in which Ophelia lies. Moreover, in the museum subjects may become interested in how the different details were painted, something one cannot appreciate in the lab. In other words, if we zoom into details in the museum, we see the brushstrokes and the texture of the paint, whereas if we do the same in the lab, we just see pixels. And unless one have telescopic vision this analysis of details follows a gradual approach to the artwork where the visitor has been drawn or directed to get closer and inspect the painting. Moreover, the onset of viewing a digital image

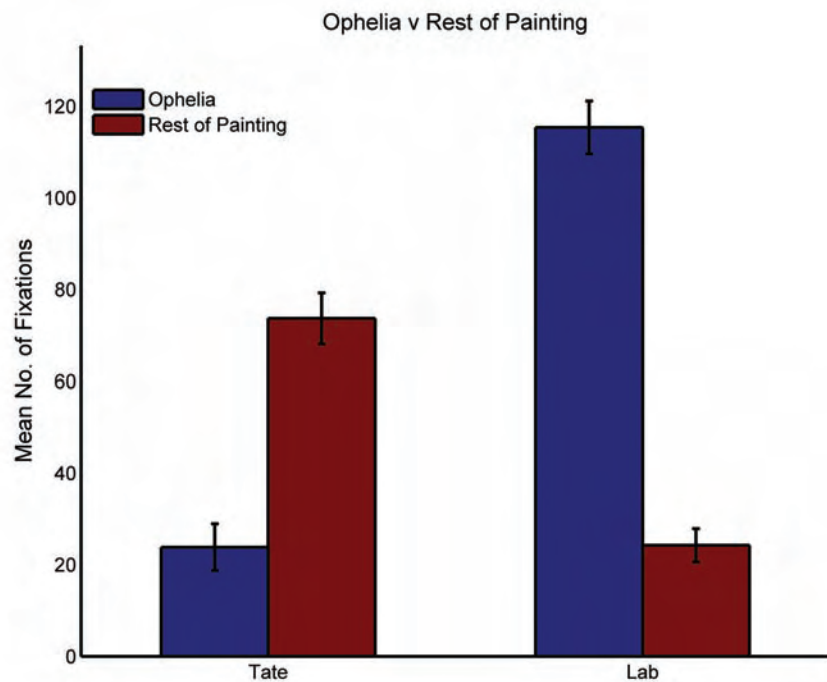


Figure 3: Mean Number of Fixations over First Minute of viewing for the subjects looking at Millais' Ophelia at Tate Britain and in the lab (Error bars denote SEM).

in a lab environment is completely different, where by participants are immediately faced with a presented image at a set distance and for a predefined length of time.

The actual physical behavior of the viewer differs when in the lab compared to when in the art gallery. In the lab the participants were sitting down instead of standing and being free to walk about in the gallery, however, those in the lab did not feel so restricted as to stop them pointing, or tilting their heads to look at the image from a different angle. While at Tate, participants would alter their stance to adjust their viewing position or distance (as can be seen from figure 2c) and when looking at Ophelia this head tilt behaviour was much more prominent than in the Lab. Participants tilted their heads towards the left which brought them closer to a face on position with Ophelia which would corroborate with previous research which suggests the pull for viewers to read figures faces and to see them the correct way up.^{19,24}

So what is it that causes this change in viewing behavior? Is it the physicality of the image or the 'aura' of the original, as Walter Benjamin puts it, the context from which it comes and where it is seen?²¹ Of course the ideal situation would be to show both the original artwork in the lab and the digital image in

the art gallery in order to get a full view of how image format and environment influence visual exploration. Although it would be possible to take a laptop into Tate to display the digital image of Ophelia it is obviously unfeasible to take Millais' original out of Tate and into a lab setting. We can only speculate how this would influence the viewing behavior. Another point to be taken into consideration is that while the size of the original painting was close to that of the displayed digital image, it was still slightly larger, something that could also influence the eye fixation patterns. Despite the small group sizes and variety of individuals involved, this differentiation of viewing pattern between these two environments was clear. Since it could be extrapolated from this study that viewers are likely to explore artworks more fully when seen in their original form within a museum, an emphasis must be put upon the importance of the viewing environment to art appreciation. This poses a challenge to scientists to be able to conduct experiments in the real world, removed from the controlled environments of the lab. Moreover, it would be then interesting to see if these findings generalise when also taking into account the individuality of the participants, their cultural backgrounds, prior knowledge and experience.

If we zoom into details in the museum, we see the brushstrokes and the texture of the paint, whereas if we do the same in the lab, we just see pixels

Today with the Internet and the increasing use of digital media, it could be asked what is the point in visiting a museum or gallery to view art? One can access many artworks on the Internet along with the relevant information, but these are all just digital images, representations of the real thing. It could be argued that seeing the genuine piece of art really makes a difference to the experience, and indeed from this study alone, and for at least this one artwork, viewers do look at the original differently than a digital representation. Whether it is the texture and physicality of the artwork itself, the gallery environment or both that directs this wider exploration of the painting, it is clear that through the experience of the original the viewers are looking for more than just the most salient features. While digital images can capture increasingly high details to the point where the naked eye cannot see, they often lack this propensity to encourage the curiosity of the viewer; thus museums, art galleries and the art and objects they hold, still have the power to enthrall their patrons and make us look at the world in a different way. ♦

REFERENCES

1. Benjamin W. *The work of art in the age of mechanical reproduction*. In Arendt H (ed.) *Illuminations*. (New York: Schocken Books, 1985 [1936]).
2. Berlyne DE. *Aesthetics and Psychobiology*. (New York: Appleton-Century-Crofts, 1971).
3. Buswell GT. *How People Look at Pictures: A study of the psychology of perception in art*. (Chicago: University of Chicago Press, 1935).
4. Cavanagh P. *The artist as neuroscientist*. *Nature* 2005;434(7031):301-307.
5. Curnow H. *Tate | Work in Focus: Millais' Ophelia* http://www.tate.org.uk/ophelia/subject_symbolism.htm [accessed on 28.04.2011]
6. Duchowski AT. *Eye tracking methodology: theory and practice*. (London: Springer, 2007).
7. Eagleman DM. *Visual Illusions and Neurobiology*. *Nature Reviews Neuroscience* 2001;2(12):920-926.
8. Edwards E. *Photographs and history: emotion and materiality*. In Dudley S (ed.) *Museum Materialities* (London: Routledge, 2010):21-38.
9. Gazzaniga M. *Human: The science behind what makes us unique*. (New York: Ecco, 2008)
10. Humphrey K, Underwood G. *The potency of People in Pictures: Evidence from sequences of eye fixations*. *Journal of Vision* 2010;10(10):19.
11. Ison MJ, Quian Quiroga R. *Selectivity and invariance for visual object perception*. *Frontiers in Bioscience* 2008; May 1: 4889-4903.
12. Karacan H, Hayhoe M. *Is attention drawn to changes in familiar scenes?* *Visual Cognition* 2008;16(2-3):356-374.
13. Kawabata H, Zeki S. *Neural Correlates of Beauty*. *Journal of Neurophysiology* 2004;91(4):1699-1705.
14. Leder H, Belke B, Oeberst A, Augustin D. *A model of aesthetic appreciation and aesthetic judgments*. *British Journal of Psychology* 2004;95:489-508.
15. Livingstone M. *Vision and Art: The biology of seeing*. (New York: Abrams, 2002).
16. Locher PJ, Smith JK, Smith LF. *The influence of presentation format and viewer training in the visual arts on the perception of pictorial and aesthetic qualities of paintings*. *Perception* 2001;30:499-465.
17. Logothetis NK, Sheinberg DL. *Visual Object Recognition*. *Annual Review of Neuroscience* 1996;19:577-621.
18. Parry R. *Recoding the Museum: digital heritage and the technologies of change*. (London: Routledge, 2007).
19. Pascalis O, Kelly DJ. *The Origins of Face Processing in Humans: Phylogeny and Ontogeny*. *Perspectives on Psychological Science* 2009;4(2):200-209.
20. Quian Quiroga R, Pedreira C. *How do we see art: an eye-tracker study*. (2011 submitted).
21. Ramachandran VS, Hirstein W. *The Science of Art: A Neurological Theory of Aesthetic Experience*. *Journal of Consciousness Studies* 1999;6(6-7):15-51.
22. Sassoon J. *Photographic materiality in an age of digital reproduction*. In Edwards E and Hart J (eds.) *Photographs Objects Histories: on the materiality of the image* (London: Routledge, 2004) 186-202.
23. Taylor BL. *Reconsidering Digital Surrogates: Towards a viewer-orientated model of the gallery experience*. In Dudley S (ed.) *Museum Materialities: Objects, Engagements, Interpretations* (London; New York: Routledge, 2010).
24. Van Belle G, De Graef P, Verfaillie K, Rossion B, Lefevre P. *Face Inversion Impairs Holistic Perception: Evidence from gaze-contingent stimulation*. *Journal of Vision* 2010;10(5):10.
25. Yarbus AL. *Eye-Movements and Vision*. (New York: Plenum Press, 1967).
26. Zeki S. *Inner Vision: An Exploration of Art and the Brain*. (Oxford: Oxford University Press, 1999).

Grete Lundbeck European Brain Research Foundation Call for Nominations for

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Epilepsy simplified

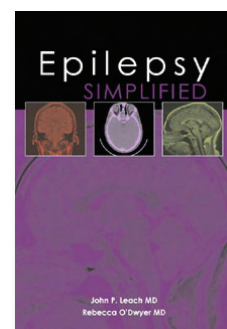
Simplified! How one wishes that neurological practice could be so! Hence an initial tentative welcome to a book promising this in the complicated field of epilepsy. Do the two authors, based on opposite sides of the Atlantic, deliver?

Chapters are brief, easy to read, and occasionally leavened with the wit for which one of the authors (JPL) has become famous (or is that infamous?). Definitions precede epidemiology, aetiology and pathophysiology, history taking, differential diagnosis, classification (including a few words on the 2010 ILAE classification), seizure types and antiepileptic drugs. The practical nature of the text is illustrated by the inclusion of chapters entitled "When things go well" and "When things are not going well", as well as accounts of epilepsy at the extremes of age, specific "situations" (viz. Women; Single seizure; Pseudoseizures), and rounded off with "Common questions". The absence of an index is a deficiency.

One of the potential risks of "simplified" is, of course, oversimplification, but to my reading the authors do not fall into this trap (including SLE with the vasculitides, p12, may be one, nit-picking, example). Indeed there are wise words: "more harm is done by hasty diagnosis which has to

be reversed in later years than is caused by a delay in commencing treatment" (p26). Use of the first person singular in some chapters is a little confusing (perhaps the authors wrote specific chapters individually?), and there is some repetition (e.g. re lacosamide, pp78 and 90; tables on pp8 and 148, 31 and 153), not necessarily a bad thing in a didactic work. Some mix up in scan labelling (T1 for T2; pp63, 64, 66) might have been resolved at copy editing/proof reading, as may infelicitous expression (p31) which might engender the belief that recovery from seizure is quicker than from syncope. I was not sure about the place of a chapter on "Future developments in the treatment of epilepsy" in a such a volume, and would have liked some comment on eyes open or closed in the differentiation of seizures and pseudoseizures (pp28, 155): useful or useless? Classifying lamotrigine amongst those antiepileptic drugs "without an effect on contraceptive efficacy or pharmacokinetics" (p141) is not, I think, correct.

Overall, this book is a welcome addition to short epilepsy texts, presenting information at high density whilst still being practical, and can be confidently recommended to any student, undergraduate or postgraduate, who needs to be brought up to speed in epilepsy.



Reviewed by:
AJ Larner, WCNN, Liverpool.

One of the potential risks of "simplified" is, of course, oversimplification, but to my reading the authors do not fall into this trap

Authors: JP Leach, R O'Dwyer. Published by: tfm publishing (2011). ISBN: 978-1-903-37873-1. Price: £30.00.

Case Studies in Dementia

This volume contains a series of case reports on non-acute presentations in cognitive neurology. In just under 300 A5 pages, there are 39 cases, with some conditions covered more than once, from different perspectives.

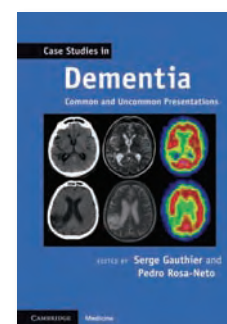
The patient-centred format of course provides immediate engagement, especially as many of the contributing authors are of international repute. The chapters on dementias associated with motor neurone disease were particularly strong, as were those on HIV dementia and normal pressure hydrocephalus.

Conversely, I would have liked to see more on sub-acute cognitive syndromes associated with autoimmunity (e.g. limbic encephalitis). I also thought that the progressive aphasia presentations might have been compared and contrasted more effectively.

My objective criticisms are largely matters of copy editing.

There were a few abbreviations not defined when first used (though most were the names of testing instruments familiar to many readers). More distractingly, the language register veered from the colloquial to the literary. 'Pertinaciously' (p177) may be permitted in a book on cognitive neurology (maybe not one on molecular neuroscience ...) but might be more at home in Henry James.

All in all, Gauthier and Rosa-Neto's book is accessible and insightful, and easily digested. It could be of interest to any neurologist or any clinician seeing patients with cognitive complaints. It sits comfortably between weighty reference tomes, on the one hand, and the lighter cognitive assessment manuals on the other (e.g. Hodges' Cognitive Assessment for Clinicians, OUP). To the trainee (perhaps embarking on a posting in cognitive neurology), however, I would recommend one of the latter first.



Reviewed by: Rhys Davies

The patient-centred format of course provides immediate engagement, especially as many of the contributing authors are of international repute

Editors: Serge Gauthier, Pedro Rosa-Neto. Published by: Cambridge University Press, (2011). ISBN: 978-0-521-18830-2. Price: £40.00.

Authors

**Koen V Haak**

is about to complete his PhD in Visual Neuroscience at the Laboratory for Experimental Ophthalmology and BCN Neuroimaging Center, University Medical Center Groningen, University of Groningen, The Netherlands. His research interest is in how visual areas of the brain are organised in health and disease.

**Philip Clatworthy**

MB BChir, PhD, is a clinical neuroscientist studying recovery and rehabilitation of vision in neurological disorders, particularly stroke, and has published on psychophysics, computational modelling, and neuroimaging in the human visual system. He is a specialist registrar in neurology and stroke medicine at Frenchay Hospital, Bristol, UK.

**Tony Morland**

BSc, ARCS, PhD, DIC, is a visual neuroscientist studying human visual function in health and disease. He has used EEG and fMRI to characterise visual signals in the brain, particularly in patients with visual dysfunction. He is a professor in the University of York's Psychology Department, is Deputy Director of the York Neuroimaging Centre and is Head of the Centre for Neuroscience in the Hull-York Medical School.

Correspondence to:

Professor Tony Morland
Department of Psychology,
University of York,
York, YO10 5DD, UK.

Series Editor

**Simon Hickman**

Series editor Simon Hickman is a Consultant Neurologist at the Royal Hallamshire Hospital, Sheffield. He is also an Honorary Senior Lecturer at the University of Sheffield. He graduated from the University of Cambridge. He trained in Neurology in Nottingham and London and obtained a PhD in magnetic resonance imaging in optic neuritis. He has continued his research interest in optic neuritis with his clinical practice.

Welcome to the first in a series of articles on Neuro-Ophthalmology in ACNR. Neuro-ophthalmology, by definition, lies at the interface of neurology and ophthalmology, but I believe it should not fall between the two in terms of interest and expertise. I hope this series of articles will be of use in both conveying recent developments in the field and in informing clinical practice.

Assessing visual dysfunction with fMRI

Functional magnetic resonance imaging (fMRI) is a well-established technique in visual neuroscience, but is not widely used in ophthalmology or neuro-ophthalmology practice, despite the information it can provide about neural function and dysfunction in patients. Here, we review some of the ways that we have used fMRI to characterise visual dysfunction, and discuss fMRI generally as a candidate for assessing visual function clinically.

The studies described largely take advantage of the fact that visual cortex is arranged retinotopically as Holmes revealed almost a century ago.¹ Selectively stimulating different regions of the visual field allows multiple visual field mappings to be identified reliably in individuals with fMRI (as shown in Figure 1, see also refs 2,3). This ability to produce informative data from a single individual is vital for a clinically viable tool and sets this method apart from many other fMRI methods.

We have used the retinotopic mapping procedures to characterise visual dysfunction that arises from a number of different causes, at different stages in the human visual system.

Retinal lesions: Recently, we assessed cortical signals in patients with retinal lesions. We were motivated by neuroscientific questions concerning reorganisation of cortical maps, something previously reported in patients who are born without functioning foveal photoreceptors.⁴ We tested a relatively large number of patients with macular degeneration (those with Stargardt's disease and the more common age-related form), finding that the cortex does not remap visual information in these patients.⁵ This allows for the intriguing possibility that assessing cortical signals might helpfully determine retinal sensitivity in ophthalmological disease; the activity at a particular spatial location within the map should predict visual sensitivity. This might be used in a number of ways. We are currently assessing the effectiveness of antiangiogenic treatment for age-related macular degeneration, and changes in activity in the calcarine map largely reflect the changes in conventional visual measures of acuity and perimetry.⁶ One of the advantages of measuring cortical signals is that the map is fixed, so no matter where the eyes are pointing, if the retina is stimulated (with a Ganzfeld stimulus for instance) activity in the cortex must reflect intact retinal processing. This is helpful in patients who find it hard to fixate for perimetry measurements.

Cortical lesions: We derived visual maps in the early visual areas of a patient, GY, who exhibits residual

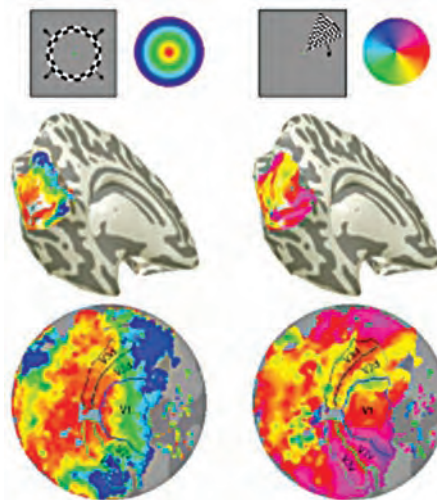


Figure 1: Retinotopic maps in a normally sighted individual. Top: the two stimuli that systematically move through eccentricity (left) and polar angle (right). Such stimuli elicit a travelling wave of activity in cortical retinotopic representations. The location in the visual field that elicits activity is colour coded (as indicated in the key to the right of the stimuli). When this colour coding of activity is presented on 3-D (middle row) and flattened (bottom row) surface reconstructions of the cortex, multiple visual maps in the occipital lobe can be identified. To the left and right data are given for activity elicited by rings and wedges, revealing maps of eccentricity and polar angle, respectively. On the flattened reconstructions the early visual areas, V1, V2 and V3, are outlined, demarcated by the representations of the vertical and horizontal meridians, visible on the polar angle maps (right).

visual capacities in his right, "blind" visual field following a lesion to the calcarine cortex in the left hemisphere.⁷ This patient displayed maps in early visual areas that largely reflected his scotoma, but subtle differences in the mapping of extrastriate regions were also evident when only the regions of the scotoma were stimulated. This modified mapping in the early visual cortex could be explained on the basis of changes in local connections, indicative of reorganisation. Reorganisation in this case may not come as a surprise given that the patient was tested over 30 years after a lesion sustained at the age of 8. Interestingly, recent evidence from diffusion tensor imaging also seems to indicate reorganisation of the visual pathways in this patient.⁸

Over recent years we have been consulted by neurosurgeons, keen to evaluate the potential visual effects of removing lesions close to the visual representations of the brain. In one such case a mass was located in a

lateral area of the occipital pole. Although the location of visual maps is broadly consistent across individuals, the specific location of the representation of the central visual field varies considerably. Our mapping procedures showed that the mass was proximate to representations of the fovea in early visual areas allowing the surgeon to gauge the potential impact of the procedure on visual function. In addition to the primary visual cortex more than twenty extrastriate visual maps can be identified. Many of these have specific roles in visual perception, with localised lesions giving rise to specific visual deficits such as cerebral achromatopsia.^{9,10} Knowing the spatial relationship between a potential site for surgery and a patient's extrastriate visual maps allows the impact of surgery on perception to be predicted.

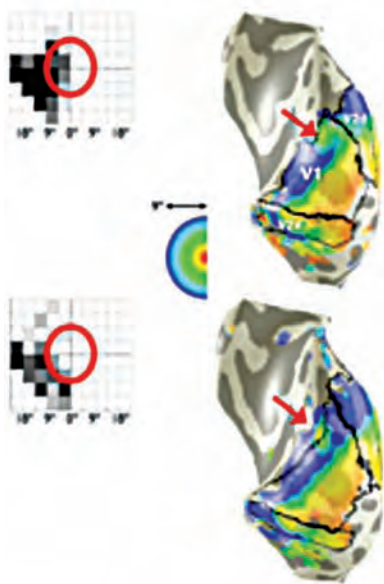


Figure 2 Visual fields as assessed behaviourally, left, and with fMRI, right. Data are given for two exams (first – top; second – bottom) separated by 12 weeks. At first the scotoma is dense in the lower left quadrant, but becomes less so by the second exam. This change is mirrored by a change in the cortical map in primary visual cortex, V1 (arrows). The map originally represents central locations but not peripheral (coded blue). Later the more peripheral locations are mapped.

Afferent visual pathways: Some developmental disorders can give rise to abnormal routing of visual information from the eye to the brain, which would escape detection with anatomical imaging. In individuals with albinism the decussation of the optic nerve at the optic chiasm is abnormal with a larger number of fibres originating from the temporal retina crossing to the hemisphere contralateral to the eye. This gives rise to abnormal lateralisation and mapping of signals in the visual cortex. We found that in humans the cortical map of the abnormal retinal input coexists with the map of the normal retinal input such that a region of primary visual cortex will respond to equal but opposite locations in the ipsilateral and contralateral visual fields.¹¹ When we evaluated how fMRI might be used to detect the presence of albinism,^{12,13} we found that fMRI is very effective for detecting the abnormal lateralisation of visual signals. Indeed it was equal to if not better than current electrophysiological methods used

clinically.¹³ Detecting albinism can be a challenge because pigmentation alone is not diagnostic.

When lesions occur in white matter, visual field defects are less straightforward to predict on the basis of anatomical imaging alone. We described how the brain signals we measured in response to visual stimuli could be used to generate a map of visual locations to which the brain responded in one such patient.¹⁴ In other words, we could use the brain activity to predict where the patient could see. The individual in question had undergone surgery to remove a left hemisphere parieto-occipital mass. The medial occipital cortex was intact following surgery, but the patient complained of difficulty reading and initial perimetry measurements pointed only to a questionable central field defect. Our fMRI mapping experiments indicated that left calcarine cortex no longer responded to a central (<3 deg) region of the lower right quadrant. Following up on this finding, finer perimetry measures of central visual field revealed a scotoma in the predicted location. It was likely therefore that the surgery resulted in a lesion of the optic radiation.

In more recent work we have looked at a series of patients with known optic radiation lesions due to stroke. We followed one case over time and here we report on the changes in the patient's visual sensitivity and cortical activity. Figure 2 shows that the visual field recovers, particularly within the red circled region. The visual field maps represented on the surface reconstructions of the occipital lobe also exhibit a change between the examinations. Specifically, the part of dorsal primary visual cortex (V1) that would normally represent the visual field defect exhibits a disrupted map that later becomes largely normal, reflecting the change in visual sensitivity. As with the previously discussed case, the cortex initially fails to respond strongly to the region of the field deficit, but in this case as visual sensitivity recovers, so too do the cortical signals. It is noteworthy that the cortical representation of the field deficit is not silenced, but instead responds to a different field location. This could be interpreted as reorganisation, but the alternative explanation, which we currently favour, is that the normal receptive field properties of neurons could lead to the signals we record (see refs 4,5).

What issues have been and need to be overcome to allow fMRI to be translated into clinical assessments of vision? First, reliable information must be obtainable from a single individual. This has been largely overcome, however it still remains to document carefully the reliability of signals within an individual from session to session and within sessions. Second, and related to reliability, the time it takes to gather sufficient data to characterise an individual's visual capacity has not been systematically explored. While our early research used examination times of 30 minutes, we have more recently gathered data over longer repeated examination periods. Clearly, a clinical application would need to minimise examination time and establishing a suitable trade-off between examination duration and data quality needs to be established. Third, validation against other measures is required. We have done this to some extent, but further work is required. Fourth, as for other measures, norms

need to be established, a process that is time consuming and may require separate values for each site at which measurements are taken. Fifth, fMRI yields large data sets that need to be processed and then assessed by experts. This process is time consuming compared to the examination time. More work is required on automated procedures to process data. Finally, fMRI is expensive, and cost will always be a consideration and perhaps the determining factor. However, if examination durations can be made short and added to an already required anatomical examination, and if much of the analysis can be automated, then costs will be reduced substantially.

While there are clearly factors holding fMRI back from clinical application, techniques continue to benefit from rapid technological advances that will likely feed through to clinical imaging systems. For example, increasing field strength and the number of coil channels on scanners has increased signal quality. Developments of this type have not hit a ceiling so much more can be expected in the future. Moreover, recent research has shown that novel contrast agents could yield enormous increases in signal over noise.¹⁵ Taken together such technological advances will improve the efficiency of fMRI data acquisition, which in turn could lead to faster, cheaper visual testing with fMRI. ♦

REFERENCES

- Holmes G. Disturbances of vision caused by cerebral lesions. *British Journal of Ophthalmology* 1918;2:353-84.
- Sereno MI, Dale AM, Reppas JB, et al. Borders of multiple visual areas in humans revealed by functional magnetic resonance imaging [see comments]. *Science* 1995;268:889-93.
- Engel SA, Glover GH, Wandell BA. Retinotopic organization in human visual cortex and the spatial precision of functional MRI. *Cereb Cortex* 1997;7:181-92.
- Baseler HA, Brewer AA, Sharpe LT, Morland AB, Jagle H, Wandell BA. Reorganization of human cortical maps caused by inherited photoreceptor abnormalities. *Nat Neurosci* 2002;5:364-70.
- Baseler HA, Gouws A, Haak KV, et al. Large-scale remapping of visual cortex is absent in adult humans with macular degeneration. *Nat Neurosci* 2011;14:649-55.
- Baseler HA, Gouws A, Crossland MD, et al. Objective Visual Assessment of Anti-Angiogenic Treatment for Wet AMD. *Optom Vis Sci* 2011;88:X.
- Baseler HA, Morland AB, Wandell BA. Topographic organization of human visual areas in the absence of input from primary cortex. *J Neurosci* 1999;19:2619-27.
- Bridge H, Thomas O, Jbabdi S, Cowey A. Changes in connectivity after visual cortical brain damage underlie altered visual function. *Brain* 2008;131:1433-44.
- Meadows JC. Disturbed perception of colours associated with localized cerebral lesions. *Brain* 1974;97:615-32.
- Kennard C, Lawden M, Morland AB, Ruddock KH. Color Identification and Color Constancy Are Impaired in a Patient With Incomplete Achromatopsia Associated With Prestriate Cortical Lesions. *Proceedings of the Royal Society of London Series B-Biological Sciences* 1995;260:169-75.
- Hoffmann MB, Tollhurst DJ, Moore AT, Morland AB. Organization of the visual cortex in human albinism. *J Neurosci* 2003;23:8921-30.
- Morland AB, Hoffmann MB, Neveu M, Holder GE. Abnormal visual projection in a human albino studied with functional magnetic resonance imaging and visual evoked potentials. *J Neurol Neurosurg Psychiatry* 2002;72:523-6.
- von dem Hagen EA, Hoffmann MB, Morland AB. Identifying human albinism: a comparison of VEP and fMRI. *Invest Ophthalmol Vis Sci* 2008;49:238-49.
- Morland AB, Baseler HA, Hoffmann MB, Sharpe LT, Wandell BA. Abnormal retinotopic representations in human visual cortex revealed by fMRI. *Acta Psychol (Amst)* 2001;107:229-47.
- Adams RW, Aguilar JA, Atkinson KD, et al. Reversible interactions with para-hydrogen enhance NMR sensitivity by polarization transfer. *Science* 2009;323:1708-11.

Series Editor



Alan Carson

Series editor Alan Carson is a Consultant Neuropsychiatrist and Part-time Senior Lecturer. He works between the Neurorehabilitation units of the Astley Ainslie Hospital and the Department of Clinical Neurosciences at the Western General Hospital in Edinburgh. He has a widespread interests in neuropsychiatry including brain injury, HIV and stroke. He has long-standing research and teaching collaboration with Jon Stone on functional symptoms in neurology.

Series Editor



Jon Stone

Series editor Jon Stone is a Consultant Neurologist and Honorary Senior Lecturer in the Department of Clinical Neurosciences in Edinburgh. Since 1999 he has developed a research and clinical interest in functional symptoms within neurology, especially the symptom of weakness. He writes regularly on this topic in scientific papers and for textbooks of neurology and psychiatry.

Correspondence to: Email: Jon.Stone@ed.ac.uk

Welcome to the seventh in a series of articles in *ACNR* exploring clinical dilemmas in neuropsychiatry. In this series of articles we have asked neurologists and psychiatrists working at the interface of those two specialties to

write short pieces in response to everyday case-based clinical dilemmas. We have asked the authors to use evidence but were also interested in their own personal views on topics. We would welcome feedback on these articles, particularly from readers with an alternative viewpoint.



Dr Killian Welch

is a Consultant Neuropsychiatrist working in the Neurorehabilitation units of the Astley Ainslie Hospital and the Department of Clinical Neurosciences in Edinburgh. He has a clinical and research interest in Substance Misuse Psychiatry, this focusing particularly on the relationship between substance misuse and psychosis.

Correspondence to:

Robert Ferguson Unit,
Royal Edinburgh Hospital,
Edinburgh EH10 5HF, UK.
Tel: 0131 5561282
Email: Killian.Welch@
nhslothian.scot.nhs.uk

When is an Alcohol Problem a Problem?

Case

A 35-year-old man was found collapsed in the street following an assault. On admission he smelt strongly of alcohol and he had a GCS score of 10. CT scan showed minor intracerebral bleeds compatible with a moderate brain injury. The trauma required no acute medical intervention aside from suturing of a laceration on his forehead. Given an elevated GGT and a history of substantial alcohol intake from his wife a reducing regime of benzodiazepines was initiated. Two days post admission he was orientated, and when reviewed the following day a coherent history was taken. On assessment there were moderate impairments of memory and executive function, but he was thought to be safe to discharge on proviso that his wife took care of him. Alcohol history revealed that although he does not give a history of significant withdrawal symptoms, he does consume approximately 4 pints of continental lager (12 units) a day, and experiences strong cravings for alcohol. He doesn't drink in the mornings. Does this man have an alcohol problem? Is his alcohol consumption likely to impact on current clinical findings? Is his alcohol consumption putting him at future risk? What should you do?

Does this man have an alcohol problem?

'Problem drinking' is a broad term encompassing people not dependent on alcohol but whose consumption is causing harm (physical, psychological or social) through to the severely physiologically dependent. A diagnosis of alcohol dependence is made when three from the following six symptoms are present: craving; impaired ability to control use; withdrawal; tolerance; neglect of alternative pleasures/interests; and continued use despite harmful consequences.¹ It is craving rather than withdrawal that is the central feature of the syndrome. The patient was consuming 84 units of alcohol a week and clearly described craving; a more detailed history will likely demonstrate alcohol dependence.

Is his alcohol problem relevant to current clinical findings?

The archetypal picture of alcohol-associated cognitive deficits is Korsakoff's syndrome. This is associated with thalamic and mamillary body atrophy,² and arises as a consequence of the thiamine deficiency. In its purest form patients are unable to form new declarative memories in the context of relatively intact attention and working memory. It is recognised however that people with no history of Wernicke-Korsakoff's syndrome can still manifest alcohol-related cognitive impairment. This is believed to be due to the direct toxic effect of alcohol on the brain. The frontal and parietal lobes are particularly vulnerable,³ and deficits include attentional, visuospatial and executive impairment.

The cognitive deficits associated with alcohol use and traumatic brain injury (TBI), are similar. Given that co-occurrence of the two conditions is common, this means that determination of the aetiology of cognitive impairments in a heavy-drinking individual who has experienced a TBI is difficult. Visuospatial deficits may be particularly pronounced in alcohol-related damage, but this observation has little clinical utility; in a recent comparative study patients with mild TBI and alcohol abuse could not be reliably differentiated by cognitive testing.⁴ While impairment temporally associated with a TBI can be attributed to it, in practice establishing if cognitive deficits are new or established can be very difficult. Collateral history is frequently unobtainable in socially isolated individuals with alcohol problems. Cognitive deficits solely attributable to alcohol in uncomplicated alcoholics (i.e. no history of medical complications) are uncommon before the fifth decade.⁵ This, particularly if the history indicated deficits were new, would suggest they were caused by the TBI. Deficits of either aetiology should improve with time but this will be jeopardised by ongoing alcohol use.

Is his alcohol problem putting him at future risk?

Use of alcohol has long been associated with TBI. 1/3 to 2/3 of patients with TBI are intoxicated at the time of injury, and approximately half of alcoholics have a history of TBI with loss of consciousness and/or hospitalisation.^{6,7} A TBI often encourages individuals to address their alcohol problem; one year post TBI 30% of individuals were completely abstinent from

alcohol, compared to only 8.4% reporting abstinence pre-injury.⁸ Unfortunately the effects appear transient and consumption increases again with time. Young males are most likely to return to drinking.^{8,10} Several studies have reported an association between a history of alcohol abuse / dependence at the time of injury and poorer outcomes,⁶ but few have explored this by actually ascertaining alcohol use after TBI. Nonetheless, it is generally accepted that alcohol use after TBI can contribute to seizures, increase risk of further head injury, diminish the benefits of rehabilitation, exacerbate cognitive and behavioural impairments and lower mood.¹¹ Individuals with a history of alcohol abuse/dependence require additional interventions, including substance abuse treatment and longer-term follow-up.¹²

What treatment is available?

Few studies have investigated the efficacy of alcohol treatments in the TBI population, so evidence must be extrapolated from the general population. This demonstrates that alcohol-based 'brief interventions' are useful and very cost-effective.^{13,14} They consist simply of identifying an alcohol problem and discussing the benefits of change. A motivational interviewing style maximises impact.¹⁵ This is a non-judgemental style of questioning which avoids confrontation and lecturing but helps the individual weigh up the pros and cons of change. The aim is for the patient to make their own arguments for change. In the TBI context the patient would be encouraged to consider the role alcohol played in acquisition of their injury, and the negative consequences ongoing use will have for recovery. It should be emphasised that consumption levels considered relatively low risk in the general population may be very detrimental post-TBI, and abstinence the aim, although any reduction is beneficial.

Brief interventions are primarily aimed at hazardous, but not yet dependent drinkers. The latter generally require more sophisticated treatment. The medical need for detoxification must always be considered, but maintaining abstinence poses the greatest challenges. Alcoholics Anonymous should always be suggested and local meeting times are available from their website (www.alcoholics-anonymous.org.uk). Patients often object to an assumed religiosity associated with the AA 'first step' of accepting one's powerlessness over drinking and turning control over to a 'Higher Power'. Interpretations of this vary however, and avowed atheists should not be deterred from attending AA. Attentional impairments or behavioural disturbance related to TBI may hamper or preclude attendance. Having a friend/relative/support worker accompany TBI individuals to the first few sessions can be helpful. This enables impaired insight to be addressed by subsequent reflection on how the issues discussed relate to them.

Referral to specialist alcohol problems services should be considered, directly or via the

GP. Outlining the patient's cognitive and other deficits will be of great assistance in planning treatment. As well as psychological treatment (again centring on fostering motivation for change), medically led alcohol services will consider pharmacological interventions. Most commonly used are antabuse, acamprosate and naltrexone, initiation of the former two also being possible in general practice.¹⁶ Antabuse works through its aversive effect, the 'flushing response' occurring on consumption of alcohol. It is contra-indicated in those with substantial medical co-morbidity (in whom hypotension would be hazardous) or cognitive impairment. If an individual can not remember they are on the drug then use is not feasible! Recent evidence suggests that baclofen, a GABA receptor agonist, may reduce craving and intake of alcohol.¹⁷ This requires further research. Relatives of alcoholics often request help. AlAnon (www.al-anonuk.org.uk) can be a useful resource for them.

Prognosis for alcohol misusers varies, this being influenced by social factors and severity of dependence. Overall approximately 2/3 of individuals receiving treatment show improvement.

What if the patient does not want to stop drinking

The patient states that he wishes to return home, where he intends to resume drinking. His wife states that she is not willing to take responsibility for his care in the present circumstances, and wishes him to remain in hospital. Can he be kept in hospital against his will?

The patient has documented cognitive deficits. This constitutes an 'impairment of functioning of mind', and raises the question of whether he has capacity to make the decision to leave hospital. Though he was deemed safe for discharge on the basis of his cognitive and general assessment, this was on the basis that his wife was willing to provide care for him in a safe environment. His wife's concerns now call this in to question, and the patient's capacity to make the decision to discharge himself must be specifically assessed.

To be able to ascertain this we must first be clear what risks the patient's cognitive impairment will place him in. These will not be limited to resumption of drinking, and other potential risks must also be identified. At the least this will necessitate occupational therapy functional assessment, addressing issues such as self care and safety in the kitchen.

Once the risks of discharge are clear, the central question is whether the patient has capacity to discharge himself given these risks. To have this capacity the patient must be aware of the potential adverse consequences of leaving hospital, understand the nature of these adverse consequences, consider them when making the choice to discharge himself and be able to communicate his reasons for making that choice. It is conceivable that his impairments of memory and executive function are such that he lacks the capacity to discharge himself. If this is the case, use of legislation could be considered to keep him in hospital. In

the UK it specifically states that a person is not regarded as mentally disordered by reason only of dependence on, or use of, alcohol or drugs. However, the mental disorder on the basis of which he could be detained would be the ongoing cognitive deficits consequent to TBI. Detention would be an outcome of last resort with less restrictive solutions being sought. One potential outcome would be the patient agreeing to remain in hospital a little longer (on a voluntary basis), until further improvements in memory and executive function meant he had capacity to make decisions about discharge; alternatively, discharge may be feasible with the input of community services. ♦

REFERENCES

1. World Health Organization. *The ICD-10 classification of mental and behavioural disorders: Diagnostic criteria for research*. 1993.
2. Kopelman MD, Thomson AD, Guerrini I, Marshall EJ. *The Korsakoff syndrome: Clinical aspects, psychology and treatment*. Alcohol and alcoholism. 2009;44(2):148.
3. Sullivan EV, Pfefferbaum A. *Neurocircuitry in alcoholism: A substrate of disruption and repair*. Psychopharmacology. 2005;180(4):583-94.
4. Iverson GL, Lange RT, Franzen MD. *Effects of mild traumatic brain injury cannot be differentiated from substance abuse*. Brain Injury. 2005;19(1):11-18.
5. Zinn S, Bosworth HB, Edwards CL, Logue PE, Swartzwelder HS. *Performance of recently detoxified patients with alcoholism on a neuropsychological screening test*. Addict Behav. 2003;28(5):837-49.
6. Parry-Jones BL, Vaughan FL, Cox WM. *Traumatic brain injury and substance misuse: A systematic review of prevalence and outcomes research (1994-2004)*. Neuropsychological rehabilitation. 2006;16(5):537-60.
7. Corrigan JD, Deuschle Jr JJ. *The presence and impact of traumatic brain injury among clients in treatment for co-occurring mental illness and substance abuse*. Brain Injury. 2008;22(3):223-31.
8. Ponsford J, Whelan-Goodinson R, Bahar-Fuchs A. *Alcohol and drug use following traumatic brain injury: A prospective study*. Brain Injury. 2007;21(13-14):1385-92.
9. Bombardier CH, Temkin NR, Machamer J, Dikmen SS. *The natural history of drinking and alcohol-related problems after traumatic brain injury*. Arch Phys Med Rehabil. 2003;84(2):185-91.
10. Kreutzer JS, Doherty KR, Harris JA, Zaster ND. *Alcohol use among persons with traumatic brain injury*. J Head Trauma Rehabil. 1990;5(3):9.
11. Kolakowsky-Hayner S, III EVG, Kreutzer JS, Marwitz JH, Meade MA, Cifu DX. *Post-injury substance abuse among persons with brain injury and persons with spinal cord injury*. Brain Injury. 2002;16(7):583-92.
12. Horner MD, Ferguson PL, Selassie AW, Labbate LA, Kniele K, Corrigan JD. *Patterns of alcohol use 1 year after traumatic brain injury: A population-based, epidemiological study*. Journal of the International Neuropsychological Society. 2005;11(03):322-30.
13. Crawford MJ, Patton R, Touquet R, et al. *Screening and referral for brief intervention of alcohol-misusing patients in an emergency department: A pragmatic randomised controlled trial*. The Lancet. 2004;364(9442):1334-9.
14. Solberg LI, Maciosek MV, Edwards NM. *Primary care intervention to reduce alcohol misuse*. Am J Prev Med. 2008;34(2):143-52.
15. Miller WR, Rollnick S. *Motivational Interviewing: Preparing People for Change*. The Guilford Press; 2002.
16. Scottish Intercollegiate Guidelines Network (SIGN). *The management of harmful drinking and alcohol dependence in primary care*. 2003. <http://www.sign.ac.uk/guidelines/fulltext/74/index.html>.
17. Flannery BA, Garbutt JC, Cody MW, et al. *Baclofen for alcohol dependence: A preliminary open-label study*. Alcoholism: Clinical and Experimental Research. 2004;28(10):1517-23.

Unconscious Processing Following Visual Cortex Damage



Sara Ajina

is a Specialist Registrar in Rehabilitation Medicine in London whose research focuses on unconscious visual processing both in health and in disease, and how this may be applied to rehabilitation following visual cortex damage.



Geraint Rees

is a Professor of Cognitive Neurology and Director of the UCL Institute of Cognitive Neuroscience. His work focuses on the neural basis of consciousness in health and disease.

Correspondence to:

Sara Ajina,
Royal National Orthopaedic Hospital,
Brockley Hill, Stanmore,
Middlesex, HA7 4LP, UK.
Email: Sara.Ajina@rnoh.nhs.uk

Damage to visual cortex leads to direct impairment of vision with significant consequence to everyday life. Homonymous hemianopia, a loss of visual function on one side of space, is an extremely common and debilitating condition, yet it remains poorly understood and there are no effective treatments currently available. Despite this, considerable evidence exists to suggest stimuli presented to a blind hemifield can undergo processing and influence behaviour in a phenomenon known as 'blindsight'.¹ This can occur despite the individual often being completely unaware of the stimulus. The full nature and extent of such processing remains unclear, but it suggests residual processing within damaged cortex or recruitment of alternate visual pathways may occur. Here we evaluate the literature including important recent advances, and discuss how such residual processing may serve as a potential substrate for rehabilitation.

Clinical problem

Every year there are approximately 150,000 new cases of stroke in the UK, with at least a sixth estimated to have persistent hemianopia.² Similar deficits may follow traumatic brain injury and neoplasia. Hemianopia is notoriously difficult to treat, with spontaneous recovery unlikely after six months. Therapeutic targets to date include attempts to restore the deficit itself (the focus of this review), enlarge the field of gaze through compensatory mechanisms including saccadic eye-movements, and use of orthotic devices to increase the angle of vision in intact fields. In the majority of cases, such techniques have very limited benefit.

Residual processing

Past research hinted at great promise for the recovery of visual cortical disorders. With time, however, early positive findings have been questioned and the current situation is less clear. One critical issue is that the physiological target for rehabilitation has been unclear, in particular for complete hemianopia. We suggest that to make real progress, we must understand whether any residual processing takes place within a scotoma or blind hemifield. Such processing could then form a substrate for rehabilitative interventions.

In support of this notion, there is now substantial evidence for unconscious processing for stimuli presented in the blind field of hemianopes. One group of patients in particular has been investigated extensively, and may provide us with specific insights.

'Blindsight' is a term first used by Weiskrantz in the 1970's in association with research on residual

visual function after occipital cortex damage. The syndrome was defined following work on primates and the discovery that unlike humans, monkeys with lesions to primary visual cortex (V1 – see Figure 1) were still able to respond to visual events.¹ Some interpreted this as an evolutionary distinction between species, but it inspired research to match experimental scenarios (as best as possible) by demanding forced-choice responses from human subjects. This revealed – somewhat paradoxically – that some humans with blindness associated with V1 damage could also make a wide range of forced-choice visual discriminations including whether an object was present/absent, or coloured red/green, despite a complete lack of acknowledged awareness.

Extensive work was undertaken subsequently to characterise responses in patients with 'blindsight' to stimuli distinguished by their motion, colour, and contrast, with the degree of subjective awareness varying considerably across these different manipulations.³ It was initially suggested that residual processing might be due to surviving 'islands' of V1 that could process the stimuli. However, there is now substantial evidence refuting this claim.⁴ Using a broad range of imaging and neurophysiology techniques to investigate the correlates of psychophysical findings, there is now evidence for activity in ipsilesional extrastriate cortex for stimuli presented within the 'blind' hemifield.^{5,6,7} In particular, activation of the dorsal 'where' pathway (V5/MT) is common, often accompanied by a vague awareness of motion (at least via forced-choice) but little or no appreciation for the spatial structure of stimuli.

More recent work has measured responses in the ventral visual pathways of patients with blindsight using images of natural, stationary objects such as faces or fruit. In one study, event-related potentials gave a typical positive occipital deflection ('P1 response') in ipsilesional occipital cortex for stimuli presented in the scotoma.⁸ Similar targets were used in functional MRI (fMRI) experiments⁹ comparing ventral with dorsal stimuli (rotating spirals), and activity in extrastriate cortex was found despite the patients having no awareness for any of the targets (see Figure 2). However the full extent of such processing remains unknown, including whether cortical responses are non-specific, or depend upon the category or features of individual objects.

Concerns

Most of the studies reviewed above investigated only one or two patients, often recruiting the same 'blindsight' subject, GY. At times he exhibited blindsight,¹³ at others not, and on occasions it was

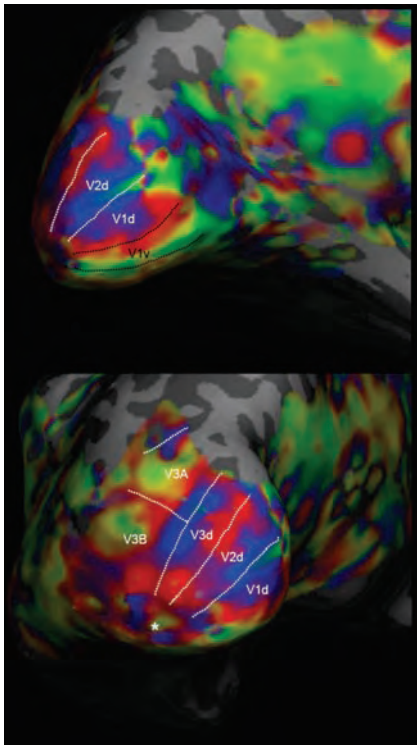


Figure 1: Visual cortex consists of V1-V5/MT with V1 (striate cortex) situated in the posterior pole of the occipital lobe. Shown are computationally inflated anatomical MRI scans (where gyri are light gray and sulci dark gray) of the occipital lobe on which have been superimposed functional MRI data, coloured to represent the retinotopic region of the visual field to which these areas respond. This is used to delineate the borders of retinotopic visual cortices, shown by dotted lines and labelled (the foveal representation is indicated by a star). Extrastriate retinotopic areas comprise dorsal ('d') and ventral ('v') regions representing the lower and upper visual fields respectively. Damage to the inferior division of the middle cerebral artery supplying lateral parietal and superior temporal cortices, as well as posterior cerebral artery damage supplying inferior temporal and occipital lobe, can result in prominent homonymous hemianopia.

claimed that he showed conscious awareness of stimuli in the hemianopic field.⁵ This could be explained if such situations depend upon saliency.^{10a} It was acknowledged for some time that stimuli particularly high in contrast or speed may be more effective at evoking sensations that blindsight patients (or others interacting with them) might interpret as visual consciousness – even if the visual experience cannot be described in any detail.

More recently, it has been found that stimuli with specific spatio-temporal properties are particularly effective at inducing blindsight in patients with hemianopia. Using stimuli opti-

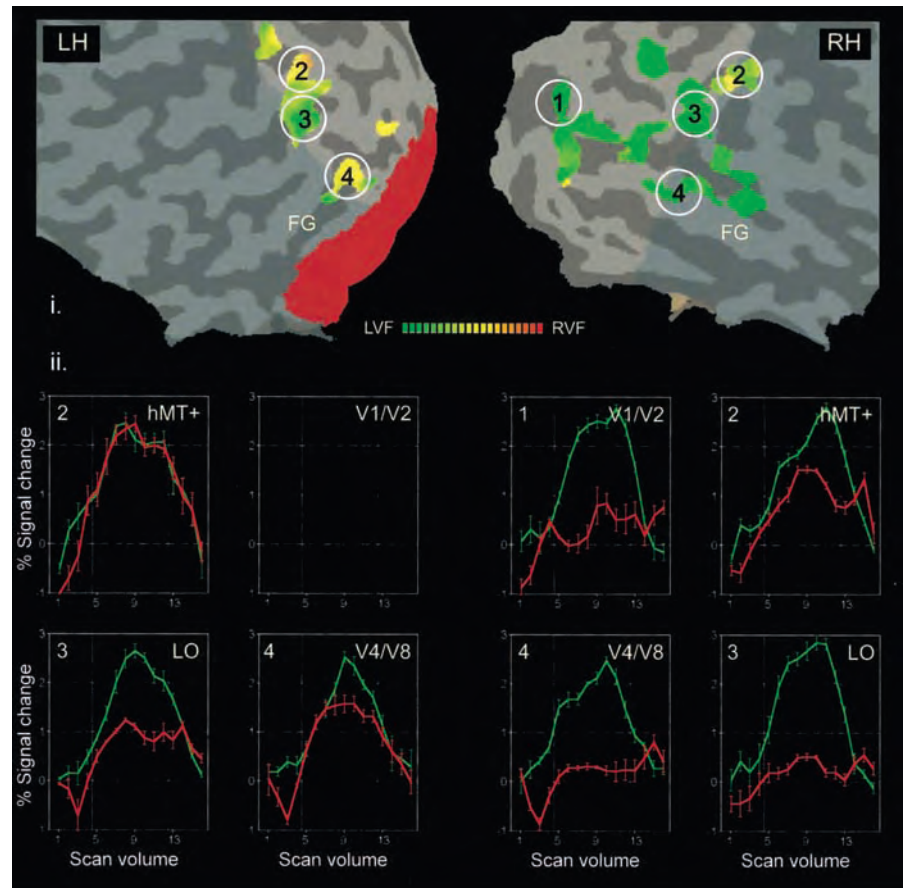


Figure 2: Brain activation data for blindsight patient GY, presented with coloured images of natural objects in either sighted or blind hemifields. i. fMRI results superimposed on a subpart of the flattened cortical representation of each hemisphere. Dark red regions correspond to the lesion. Activated regions responding solely to objects in the left hemifield are coloured green, with regions responding to the 'blind' right hemifield in red. Areas responding with equal strength to stimuli in either hemifield are shown in yellow. In GY, the normal hemisphere (RH) responds to

stimuli in the normal left hemifield with a similar activation pattern to controls. When stimuli were presented in the right hemifield, there was also response seen in ventral areas of the lesioned left hemisphere (LH), including a region in the fusiform gyrus (FG) and lateral occipital region. ii. These graphs illustrate time course in different cortical areas for left and right hemifield stimulation (green and red curves respectively); location of plotted areas are indicated by numbers 1-4. Adapted from Goebel et al with permission⁹

mised in this way, it appears that 'blindsight' may exist in a large proportion of patients with hemianopia, suggesting blindsight is more common than first imagined.¹¹ Clinically this is interesting because after documenting hemianopia, clinicians rarely attempt to elicit forced-choice responses for stimuli presented in the blind hemifield. Blindsight may therefore not be a small subgroup but instead might represent the majority of hemianopes.

Plasticity and Pathways

It is important to establish the route and mechanism for residual visual processing following

V1 damage. There has been much speculation whether information may be transmitted subcortically via superior colliculus and pulvinar (the retinotectal route), or directly from thalamus to extrastriate cortex. Several groups used the temporal resolution afforded by electrophysiology to attempt to infer which anatomical route reflected residual processing by studying the timing of evoked responses to visual stimuli, but results were extremely variable.^{6,7} While one study suggested extrastriate activity occurred early relative to V1 activity, another suggested that extrastriate activity followed normal V1 activity, suggesting a

By understanding the nature and extent of unconscious processing, as well as how such changes may occur within the visual system, we hope to achieve a reliable target for neurorehabilitation of hemianopia – an extremely common and debilitating condition

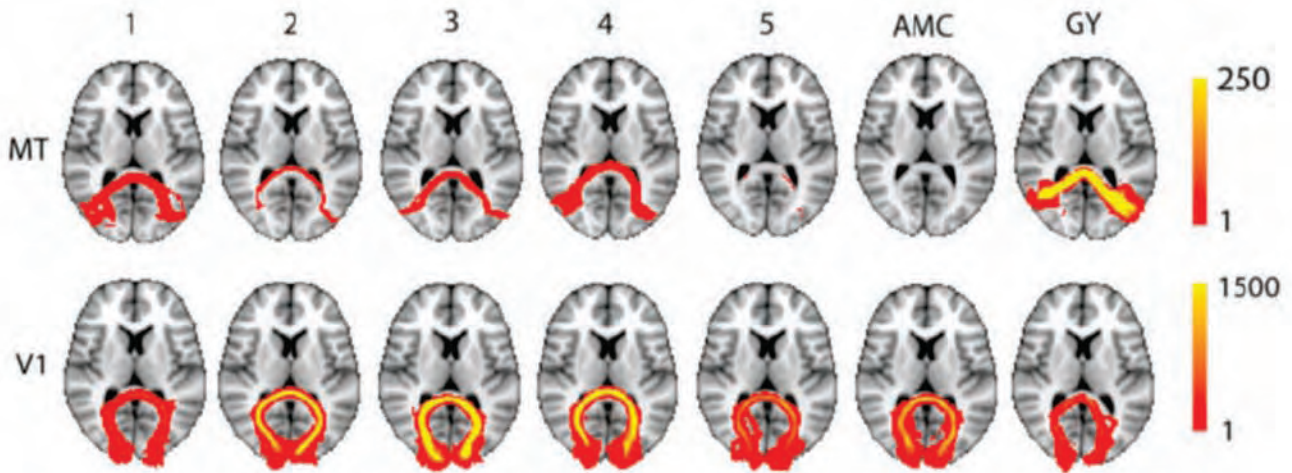


Figure 3: Cortico-cortical pathways in control subjects and GY, who has left V1 destroyed. The top row shows the connection through the splenium between MT+/V5 bilaterally, and the lower row shows the connection between V1 bilaterally. The strength of the pathways from the centre of the splenium to MT+ /V5 bilaterally in GY is suggestive of an increase in

cortico-cortical connectivity between this area in the two hemispheres. There is a 16-fold increase in the strength of the connection when the tract is seeded from the left and runs to the right. The size of the connection from unlesioned right hemisphere to left MT+ /V5 is 10 times greater than the mean for the controls. Adapted from Bridge et al., with permission⁹.

slower alternate route.

Recent work in non-human primates with chronic V1 lesions shows a clear causal role for the LGN and pathways from LGN to extrastriate cortex in V1-independent processing of visual information.¹² Monkeys were able to detect targets presented within a scotoma caused by V1 damage, and this was associated with contralateral extrastriate cortical responses. However, chemical inactivation of the LGN led to abolition of virtually all these extrastriate responses. This suggests that direct projections from LGN to extrastriate cortex support residual vision.

However, such findings do not explain whether activity observed in human extrastriate cortex following V1 damage comes from intact residual pathways, or the innate ability of the human cortex to reorder and organise following injury. Bridge and colleagues¹³ recently utilised diffusion-weighted MRI tractography to investigate structural plasticity in the visual cortex of a patient with chronic V1 damage (Figure 3). They showed that normal pathways bypassing V1 from LGN to extrastriate cortex (MT+/V5) remain intact. They also demonstrated two new connections not seen in healthy individuals, from contralesional LGN to ipsilesional extrastriate cortex, and extrastriate cortico-cortical connections bilaterally. This certainly suggests plasticity may be involved following visual cortex damage through rearrangement of long-range connections, perhaps driven by a compensatory reaction to brain damage. Such findings in humans do not necessarily contradict the findings in non-human primates, if information is required from LGN bilaterally to generate blindsight.²²

Rehabilitation

Visual rehabilitation for hemianopia has often proved unsuccessful and current treatment strategies are limited. One recent development is ‘visual restoration therapy’ (VRT), a simple

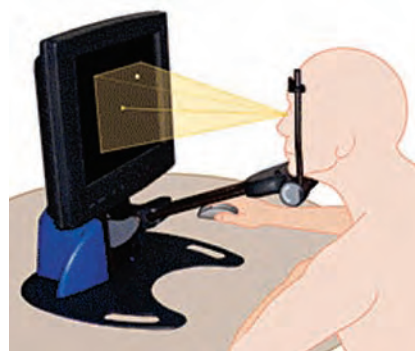


Figure 4: Example set-up for visual rehabilitation therapy. The patient fixates upon the central fixation point, whilst being presented with successive stimuli within the blind (right) hemifield. For example in Sahraie et al.,¹⁸ stimuli would be presented for 2 seconds to three different regions of the receptive field per session, and 50 trials in each. After each trial, the patient reports the interval containing the grating patch by pressing one of two response buttons. This task was carried out everyday over a 3-month period.

computer-based programme for patients to use for an hour a day (Figure 4).^{14,15} Despite early suggestions that VRT benefited vision following hemianopia, attempts at replication with more rigorous methods did not support earlier findings.¹⁶ One concern is that saccadic eye movement was not fully controlled for, nor appropriately taken into account. This was clearly demonstrated in a subsequent study by using a scanning laser ophthalmoscope, considered one of the most effective ways to control eye movement as experimenters visualise fixation on the fundus throughout the task, and discard trials whenever saccades are made. Using such eye movement control, whether VRT was efficacious was questioned and other criticisms have also arisen.¹⁷ One consideration was that it did not take into account the extensive research on unconscious processing in hemianopia.

More recently it has been suggested that hemianopia can be rehabilitated by employing stimuli custom-designed to

undergo processing by the pathways mediating ‘blindsight’ or residual vision. By using salient targets with particular spatial and temporal properties in a rehabilitation tool, Sahraie and colleagues demonstrated improvement in sensitivity and awareness deep within visual field defects in 12 patients trained for three months.¹⁸ They also suggest that feedback accelerates the effect.^{10b} This approach seems promising, and represents one of the first approaches that can generate improvement deep within the scotoma. Nevertheless these early findings require replication and extension.

Moreover, some of the criticisms of other rehabilitative approaches may also be relevant. Sahraie’s study also did not control eye movements, although they argue that there is now evidence that recovery is independent of eye movement strategies. The previous group responded to concerns by applying quantitative analysis to eye movements before and after VRT. They found no change, suggesting instead that the time-consuming microperimetry was too difficult for subjects to accurately engage in.¹⁹

Future

The visual system is the major sensory system in humans, yet it is still not clear whether it has the same capacity for recovery as, for example, the motor cortex. There remains significant disparity between studies, contributed to by differences in paradigms, stimuli, as well as measures of outcome. Recently, however, there is a trend towards consistent reports, and the use of blindsight as a way of defining potentially spared pathways that could be targeted by novel rehabilitative approaches is promising.

One approach is to systematically explore unconscious processing in the ventral visual pathway of healthy volunteers, and to generalise this to patients with brain damage causing hemianopia. Although beyond the scope of this article, the findings in hemi-

naopia are strikingly similar to recent evidence in healthy volunteers that substantial unconscious processing takes place when visual stimuli are rendered invisible through masking or other paradigms [see 20 for a detailed review]. Also, one can look further at structural plasticity, and whether functional changes following rehabilitation^{18,21} are reflected in changes of connectivity.

Conclusion

Residual visual processing can undoubtedly occur following brain injury in homonymous hemianopia. Recently, evidence has started to emerge to suggest a viable pathway for this, and that plasticity in the brain may alter these connections following brain injury. By understanding the nature and extent of unconscious processing, as well as how such changes may occur within the visual system, we hope to achieve a reliable target for neurorehabilitation of hemianopia – an extremely common and debilitating condition. ♦

REFERENCES

- Weiskrantz L Roots of blindsight. *Prog Brain Res*. 2004; 144: 229-41.
- Townend BS, Sturm JW, Petsoglou C, O'Leary B, Whyte S, & Crimmins D Perimetric homonymous visual field loss post-stroke. *J Clin Neurosci* 2007; 14(8):754-6.
- Stoerig P, & Cowey A Wavelength sensitivity in blindsight. *Nature* 1989; 342 (6252): 916-918.
- Stoerig P, Kleinschmidt A, & Frahm J No visual responses in denervated V1: high-resolution functional magnetic resonance imaging of a blindsight patient. *Neuroreport* 1998; 9(1):21-5.
- Barbur JL, Watson JD, Frackowiak RS, & Zeki S Conscious visual perception without V1. *Brain* 1993; 116(6):1293-302.
- ffytche DH, Guy CN, & Zeki S Motion specific responses from a blind hemifield. *Brain* 1996; 119(6): 1971-82.
- Holliday IE, Anderson SJ, & Harding GF Magnetoencephalographic evidence for non-geniculostriate visual input to human cortical area V5. *Neuropsychologia* 1997; 35(8): 1139-46.
- Rossion B, de Gelder B, Pourtois G, Guérit JM, & Weiskrantz L Early extrastriate activity without primary visual cortex in humans. *Neurosci Lett*. 2000; 279(1):25-8.
- Goebel R, Muckli L, Zanellac FE, Singer W, & Stoerig P Sustained extrastriate cortical activation without visual awareness revealed by fMRI studies of hemianopic patients. *Vis Res* 2001; 41: 1459-74.
- Sahraie A, Hibbard PB, Trevethan CT, Ritchie KL, Weiskrantz L Consciousness of the first order in blindsight. *Proc Natl Acad Sci U S A*. 2010; Nov 15. Ahead of print.
- Sahraie A, Macleod MJ, Trevethan CT, Robson SE, Olson JA, Callaghan P, & Yip B Improved detection following Neuro-Eye Therapy in patients with post-geniculate brain damage. *Exp Brain Res*. 2010; 206(1):25-34.
- Sahraie A, Trevethan CT, & Macleod MJ Temporal properties of spatial channel of processing in hemianopia. *Neuropsychologia* 2008; 46: 879-85.
- Schmid MC, Mrowka SW, Turchi J, Saunders RC, Wilke M, Peters AJ, Ye FQ, & Leopold DA Blindsight depends on the lateral geniculate nucleus. *Nature* 2010; 466: 373-7.
- Bridge H, Thomas O, Jbabdi S, & Cowey A Changes in connectivity after visual cortical brain damage underlie altered visual function. *Brain* 2008; 131: 1433-1444.
- Zihl J, & von Cramon D Visual field recovery from scotoma in patients with postgeniculate damage. A review of 55 cases. *Brain* 1985; 108(2):335-65.
- Kasten E, Wüst S, Behrens-Baumann W, & Sabel BA Computer-based training for the treatment of partial blindness. *Nat Med*. 1998; 4(9):1083-7.
- Reinhard J, Schreiber A, Schiefer U, Kasten E, Sabel BA, Kenkel S, Vonthein R, & Trauzettel-Klosinski S Does visual restitution training change absolute homonymous visual field defects? A fundus controlled study. *Br J Ophthalmol*. 2005; 89(1):30-5.
- Horton JC Vision restoration therapy: confounded by eye movements. *Br J Ophthalmol*. 2005; 89(7):792-4.
- Sahraie A, Trevethan CT, Macleod MJ, Murray AD, Olson JA, & Weiskrantz L Increased sensitivity after repeated stimulation of residual spatial channels in blindsight. *PNAS* 2006; 103: 14971-14976.
- Kasten E, Bunzenthall U, & Sabel BA Visual field recovery after vision restoration therapy (VRT) is independent of eye movements: an eye tracker study. *Behav Brain Res*. 2006; 175(1):18-26.
- Lin Z, & He S Seeing the invisible: The scope and limits of unconscious processing in binocular rivalry. *Progress in Neurobiology*. 2009; 87: 195-211.
- Nelles G, de Greiff A, Pscherer A, Forsting M, Gerhard H, Esser J, & Diener HC Cortical activation in hemianopia after stroke. *Neurosci Lett*. 2007; 426(1):34-8.
- Silvanto J, Cowey A, Lavie N & Walsh V Making the blindsighted see. *Neuropsychologia*. 2007; 45(14):3346-50.



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European Federation of Neurological Societies (EFNS)

The EFNS was founded in 1991 in Vienna, Austria.

The role of the EFNS is

- To advance the development of neurology as an independent specialty caring for all patients with a disease of the nervous system
- To support that these services become available to all Europeans
- To support research and dissemination of research results throughout Europe
- To organise and support neurological teaching at the pregraduate as well as the postgraduate level throughout Europe
- To handle the current political issues in European neurology on behalf of its members

The EFNS is a federation of 44 European national neurological societies, 8 associate member societies and welcomes individual members from all over the world.

The federation is governed by a Council constituted of one representative elected by each affiliated national neurological society in Europe.

The Council delegates the day-to-day management of the EFNS the Management Committee, empowered to decide on all matters of the Federation when such decisions cannot be delayed until the next Council meeting. Important decisions made by the Management Committee must subsequently be ratified by the Council.

The European Federation of Neurological Societies is based in Vienna, Austria. We also have Branch Offices in Florence, Italy, and Prague, Czech Republic.

Committees and Scientist Panels:

The EFNS has 8 standing committees and 24 Scientist Panels. The standing committees perform the ongoing functions vital to the EFNS on a long-term basis.

- Congress Programme Committee
- Training and Education Committee including the CME, E-learning and Teaching Course Sub-committees

- Liaison Committee
- Scientific Committee

The aims of the scientist panels are:

- to co-ordinate clinical research at a European level
- to disseminate good neurological practice throughout European countries
- to assist the Congress Programme Committee in organising congresses
- to assist the EFNS in training neurologists and in supporting continuing medical education.
- to develop European Neurological Guidelines

Topics:

Amyotrophic Lateral Sclerosis, Autonomic Nervous System disorders, Critical care, Dementia, Demyelinating diseases, Epilepsy, Genetics, Headache, History, Infectious diseases, EFNS/MDS-ES, Muscle disorders, Neuroimaging, Neuro-immunology, Neuro-oncology, Neuro-ophthalmology, Neuropathic pain, Neuropathies, Neurorhabilitation, Neurotraumatology, Palliative care, Public health, Sleep disorders, Stroke, Substance abuse.

Congresses and meetings:

At its annual congresses, usually taking place in September, the EFNS provides an unmatched opportunity for neurologists to join over 5,000 colleagues to study and disseminate the latest research, clinical practices and treatments.

- 15th EFNS Congress, Budapest, Hungary 10-13 September 2011
- 16th EFNS Congress, Stockholm, Sweden 8-11 September 2012
- 17th EFNS Congress, Istanbul, Turkey Autumn 2014

Furthermore, the EFNS organises Regional Teaching Courses in Eastern Europe as well as in Africa. At these courses participants only pay for travel and accommodation. EFNS-RTCs are specially designed to disseminate best neurological practice directly to the countries in the East so that younger

neurologists do not have to travel long distances to congresses which may not be affordable for them. RTCs provide basic teaching in neurology and contribute to the development of collaboration and friendship between neurologists in different European countries.

At the annual EFNS Academy in Czech Republic, 120 young neurologists from all over Europe meet and listen to contributions by European experts. Participants only pay for their travel.

Grants and Awards

Bursaries to EFNS Congresses:

The EFNS offers up to 200 bursaries consisting of free registration to the congress and hotel accommodation for four nights to European neurologists up to the age of 35 who are not yet in permanent positions and whose abstract has been accepted for presentation at the congress.

Department-Department co-operation programme

Up to 80 young neurologist per year, each receive a grant of €1500 plus travel expenses up to €300. The purpose of this award is to support their board and accommodation expenses in the host city. The grant is designed to allow for a visit of up to six weeks. If a participant is able to accept a low budget board, it may be possible to stay longer than six weeks in the hosting department. Candidates from all European countries are eligible. Applicants must be under the age of 40, and must be fluent in English or in the local language.

Fellowship programme

The EFNS offers up to 10 scientific and 5 educational fellowships per year to support young European neurologists to carry out research projects in clinical and basic neurology.

The objective is to support young and active neurologists wishing to expand their knowledge in neurology by working on scientific projects, and most of all, to study the practice of neurology in different countries, and thereby also create new international connections. Accordingly, the research work must be carried out at a European academic neurological department outside the country of residence.

Amount: Net salary in accordance with the salary scale of the host institution up to a maximum of €2,000 per month plus travel expenses.

Investigator award:

All free presentations (short communications, posters), selected for presentation at the annual EFNS Congress automatically



Council of delegates.



EFNS Academy 2011.

compete for an Investigator Award. The EFNS Scientist Panels are responsible for the evaluation process (independent from other awards and the programme organisation). The award for each selected presentation will be €500, a diploma, and the winners will be announced in the European Journal of Neurology and the EFNS Newsletter. The award will be given to the first author who needs to be the person to present the work at the congress.

Tournament for young neurologists

A tournament for young neurologists takes place at each EFNS Congress. It will be carried out in two groups, one on clinical related research, and one on basic neurological science. Neurologists in training not older than 35 years are entitled to participate. The Congress Programme Committee will select 6 candidates for each tournament on the basis of the contents of the abstracts submitted. The clinical subjects should be received from authors who work and carry out their projects in Europe. Candidates selected for the tournament receive a bursary consisting of free registration to the Congress, up to four nights hotel accommodation, and a travel grant.

Prize: The winner of each group will receive the *Uschi Tschabitscher Prize for Young Neurologists* consisting of: Free registration at the upcoming EFNS Congress, up to four nights hotel accommodation, a travel grant, as well as €1,000. The second prize will consist of €200 and a certificate.

CME articles online

All registered users of the EFNS website do have the possibility of answering questions related to articles selected from the *European Journal of Neurology* and receiving a CME certificate.

Partners and collaborators

Our Partners and Collaborating Societies consist of:

- European organisations dedicated to any associated speciality related to clinical neurology

- European subgroups of clinical neurology
- European patient organisations and
- Neurological organisations outside of Europe.

Collaboration with the EFNS promotes co-operation and co-ordination in mutual areas of interest and creates more representative (and therefore more powerful) influence on national health authorities and the European Union.

Our partners are:

European Association of Young Neurologists and Trainees, European Brain Council, European Board of Neurology, European Federation of Neurological Associations, European Federation of Autonomic Societies, European Headache Federation, European Epilepsy Academy, European Neurological Society, Movement Disorders Society-European Section, World Federation of Neurology.

Publications

European Journal of Neurology (EJoN): 12 issues per year – FREE OF CHARGE online access for members of the EFNS.

The European Journal of Neurology covers all areas of clinical and basic research in neurology, including pre-clinical research of immediate translational value for new potential treatments. Emphasis is placed on major diseases or disorders with a large clinical and socio-economic importance (dementia, stroke, epilepsy, headache, multiple sclerosis, movement disorders, and infectious diseases).

The journal provides a forum for European activity in clinical neuroscience and medical practice and helps strengthen the links between research workers and clinicians in Europe and other parts of the world. The journal also publishes the official EFNS task-force papers and CME Articles which can be read to gain CME credits. ISI Journal Citation Reports® Ranking: 2009: 66/167 Clinical Neurology; 129/230 Neurosciences New 2009 Impact Factor: 2.51 <http://www.europeanjournalofneurology.com>

EFNS Newsletter

Four issues per year; free of charge for everybody who is interested.

European Handbook of Neurological Management

The European Handbook of Neurological Management, is a unique book that brings together peer-reviewed guidelines for the treatment and management of neurological disease. For the first time, neurologists can find advice on management aspects of most neurological disorders that is either evidence-based or, where the evidence is inadequate, the consensus guidance of an international European panel of experts. Each chapter of the handbook is written by task forces with a multinational European authorship in accordance with prespecified guidance for collecting evidence and reaching consensus. Whenever possible, these task forces have collaborated with the corresponding disease-specific European society. In some cases societies and authors from outside Europe have contributed.

EFNS Guideline papers are included in the *European Journal of Neurology, Handbook* and are also available to all FREE OF CHARGE on the EFNS website. An important aim of the EFNS is to establish European standards of diagnosis, treatment and care within the various subfields of neurology. Teaching course syllabi are available in the e-education area of the EFNS website as well as on CD-Rom.

For further details and information on the EFNS, please visit the EFNS Website www.efns.org or contact



The History of the European Federation of Neurological Societies



RICHARD HUGHES
PRESIDENT OF THE EFNS

The birth of the EFNS

This will be the fifteenth EFNS Congress and marks 20 years since the foundation of the EFNS, a good time to take stock of our history and look forward to the future. The first glimmerings of the EFNS appeared in 1986 at the Danube-Neurology Congress where Professor Mieczyslaw Wender, Poland, proposed a unified European neurological society. In 1989 Professor Daniel Bartko, President of the Czechoslovakian Neurological Society, picked up the idea and organised a pan European congress for neurology attended by 1500 participants. In 1991 a second pan European congress for neurology was held in Vienna under the Presidency of Professor Franz Gerstenbrand. At that congress with the encouragement of Professor John, now Lord, Walton, the Federation of European Neurological Societies was founded with Professor Gerstenbrand as its first President and a Council of Delegates consisting of representatives from each founding national European society. Dr. Friederike Tschabitscher was appointed as executive director and ran the secretariat from the first EFNS office in Rosenhügel, Vienna.



Professor Franz Gerstenbrand

except in 2001 when the EFNS collaborated with the Association of British Neurologists to host the World Congress of Neurology in London.

Growth of the EFNS

The Federation has grown steadily since 1991 with the addition of individual members almost every year so that we now include almost all countries within deliberately generously drawn geographical and political boundaries of "Europe".

National societies which have joined the EFNS since its Foundation

- 1992: Albania, Croatia, Moldova, Slovenia
- 1994: Ukraine
- 1995: Belarus, Georgia, Israel, Latvia, Luxembourg, Switzerland, Turkey
- 1999: Cyprus,
- 2003: Armenia, Lithuania
- 2004: Uzbekistan
- 2007: Bosnia and Herzegovina
- 2008: FYROMacedonia
- 2009: Montenegro

Founding National Societies

Austria	Italy
Belgium	Norway
Bulgaria	Poland
Czechoslovakia (now: Czech Republic and Slovakia)	Portugal
Denmark	Romania
Estonia	USSR (now: Russia)
Finland	Yugoslavia (now: Bosnia & Herzegovina, Croatia, FYRO Macedonia, Kosovo, Montenegro, Slovenia, Serbia)
France	Spain
Germany	Sweden
Greece	The Netherlands
Hungary	United Kingdom
Iceland	
Ireland	

There were further meetings in 1993 in Berlin organised by Professor Karl Einhäupl and in 1994 in Poznan, Poland organised by Professor Wender but the first formal EFNS Congress was organised by Georges Serratrice in Marseilles, France in 1995. Since 1998 there have been annual Congresses

As a consequence the EFNS now has 44 national societies as members representing altogether more than 19000 individual neurologists. To these must be added associate member societies from surrounding countries Algeria, Egypt, Jordan, Lebanon, Libya, Morocco, Tunisia and Syria whose delegates are also welcome at EFNS Congresses.

The expansion of the Federation in size and scope demanded more facilities and better offices. In 2002 the Head Office moved to the Wiener Medizinische Akademie, Vienna and in 2005 to its own premises in Breite Gasse in the vicinity of the Museum Quarter of Vienna. Branch offices were opened in Florence in 1998 and Prague in 1999.



Scientist Panels and Guidelines

One of the tremendous advantages of a European Federation is the ability to bring together sub- (or super- according to your viewpoint) specialists together in sufficient numbers to reach critical mass, an ability not shared for all topics by national societies. From the founda-

EFNS Congresses				
1st	EFNS Congress	Marseilles, France	1995	1500 Participants
2nd	EFNS Congress	Rome, Italy	1996	2000 Participants
	EFNS Meeting	Prague, Czech Republic	1997	1500 Participants
3rd	EFNS Congress	Seville, Spain	1998	4200 Participants
4th	EFNS Congress	Lisbon, Portugal	1999	3000 Participants
5th	EFNS Congress	Copenhagen, Denmark	2000	2200 Participants
	WCN	London, UK	2001	Co-organiser
6th	EFNS Congress	Vienna, Austria	2002	3500 Participants
7th	EFNS Congress	Helsinki, Finland	2003	3200 Participants
8th	EFNS Congress	Paris, France	2004	4300 Participants
9th	EFNS Congress	Athens, Greece	2005	4500 Participants
10th	EFNS Congress	Glasgow, UK	2006	4500 Participants
11th	EFNS Congress	Brussels, Belgium	2007	4000 Participants
12th	EFNS Congress	Madrid, Spain	2008	5100 Participants
13th	EFNS Congress	Florence, Italy	2009	5500 Participants
14th	EFNS Congress	Geneva, Switzerland	2010	5100 Participants
15th	EFNS Congress	Budapest, Hungary	2011	

tion of the federation, Scientist Panels have existed to foster research, practice and training in their own specialist fields. The most obvious output from these panels has been the European guidelines which aim to provide unbiased evidence based guidelines on important, and often controversial, neurological management problems. These are regularly updated and freely available on the EFNS website. The first collection of 40 guidelines was collected into a popular European Handbook of Neurological Management in 2006 which was republished as Volume 1 of a revised second edition in 2010. Volume 2 will be issued shortly.

Continuing Education

One of the major functions of the EFNS is education, most obviously delivered in the teaching courses but also in the scientific sessions at the Congresses. The EFNS has awards 200 bursaries to enable young European neurologists to attend each congress. However the Federation supports many other educational activities apart from the Congress. Three regional teaching courses are held in Eastern European countries every year to which local neurological trainees are invited. For the past three years the EFNS has also run an African regional teaching course in partnership with the Pan African Neurological Society. Since 2000 the EFNS has run a summer school or Academy for about 120 young neurologists at Staré Splavy in the Czech Republic. Since 2001 short interdepartmental visits for trainees to visit centres in other European countries are enabled by popular competitive grants. Since 2004 there have been opportunities for interdepartmental training and research fellowships lasting three to twelve months.

European Journal of Neurology

The EFNS founded its own journal in 1995 which contributes to its educational activities and disseminates European and international research. EFNS guidelines are published first in the European Journal of Neurology. Under the editorship of Professor François Boller and now Professors Matti Hillbom and Anthony Schapira its impact factor rose steadily to 2.5 and is set to rise further.

Staff

Professor Jes Olesen, Denmark, succeeded Professor Gerstenbrand as President and served for a unique six years until 2001. He was in turn succeeded by Professor Wolf-Dieter Heiss, Germany, Jacques De Reuck, Belgium in 2005 and myself in 2009. The achievements of the EFNS would not have been possible without excellent staff. The founding Executive Director, Dr Friederike Tschabitscher, sadly died in 2003 and



Staff: Anja Sander, Lisa Müller, Eveline Sipido, Julia Mayer, Julia Scheidl, Magda Dohnalova.

was succeeded by Lisa Müller who continues to oversee all our activities now. She is assisted in the Vienna office by Anja Sander, Julia Mayer and Julia Scheidl, in the Prague office by Magda Dohnalova and in the Florence office by Eveline Sipido. We are fortunate to have such devoted staff and owe them our thanks.

The future

No institution can afford to stand still and there are exciting developments in prospect. This year in collaboration with the British National Health service, University College London and the European Neurological Society we will be launching e-Brain an on line neurological education programme with several hundred sessions.

Planning for future Congresses is well advanced. The 16th EFNS Congress will be held in Stockholm, Sweden from 8-11 September 2012. The World Congress of Neurology will be held in Vienna, Austria, from 22-27 September 2013 as guests of the Austrian Neurological Society. Since the EFNS traditionally does not hold a Congress in the year in which the World Congress is in Europe, the Austrians have kindly invited with them in hosting this meeting. The 17th EFNS Congress will be held in Istanbul, Turkey in 2014.

During the last 20 years, our sister institution the European Neurological Society has been developing in parallel and offering a series of equally exciting and educational annual congresses; negotiations between the two organisations are under way with the intention of organising a giant joint Congress in Germany in 2015 and further closer collaboration thereafter. This collaboration should help make European neurological congresses and European neurology the best in the world.



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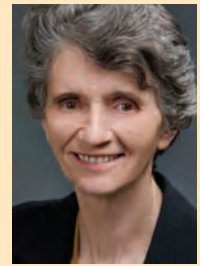
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The widening spectrum of antibody-mediated neurological diseases: from neuromuscular junction to brain

ANGELA VINCENT,

Nuffield Department of
Clinical Neurosciences,
University of Oxford,
John Radcliffe Hospital,
Oxford OX3 9TH, UK
angela.vincent@imm.ox.ac.uk



Abstract

There are an increasing number of relatively rare conditions that are associated with serum autoantibodies to receptors, ion channels or associated proteins in the nervous system. Particularly exciting has been the recent recognition of autoimmune central nervous system (CNS) diseases, associated with specific antibodies to neuronal targets, which improve substantially with immunotherapies. In addition, there are antibodies to glial or myelin targets in demyelinating conditions. Although rare, the identification and treatment of these conditions can be very rewarding.

Introduction

The pathogenic roles of antibodies to acetylcholine receptors, muscle specific kinase and voltage-gated calcium channels in the peripheral myasthenic disorders are well established. These diseases are usually chronic and can be associated with tumours (thymomas or small cell lung cancer) but most patients do well neurologically with a combination of symptomatic and immunosuppressive therapies. In addition, antibodies to voltage-gated potassium channel complexes (VGKC-complex) are found at low levels in some patients with acquired neuromyotonia which is associated with thymoma in about 20%.

By contrast, antibodies to CNS antigens such as Hu, Yo, Ma2 are established markers for the presence of a tumour, but the antigens are intracellular proteins and the antibodies are not thought to be pathogenic (with one or two exceptions, eg¹); these paraneoplastic conditions seldom respond well to immunotherapies. In the last ten years, however, the roles of antibodies in CNS conditions has expanded considerably with identification of antibodies binding to extracellular domains of neuronal proteins and, which are highly likely to alter neuronal function, as has been shown in a few instances;^{2,3} the presence of the antibodies is taken to define an immunotherapy-responsive disorder. Here, I will briefly describe the antigenic targets, the antibodies and the associated syndromes. Many detailed reviews can be found elsewhere.^{4,6}

New targets for autoantibodies

Until recently, it was thought that VGKC antibodies were directed against the voltage-gated potassium channels themselves. However, it is now clear that the majority of the VGKC antibodies are directed towards proteins that are tightly complexed with VGKCs in the nervous system. These VGKC-complex proteins include leucine-rich glioma-inactivated 1 (LGI1), contactin-associated protein-like 2 (CASPR2), and Contactin-2.^{7,8} These proteins are all expressed in the CNS but CASPR2 and Contactin-2 are also important components of the juxtaparanodes of peripheral motor and sensory axons. NMDA, AMPA, GABA(B) and glycine receptors are all components of brain synapses although they are also expressed to variable extents extrasynaptically. The only intracellular antigen that is relevant here is glutamic acid decarboxylase (GAD), an intracellular enzyme expressed in GABAergic neurons. In addition to these neuronal targets, the water channel aquaporin-4 (AQP4) is an important astrocytic protein, and myelin-oligodendrocyte glycoprotein (MOG) is a membrane component of myelin. With the exception of GAD, these antibodies are most appropriately identified by binding to cells that have been engineered to express the target antigen on their cell surface (cell based assays), although immunoprecipitation for VGKC-complex antibodies is a useful first screen.

Encephalopathies

Morvan's syndrome is a very rare condition that involves all parts of the nervous system. It presents typically with a combination of peripheral nerve hyperexcitability causing neuromyotonia, autonomic disturbance such as constipation, cardiac arrhythmias and sweating, and CNS disturbance, particularly insomnia and confusion. MRI and cerebrospinal fluid (CSF) abnor-

malities are uncommon, but serum VGKC-complex antibodies are present in the majority of patients, and a high proportion have thymomas. Some also have myasthenia gravis or other autoimmune diseases (Irani et al in preparation).

Limbic encephalitis is increasingly recognised as a cause of non-paraneoplastic memory loss and seizures with 100s of cases reported in the last ten years. Some patients have partial syndromes presenting with predominant psychosis, epilepsy or memory loss. High signal in the medial temporal lobes on MRI and hyponatraemia at onset are common, but not invariable, and the CSF may be inflammatory or normal. Oligoclonal bands are also variable. The exclusion of other causes (infectious, toxic, metabolic, tumours etc) and the presence of antibodies to VGKC-complex proteins particularly LGI1,⁹ AMPAR,¹⁰ or GABAB¹¹ will help to secure the diagnosis, direct the search for an appropriate tumour in a minority, and prompt immunotherapies which can be very successful. Another form of limbic encephalitis is associated with antibodies to GAD. Although these antibodies are unlikely to be pathogenic, as GAD is intracellular, the antibodies appear to be markers of an immune-mediated syndrome.¹²

A seizure-semiology has been recognised in patients with VGKC-complex antibodies directed against LGI1. These often occur preceding the full features of limbic encephalitis, and consist of brief dystonic movements usually of one arm and the ipsilateral face. There is seldom loss of consciousness but they can be very frequent (up to 70 per day). Early recognition and immunotherapy may be able to prevent development of limbic encephalitis.¹³

NMDAR antibody encephalitis has only recently been recognised but 100s of patients have now been identified.^{5,14} They present with neuropsychiatric features, seizures and amnesia but develop, over days to weeks, choreoathetoid movement disorders, facial dyskinesias, mutism, reduced consciousness, brainstem, autonomic and hypothalamic involvement. Once seen these are very characteristic features but some patients present with attenuated forms and are more difficult to recognise. MRI is seldom helpful but the CSF is usually cellular and oligoclonal bands are found, although not necessarily at presentation.¹⁴ Typically, ovarian teratomas are found in up to 50% of women between puberty and middle age, but tumours are uncommon at other ages or in males. This condition is increasingly identified in small children, some less than one year in age, who present with bizarre behaviours and movements, screaming and seizures. Although most patients make a substantial recovery following appropriate tumour treatment and immunotherapies, the course is often protracted with weeks in intensive care; prompt diagnosis and aggressive treatments are likely to be important in reducing hospitalisation and long-term disability.⁵

Stiff person syndrome (SPS) and its association with GAD antibodies is well known. Progressive encephalomyelitis with rigidity and myoclonus (PERM) is a related syndrome which is even rarer but more often fatal. Recently antibodies to glycine receptors have been identified in a few patients with PERM, SPS or related syndromes. Although uncommon, when recognised this condition can respond to immunotherapies which may prevent a fatal outcome^{15,16} (Leite et al in preparation).

Demyelinating conditions

Neuromyelitis optica is a well described condition associated with relapses of optic neuritis and extensive spinal cord inflammation; at onset the diagnosis can be confused with multiple sclerosis, particularly in children who may have florid brain lesions. The association with antibodies to AQP4¹⁷ has dramatically increased the recognition of this syndrome, and the use of immunotherapies such as plasma exchange and intravenous immunoglobulins, rather than interferon beta and other immune modifiers which may make it worse, should improve the prognosis. There is now good evidence for the pathogenicity of AQP4 antibodies⁶ although the role of cellular immunity is not yet explored.

Acute disseminated encephalomyelitis (ADEM) can present in a similar manner, or with florid brain lesions involving both white and grey matter. It is found more frequently in children than adults and is by definition a monophasic disease. The discovery of antibodies that bind native MOG^{18,19} is beginning to help define this condition at onset, and may also be useful in distinguishing ADEM from early cases of NMO.

Concluding remarks

These conditions are very satisfying to diagnose and to treat. Searching for antibodies in children and adults with more common forms of encephalitis, psychosis, epilepsy and dementia, and identification of new antigenic targets in patients with similar presentations are important future goals for everyone in this exciting field. There are many unanswered questions regarding the causes of the non-paraneoplastic conditions, the cellular targets and mechanisms of the antibodies and how they alter neuronal or glial function; more experimental studies need to be done.

References

- Geis C, Weishaupt A, Hallermann S, Grünwald B, Wessig C, Wulstsch Tet al. Stiff person syndrome-associated autoantibodies to amphiphysin mediate reduced GABAergic inhibition. *Brain*. 2010;133:3166-80.
- Hughes EG, Peng X, Gleichman AJ, et al. Cellular and synaptic mechanisms of anti-NMDA receptor encephalitis. *J Neurosci* 2010;30:5866-75.
- Lalic T, Pettingill P, Vincent A, Capogna P. Human limbic encephalitis serum enhances hippocampal mossy fibre-CA3 pyramidal cell synaptic transmission. *Epilepsia* in press.
- Vincent A, Bien CG, Irani SR, Waters P. Autoantibodies and diseases of the central nervous system: new developments and future challenges *Lancet Neurology* in press.
- Dalmau J, Lancaster E, Martinez-Hernandez E, Rosenfeld MR, Balice-Gordon R. Clinical experience and laboratory investigations in patients with anti-NMDAR encephalitis. *Lancet neurology*. 2011;10(1):63-74
- Jarius S, Wildemann B. AQP4 antibodies in neuromyelitis optica: diagnostic and pathogenetic relevance. *Nat Rev Neurol*. 2010 Jul;6(7):383-92
- Irani SR, Alexander S, Waters P et al. Antibodies to Kv1 potassium channel-complex proteins leucine-rich, glioma inactivated 1 protein and contactin-associated protein-2 in limbic encephalitis, Morvan's syndrome and acquired neuromyotonia. *Brain*. 2010;133:2734-2748
- Lai M, Huijbers MG, Lancaster E, Graus F, Bataller L, Balice-Gordon R et al. Investigation of LGI1 as the antigen in limbic encephalitis previously attributed to potassium channels: a case series. *Lancet Neurol*. 2010;9:776-85
- Vincent A, Buckley C, Schott JM, Baker I, Dewar BK, Detert N, et al. Potassium channel antibody-associated encephalopathy: a potentially immunotherapy-responsive form of limbic encephalitis. *Brain*. 2004;127:701-12.
- Lai M, Hughes EG, Peng X, Zhou L, Gleichman AJ, Shu H et al. AMPA receptor antibodies in limbic encephalitis alter synaptic receptor location. *Ann Neurol*. 2009;65:424-34
- Lancaster E, Lai M, Peng X, Hughes E, Constantinescu R, Raizer J, et al. Antibodies to the GABAB receptor in limbic encephalitis with seizures: case series and characterisation of the antigen. *Lancet Neurol* 2010;9:67-76.
- Malter MP, Helmstaedter C, Urbach H, Vincent A, Bien CG. Antibodies to glutamic acid decarboxylase define a form of limbic encephalitis. *Ann Neurol*. 2010;67:470-478
- Irani SR, Michell AW, Lang B, Pettingill P, Waters P, Johnson MR et al. Faciobrachial dystonic seizures precede LgI1-antibody limbic encephalitis. *Ann Neurol* 2010 Oct 28. doi: 10.1002/ana.22307. [Epub ahead of print]
- Irani SR, Bera K, Waters P, Zuliani L, Maxwell S, Zandi MS, et al. N-methyl-D-aspartate antibody encephalitis: temporal progression of clinical and paraclinical observations in a predominantly non-paraneoplastic disorder of both sexes. *Brain* 2010;133:1655-67.
- Hutchinson M, Waters P, McHugh J, et al. Progressive encephalomyelitis, rigidity, and myoclonus: a novel glycine receptor antibody. *Neurology* 2008;71:1291-2.
- Turner M, Irani SR, Leite MI, Nithi K, Vincent A, Ansorge O. Progressive encephalomyelitis with rigidity and myoclonus: Glycine and NMDA receptor antibodies. *Neurology* in press
- Lennon VA, Kryzer TJ, Pittock SJ, Verkman AS, Hinson SR. IgG marker of optic-spinal multiple sclerosis binds to the aquaporin-4 water channel. *J Exp Med*. 2005 Aug 15;202(4):473-7.
- McLaughlin KA, Chitnis T, Newcombe J, Franz B, Kennedy J, McArdel S, Kuhle J, Kappos L, Rostasy K, Pohl D, Gagne D, Ness JM, Tenenbaum S, O'Connor KC, Vigiotta V, Wong SJ, Tavakoli NP, de Seze J, Idrisova Z, Khoury SJ, Bar-Or A, Hafler DA, Banwell B, Wucherpfennig KW. Age-dependent B cell autoimmunity to a myelin surface antigen in pediatric multiple sclerosis. *J Immunol*. 2009 Sep 15;183(6):4067-76.
- Brilot F, Dale RC, Selzer RC, Grummel V, Kalluri SR, Aslam M, Busch V, Zhou D, Cepok S, Hemmer B. Antibodies to native myelin oligodendrocyte glycoprotein in children with inflammatory demyelinating central nervous system disease. *Ann Neurol*. 2009 Dec;66(6):833-42.

SOCIAL PROGRAMME

SATURDAY, SEPTEMBER 10, 2011

19:00

Opening ceremony at Hungexpo
Followed by a Welcome Reception

MONDAY, SEPTEMBER 12, 2011

EVENING

Special Social Event at the Budapest Market Hall

TUESDAY, SEPTEMBER 13, 2011

15:45

Closing session

TEACHING COURSES

SATURDAY, SEPTEMBER 10, 2011

09:30 – 11:00

Free Teaching Course: How do I examine...

11:30 – 13:30

Teaching Course 1: Movement disorders – basic clinical knowledge
Teaching Course 3: Stroke: neurological complications in the long term. Basic clinical knowledge
Teaching Course 5: Multiple sclerosis – basic clinical knowledge
Teaching Course 7: Luigi Amaducci teaching course on dementia – basic clinical knowledge
Teaching Course 9: Treatment of epilepsy – basic clinical knowledge
Teaching Course 11: Chronic headache: update on epidemiology, mechanisms and treatment
Teaching Course 13: Neuromuscular diseases I
Teaching Course 15: Neurosonology
Teaching Course 17: Metabolic neurogenetic disorders
Teaching Course 19: Therapy in neurology

14:30 – 16:30

Teaching Course 2: Movement disorders – advanced
Teaching Course 4: Advances in stroke in the young
Teaching Course 6: Management of multiple sclerosis by early and persistent immunotherapy – advanced
Teaching Course 8: Luigi Amaducci teaching course on dementia – advanced
Teaching Course 10: Advanced aspects of epilepsy for the clinician
Teaching Course 12: Neuroimaging of neurodegenerative diseases
Teaching Course 14: Neuromuscular diseases II
Teaching Course 16: Neuro-ophthalmology
Teaching Course 18: My most difficult cases

SUNDAY, SEPTEMBER 11, 2011

07:30 – 09:00

Teaching Course 20: Hands-on course on clinical neurophysiology – Nerve conduction
Video Teaching Course – Epilepsy Video Session

20:30

Scientific Gulyás Dinner: Neuroimmunology: a walk through the woods

MONDAY, SEPTEMBER 12, 2011

07:30 – 9:00

Teaching Course 21: Hands-on course on Doppler sonography – practical demonstration in four groups
Teaching Course 22: Hands-on course on clinical neurophysiology

15:30 – 17:00

FREE Teaching Course 23: How to do a treatment trial

TUESDAY, SEPTEMBER 13, 2011

07:30 – 09:00

Teaching Course 24: Hands-on course on clinical neurosonology
Teaching Course 25: Hands-on autonomic testing – from bedside to laboratory investigations of ANS disorders

MAIN TOPICS

SUNDAY, SEPTEMBER 11, 2011

08:30 – 10:30

Main topic 1: Translational research in movement disorders

Main Topic 2: Neurobiology of migraine

Main Topic 3: Recent advances in neurocritical care

Main Topic 4: Biotherapies for neurological diseases: mechanisms of action, efficacy and safety

MONDAY, SEPTEMBER 12, 2011

08:30 – 10:30

Main Topic 5: Invasive treatment strategies for ischemic stroke

Main Topic 6: Frontotemporal dementia (FTD) – from molecule to behaviour

Main Topic 7: Acute vertigo: neurophysiology, clinical approach, and treatment

Main Topic 8: Paradigms in epilepsy treatment

TUESDAY, SEPTEMBER 13, 2011

08:30 – 10:30

Main Topic 9: Atrial fibrillation and stroke.

New insights, new dilemmas

Main Topic 10: A translational view on narcolepsy: what we know, and what we don't know

Main Topic 11: Neuroprotection and environmental factors in multiple sclerosis

Main Topic 12: Controversies in neurology

12:00 – 13:00

EFNS Lecture on Clinical Neurology

Angela Vincent, Oxford, UK

FOCUSED WORKSHOPS

SUNDAY, SEPTEMBER 11, 2011

15:30 – 17:00

Focused Workshop 1: Optimising stroke care in Eastern European countries

Focused Workshop 2: New perspectives in neurological therapies

Focused Workshop 3: The early course of multiple sclerosis

Focused Workshop 4: New insights into treating mitochondrial disease

Focused Workshop 5: Epilepsy in resource-poor countries: an emerging issue for European public health

MONDAY, SEPTEMBER 12, 2011

15:30 – 17:00

Focused Workshop 6: Movement disorders of the face

Focused Workshop 7: Neuromodulation in headache

Focused Workshop 8: White matter changes (leukoaraiosis)

Focused Workshop 9: Common dilemmas in muscle disease

Focused Workshop 10: Neurofibromatosis and the neurologist

TUESDAY, SEPTEMBER 13, 2011

14:00 – 15:30

Focused Workshop 11: Update on multiple system atrophy

Focused Workshop 12: Cerebral microbleeds

Focused Workshop 13: Opportunistic infections of the nervous system

Focused Workshop 14: Monoclonal gammopathies of undetermined significance (MGUS) and peripheral nerve disorders

Focused Workshop 15: The chronic secondary headache

SPECIAL SESSIONS

SATURDAY, SEPTEMBER 10, 2011

16:30 – 17:30

Brain disorders in Europe: future directions
Symposium dedicated to the 70th birth anniversary of Professor Jes Olesen in recognition of his outstanding contribution to the fields of neurology and development of the EFNS and the European Brain Council

SUNDAY, SEPTEMBER 11, 2011

11:00 – 13:00

Joint Session EFNS – Mediterranean Neurological Societies:

Movement Disorders

14:30 – 17:00

European Basal Ganglia Club Session

15:00 – 17:00

EFNS-EFNA Special Session: "The Good Life"

17:30 – 18:40

EAYNT Session

MONDAY, SEPTEMBER 12, 2011

15:00-17:00

EFNS-ILAE-CEA Joint Session: Treatment of epilepsies
EFNS – EFNA Awareness Session

TUESDAY, SEPTEMBER 13, 2011

10:30 – 12:00

Music and neurology

13:30 – 15:30

Neurology in central and eastern Europe: roots and development

14:00 – 15:30

Joint Session EFNS – WSO (World Stroke Organisation): Cardinal Principles of Stroke Management

To list your event in this diary, email brief details to Anna Phelps at anna@acnr.co.uk by 6th August, 2011

2011

July

8th National Conference: Autism Today 2011
11 July, 2011; London, UK
E. flo.doel@markallengroup.com

Health & Social Care
12 July, 2011; Birmingham, UK
E. louisewilkinson@cbituk.org
www.cbituk.org

IBRO 2011
14-18 July, 2011; Florence, Italy
www.ibro2011.org/site/home.asp

SINAPSA Neuroscience Conference
14-18 July, 2011; Ljubljana, Slovenia
E. tanja.butzek@fens.org
www.sinapsa.org/SNC11/
www.sinapsa.org/en/

Cognitive Rehabilitation
15 July 2011; Cambridge, UK
T. 01353 652173
E. Rachel.everett@ozc.nhs.uk

Bridging Basic with Clinical Epileptology – Advanced International Course
17-29 July, 2011; Venice, Italy
E. epilepsysummercourse@univiu.org
www.ilae.org; www.epilearn.eu

Human Brain Anatomy Course
18-20 July, 2011; London, UK
www.neurocourses.com

2011 CMD family conference
23 July, 2011; Philadelphia, USA
www.curecmd.org/events

CNS 2011
23-28 July, 2011; Stockholm, Sweden
E. cns@cnsorg.org

Pain Management/Neurology/Compliance
28 July – 6 August, 2011; Copenhagen, Denmark
T. 1-800-422-0711
E. 072811NeuroPain@continuingeducation.net

August

Advanced course in Computational neuroscience
1-26 August, 2011; Bedlewo, Poland
E. tanja.butzek@fens.org
www.neuroinf.pl/accn

Becker Muscular Dystrophy Conference
13 August, 2011; Los Angeles, USA
E. julie.groth@cshs.org

Nemaline myopathy convention 2011
18-20 August, 2011; London, UK
www.treat-nmd.eu/events/255/

Brain Injury Association of Canada Annual Conference
24-26 August, 2011; Charlottetown, Canada
www.biac-aclc.ca

4th Congress of the Pan-Asian Committee for Treatment and Research in Multiple Sclerosis (PACTRIMS)
28-30 August, 2011; Raffles City, Singapore
E. secretariat@pactrims.org

29th International Epilepsy Conference 2011
28 August – 1 September, 2011; Rome, Italy
www.epilepsyrome2011.org/

New Horizons for Myogenesis
28 August – 2nd September, 2011; New Hampshire, USA
www.grc.org/application.aspx

Imaging brain function in animals and humans
28 August – 16 September, 2011; Lausanne/Geneva, Switzerland
E. tanja.butzek@fens.org
<http://fens.mdc-berlin.de/fens-ibro-schools/2010/schools/read.php?id=2060>

Pain Management and Neurology
29 August – 9 September, 2011; Civitavecchia Italy
E. 082911PainMgmt@continuingeducation.net

September

Neuroscience Ireland Annual Conference 2011
1-2 September, 2011; Maynooth, Ireland
T. 353 1 896 8477
E. milleram@tcd.ie

24th ENCP Congress
3-7 September, 2011; Rome, Italy
E. organisingsecretariat@ecnp2011.eu
www.ecnp.eu/emc.asp?pageld=332

European synapse summer school
4-23 September, 2011; Bordeaux, France
E. tanja.butzek@fens.org
<http://fens.mdc-berlin.de/fens-ibro-schools/2010/schools/read.php?id=2061>

British Myology Society Annual Meeting
7-9 September, 2011; Oxford, UK
www.myology.org.uk/

Society of British Neurological Surgeons Autumn Meeting 2011
7-9 September, 2011; Brighton, UK
www.sbn.org.uk

Best Practice implementation in the management of patients with NMDs
8 September, 2011; Prague, Czech Republic
www.treat-nmd.eu/events/287/

British Neuroscience Association Symposium: Neurodevelopmental Disorders Across the Lifespan
8-9 September, 2011; Edinburgh, Scotland
www.bna.org.uk/events

EAMDA 41st AGM
8-11 September, 2011; Prague, Czech Republic
www.eamda.org

15th Congress of the European Federation of Neurological Societies
10-13 September, 2011; Budapest, Hungary
E. headoffice@efns.org
www.efns.org/efns2011

World Congress on Huntington Disease
11-14 September, 2011; Melbourne, Australia
www.worldcongress-hd2011.org/

17th Congress of the European Section of the International Society on Toxinology
11-15 September, 2011; Valencia, Spain
T. 0034 96 197 4670
E. catedrasg@cac.es
www.fundacioncac.es/catedrasg

10th European Meeting on Glial Cells in Health and Disease
13-17 September, 2011; Prague, Czech Republic
www.euroeglia2011prague.cz/

14th WFNS Interim Meeting
14-17 September, 2011; Pernambuco, Brazil
www.wfns.org

AANEM Annual Scientific Meetings
14-17 September, 2011; San Francisco, California, USA
T. + (507) 288-0100
F. + (507) 288-1225
E. aanem@aanem.org

Venice Summer School on Aphasia Rehabilitation
14-17 September, 2011; Lido of Venice, Italy
E. viviana.zanin@ospedalesancamillo.net

17th Joint Annual Meeting of the German-Austrian Society Against Epilepsy
15-17 September, 2011; Prien/Chiemsee, Germany
www.epilepsiezentrumerlangen.de

Understanding Brain Injury
16 September, 2011; Cambridge, UK
T. 01353 652173
E. Rachel.everett@ozc.nhs.uk

Understanding and Dealing with Behaviour Problems following Brain Injury
16-17 September, 2011; London, UK
E. enquiries@braintretraining.co.uk
www.braintretraining.co.uk

Czech Conference on multidisciplinary care for patients with spinal atrophy
16-18 September, 2011;
Ceske Budejovice, Czech Republic
www.treat-nmd.eu/events/240/

Duchenne Family Support Group Annual Conference
17 September, 2011; Stratford-upon-Avon, UK
www.treat-nmd.eu/events/256/

International conference on Muscle Wasting
18-23 September, 2011, Ascona, Switzerland
E. musclewasting2011@demariaevent.ch

Muscle Study Group Annual Meeting
19-22 September, 2011; New York, USA
T. 585-275-1274
E. donna_ladonna@urmc.rochester.edu

Joint MS Trust and Kent ACIPN MS Study Day
20 September, 2011; Maidstone, UK
E. education@mstrust.org.uk
www.mstrust.org.uk/studydays

Dementia
21 September, 2011; London, UK
www.rcn.org.uk/events

Neurological Upper Limb for OT's
21 September, 2011; Derby, UK
T. 01332 254679
E. ncore@derbyhospitals.nhs.uk

Pain in Europe VII
21-24 September, 2011; Hamburg, Germany
E. myatsiv@kenes.com
E. eschwartz@kenes.com

17th Congress of Child Neurologists of Mediterranean
21-24 September, 2011; Piran, Slovenia
E. milivoj.velickovic@mf.uni-lj.si
www.cnm2011.eu/
child-neurologists-ofmediterranean/

35th Annual Meeting of European Society of Neuroradiology
22-25 September, 2011; Antwerp, Belgium
E. esnr2011@aimgroup.eu
www.esnr2011.org

Sinapsa Neuroscience Conference, 11
22-25 September, 2011; Ljubljana, Slovenia
E. alenka.kregar@cd-cc.si
www.sinapsa.org/snc11

The three Rs of innate immune recognition: Toll like receptors (TLRs), RIG-like receptors (RLRs) and Nod-like receptors (NLRs)
23 September, 2011; Brighton, UK
E. enquiries@euroscicon.com
www.regionline.co.uk/workihc2010

13th ILAE Specialist Registrar Teaching Weekend in Epilepsy
23-25 September, 2011; Oxford, UK
www.genesisadoration.com/epilepsy.html

136th Annual American Neurological Association Meeting
25-28 September, 2011; San Diego, USA
www.aneuroa.org

11th International Conference on Cognitive Neuroscience
25-29 September, 2011; Palma, Mallorca, Spain
www.icon11mallorca.org/

Assessment of a client with Perceptual and Cognitive Dysfunction
26-27 September, 2011; Derby, UK
T. 01332 254679
E. ncore@derbyhospitals.nhs.uk
www.ncore.org.uk

NMD – chip steering committee meeting
27-28 September, 2011; London, UK
www.treat-nmd.eu/events/200/

Co-Morbidities of Epilepsy
27-30 September, 2011; Ontario, Canada
E. mpoulter@robarts.ca

84th Annual Congress of the DGN
28 September – 1 October, 2011; Wiesbaden, Germany
E. weil@congrex.com
www.dgn2010.de/dgn2011/main.html

Exploring Gait
29 September, 2011; Derby, UK
T. 01332 254679
E. ncore@derbyhospitals.nhs.uk
www.ncore.org.uk

Asia Stroke Conference
29 September – 1 October, 2011, Colombo, Sri Lanka
T. 0094 773157688
E. infoapsc2011@gmail.com

Gene-environment interplay: shaping behaviour and CNS dysfunction
29th September, 2011; Liverpool, UK
www.bna.org.uk/events/

Cognition Disorders in MS
30 September – 1 October, 2011; Florence, Italy
www.seronosymposia.org/en/Neurology/Symposia/cognitiondisordersms/page.html

October

Muscular Dystrophy Campaign Scottish Conference
1 October, 2011; Glasgow, Scotland
T. 020 7803 4804
E. 2011conference@muscular-dystrophy.org

Congress of Neurological Surgeons Annual Meeting
1-6 October, 2011; Washington D C, USA.
Congress of Neurological Surgeons
T. +847 240 2500
F. +847 240 0804
E. info@ICNS.org
www.neurosurgon.org

HRC 2011
2-5 October, 2011; Birmingham, UK
www.hearhythmcongress.com

8th UK SMA Researchers' Conference
3-4 October, 2011; Oxford, UK
E. kevin.talbot@clneuro.ox.ac.uk

Improving the use of electromyography in paediatrics
3-5 October, 2011; London, UK
www.treat-nmd.eu/events/285/

Cognitive Behavioural Therapy Intermediate level workshop
4 October, 2011; Derby, UK
T. 01332 254679
E. ncore@derbyhospitals.nhs.uk
www.ncore.org.uk

ABN Annual Meeting
5-7 October, 2011; Newcastle, UK
www.theabn.org

One day workshop: jitter analysis in children
6 October, 2011; London, UK
www.treat-nmd.eu/events/284/

43rd International Danube Neurology Symposium 2011
6-8 October, 2011; Dresden, Germany
E. danube2011@cpo-hanser.de
T. +49-40-670 88 20

21st Alzheimer Europe Conference
6-8 October, 2011; Warsaw, Poland
E. info@alzheimer-europe.org
www.alzheimer-europe.org/EN/Conferences/Warsaw-2011

14th European Congress of Neurosurgery (EANS)
9-14 October, 2011; Rome, Italy
www.kenes.com

13th Congress of the European Federation of Autonomic Societies (EFAS)
12-15 October, 2011; Bern, Switzerland
E. mail@imk.ch
www.imk.ch/efas2011

BNA 21st National Biennial Meeting

Conference details: 17-20 April, 2011, Harrogate, UK. Reviewed by: Dr Anne Cooke, BNA Editor.

“We are all familiar with the amazing complexity of the brain. Two questions: how did the brain evolve? And how does it manage to function? - it could break in so many different ways!”



Although these were the words of Seth Grant, from Edinburgh, used in the specific context of his own talk, the same could apply to the BNA's national meeting as a whole, for the 700 plus neuroscientists from across the UK and beyond had gathered in Harrogate to listen, learn, present, and discuss exactly these questions – how does the brain develop; what are its constituent parts; how do they work together in exquisite precision to perform the multitude of tasks your brain carries out each day; and, when brains do go wrong, where exactly do the errors arise? Finally, perhaps most importantly, how can we then correct them to achieve full function again?

It would be impossible to summarise the superlative neuroscience of four days into just a short report. Social events, symposia, poster sessions, superb plenaries; please take it as read that all bases were covered. I hope, therefore, that this account provides a few fond memories for those who attended, and a tantalising taster for anyone who didn't; ensure you register early next time!

The UK's hottest neuroscience

Hot Topics in Neuroscience was introduced as a new type of session this year.

Out of the hundreds of abstracts submitted for the meeting, those judged as being of especially high calibre, on topics of high current interest, and with the potential of being the really key breakthroughs in the field, were highlighted by being presented in one of the three 'Hot Topics' symposia: Basic Neuroscience, Behavioural Neuroscience, and Models of Disease.

The 27 short talks, given by researchers at all stages of their career, gave a powerful demonstration of the quality and strength of neuroscience in the UK.

Superb plenaries

The plenary lectures were outstanding. Indeed, when asked, most delegates cited them as being the best bit of the meeting, and BNA had certainly pulled out all the stops, inviting speakers surely destined to become Nobel Laureates and neuroscience heroes of the future. Highlights from their talks include:

- Gero Miesenboeck's headless flies, optogenetically controlled to dance on command.
- Maurizio Corbetta's amazing fMRI 'movies' showing waves of spontaneous activity across the human cortex (just noise? or significant for brain function?).
- Morgan Sheng presenting the breakthroughs he has made in the science of synaptic plasticity (and more).
- David Tank's innovative use of Game Boy in his research, which must leave Safety Officers at a loss when it comes to lab paperwork.
- Li-Huei Tsai's work that shows the

Disrupted in Schizophrenia 1 (DISC1) gene is important for neurogenesis in the developing and adult brain.

- Peter Dayan explaining how psychiatric disorders can be boiled down to a single mathematical equation.
- David Nutt describing how stages of addiction – from the Latin for 'enslavement' – might map onto specific regions of the brain.

A meeting for members

Importantly, the programme offered plenty of opportunities for everyone attending the meeting to actively participate. The workshops, in particular, were designed to provide a forum for delegates to engage with a panel of experts, and address issues of fundamental concern to neuroscientists.

The workshop on how neuroscience can influence policy was chaired by Phil Willis, a former local MP.



Barbara Sahakian welcomed the high turnout of early career scientists; as leaders of the future, it is immensely important they recognise that there's a two-way street, where public policy influences research and research influences society. David Nutt reported the discrepancy, and deficiency, in money allocated to neuroscience compared to other areas of research in European funding policy. And Colin Blakemore spoke on engaging with politicians; even if it's a truism that their three top priorities are getting re-elected, getting re-elected and (you've guessed it) getting re-elected, there are ways to work effectively with local and national government, to the benefit of both society and neuroscience research.

Given the oft-repeated phrase 'current economic climate', the job cuts and reduced resources in many universities, and less money available in the industrial sector too, the packed room at the workshop on funding came as no surprise.

The BNA had invited senior figureheads of the three major funders for neuroscience – BBSRC, MRC and the Wellcome Trust – to present their organisations' policies and explain the motives behind them.

Perhaps one take-home message was that, ultimately, everyone in the room shared the same goal; to generate top-level research - and more of it - underpinned by increased investment for neuroscience. As with neuroscientists and policy-makers, what is needed is two-way engagement, conversation, and joined-up thinking. Interaction between BNA members, funders, industry, and government will be essential to achieve these joint aims.

Annual General Meetings are not known for their popularity, but this year's turned out to be an exception. It was clear that members felt the BNA had evolved under outgoing President Professor Trevor Robbins to more truly become their BNA; a genuine 'Voice of British neuroscience today', reflecting members' needs and becoming a society with which they wish to be involved.

New President Professor David Nutt, known for his passionate belief in speaking out for science, is sure to continue Trevor's good work and be a vociferous advocate for neuroscience members during his forthcoming four year term.

Talks...

BNA's 2011 national meeting was the first to have been developed with the guidance of a Scientific Advisory Board. Drawn from the highest echelons of expertise in neuroscience, the members of the board are to be commended and sincerely thanked for their voluntary input, over many months, for what was universally agreed to be an outstanding scientific programme.

...posters...

This is not to downplay the huge contribution made by poster presentations to the scientific content of the meeting. Allowing in-depth conversation, on specific projects, the discus-



BNA graduate prize to Stephanie Burnett by President Trevor Robbins.

sion that took place at poster sessions will no doubt influence research long after delegates return to the clinic and lab.

...and prizes

Two prizes were awarded at the conference: Stephanie Burnett from the UCL Institute of Neurology received the BNA's annual Postgraduate Prize. Working in Sarah-Jayne Blakemore's group, Stephanie's research into the social development of the brain has already garnered an extremely impressive publication record; the prize is undoubtedly well deserved.

The second prizewinner was Gero Miesenboeck, from Oxford University, awarded The Wolstencroft Memorial Lectureship in honour of his groundbreaking work in the emerging field of optogenetics. Developing this technology represents an exciting new way to explore a wide range of research topics, both neuroscience and beyond.

The social scene

Many people see the time spent between symposia at scientific meetings as valuable as the talks themselves, and no doubt everyone has their own highlights of Harrogate's social side, catching up with colleagues from home, friends from times and labs gone past, and making new friends and potential collaborators too.

In addition, the programme team had arranged two social events for all delegates at the meeting:

The Evening of Eclectic Activities featured knitted neurons, musicians, synaesthetic experiences, and a new way for patients and drug companies to work together, all in the splendour of Harrogate's Old Swan Hotel.

And, on the final night, the Old Swan again

played host for the 2011 conference dinner. Along with a superb four-course menu, Trevor Robbins displayed a rare talent as after-dinner speaker, rounding off the evening with merriment and much laughter all round.

And the best is yet to come

This report is a small taste of a highly successful meeting. Congratulations to all those who worked hard in its preparation and smooth running throughout. It was the first time the national meeting had been run from the new BNA office. Certainly having a dedicated BNA staff team (Arciris Garay-Arevalo; Hannah Critchlow, on secondment from Cambridge Neuroscience; and also – to produce the printed BNA Bulletin – Anne Cooke from Bristol Neuroscience) has benefited the BNA in running events as well as numerous other ways.

Plans are already underway for 2013. Instead of the national conference, BNA have taken the initiative to hold the first ever Festival of Neuroscience in the UK. The BNA are keen to engage with other brain-related organisations to hold the event; partnerships have already been made with UK societies representing different aspects of neuroscience, psychology, psychiatry, neurology and more. ♦

The Festival will be at London's Barbican Centre, 7-10 April 2013.

Make sure the date is in your diary; the BNA look forward to seeing you there.

The BNA are very grateful to the Gatsby Charitable Foundation for their commitment and ongoing support.

KCCI
2nd Keele Course on CNS Inflammation
 9th – 11th September 2011
Keele University Medical School, Keele, Staffordshire

Target audience:

Consultants and Specialist Registrars in Neurology and Allied Health Specialities.

Programme

How I would approach DMTs in MS?	Gavin Giovannoni, London
CNS vasculitis	Neil Robertson, Cardiff
Neuromyelitis optica	Mike Boggild, Liverpool
Neurosarcoid	Desmond Kidd, London
Challenges in MS diagnosis	Alasdair Coles, Cambridge
Neuro-Behcet's	Adnan Al-Araji, Stoke
Is it CNS inflammation or a functional disorder?	Jon Stone, Edinburgh
Monoclonal antibody-associated PML	David Hunt, Edinburgh
Inflammatory optic nerve disease	Clive Hawkins, Stoke
The urgency to treat multiple sclerosis	Martin Duddy, Newcastle
The management of mobility in MS	Jeremy Hobart, Plymouth
Anti-phospholipid syndrome	David D'cruz, London
HIV neurology	Hadi Manji, London
CNS antibody-mediated diseases	Angela Vincent, Oxford

Objectives & Format:

To present updates, case histories and interactive presentations on various topics related to CNS inflammation and demyelination.

Fees:

£125.00, to include registration, accommodation for two nights and meals.

Register at lisa.locklin@uhns.nhs.uk or telephone (01782) 554821
 Lisa Locklin, Secretary to Dr Al-Araji, Department of Neurology,
 University Hospital of North Staffordshire, Stoke on Trent, ST4 7LN

**MS Trust
 Annual
 conference**

13-15 November 2011



Attend the only MS event aimed specifically at specialist MS nurses and allied health professionals

Venue: Chesford Grange, Kenilworth, Warwickshire, UK

Plenary lectures to include:

The diagnostic Process
 – what is changing?
 The epidemiology of MS
 Drug treatments for MS
 It's my future as well

Seminar topics to include:

Setting up a fingolimod service
 Palliative care
 Service development
 Therapists look at Cognition

MS infozone

The place to find practical support and information on a wide variety of topics

UKMSSNA AGM

Therapists in MS (TiMS) update meeting

Contact details

For full conference programme and to book you place visit

www.mstrust.org.uk/conference

Alternatively to request a paper registration pack

Email conference@mstrust.org.uk

Tel: 01462 476314

Call for proposals

To celebrate Epilepsy Research UK's 20th anniversary, we are awarding £1,000,000 in 2012!

Epilepsy Research UK invites applications for grants to support basic and clinical scientific research in the UK, into the causes, treatment and prevention of epilepsy. We encourage applications on all aspects of epilepsy, including basic and social science, clinical management and holistic management of patients.

Project grants

Applications are invited for grants up to £150,000 to support a research project lasting a maximum of three years. Applications for smaller sums to support salary costs, purchase of equipment, or student fees are also welcome.

Fellowship grants

Applications are invited for grants of between £200,000 and £250,000, over 1-3 years, to support fellowships. Funds will cover Fellow's salary, support staff costs and project running costs.

**Deadline for receipt of completed applications:
 Friday 30 September 2011, 16:00**

For more information and an application form, please visit the Epilepsy Research UK website, www.epilepsyresearch.org.uk, or contact Delphine van der Pauw, Research and Information Executive, Epilepsy Research UK, PO Box 3004, London W4 4XT.

**Tel: 020 8995 4781,
 email: delphine@eruk.org.uk**



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**Centre for Community
 Neurological Studies**



Continuing Professional Development (CPD) (All completed by distance-learning)

Masters courses:

- Epilepsy Practice
 - Multiple Sclerosis Practice
 - Stroke Practice
 - Parkinson's Disease Practice
- (Postgraduate Certificate, Postgraduate Diploma, full MSc)

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- Epilepsy Care
 - Multiple Sclerosis Care
 - Parkinson's Disease Care
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- (All 45 credits at level 6)

Or a single module from any of the above courses.

Single module course:

- Multiple Sclerosis Care in the Community
- (15 credits at level 6)

The Centre has been delivering distance learning courses for more than a decade and over 1200 health professionals from all parts of the UK have already obtained CPD qualifications from us. Our courses are becoming essential qualifications for those who want to specialise in or lead neurological services.

The key aim of all our courses is to apply the knowledge gained into professional practice. The main outcome should be enhanced clinical practice.

Contact Details

For more detailed information on our courses please contact:
 The Centre Administrator, Tel: 0113 812 5918, Fax: 0113 812 3416
 Email: ccsenquiries@leedsmet.ac.uk

Courses developed in association with: NeuroEducation, Epilepsy Action, Multiple Sclerosis Society, Multiple Sclerosis Trust, Parkinson's UK

No Mind Left Behind – Social Brain 3

Details: 29-30 March 2011, Glasgow, UK. **Reviewed by:** Sophie Dow, Mindroom Glasgow Royal Concert Hall, March 2011.

A major international conference on autism, ADHD and other early onset neurodevelopmental disorders, organised by Scottish charity Mindroom in collaboration with Christopher Gillberg, Professor of Child and Adolescent psychiatry from The Gillberg Neuropsychiatry Centre in Gothenburg, took place at Glasgow Royal Concert Hall in March this year.

An unprecedented 51 leading world experts in the field of social communication and learning difficulties participated (all speakers giving their time for free) with some 850 delegates from 19 different countries attending.

Commenting on the significance of the conference, Christopher Gillberg, said: “No Mind Left Behind turned out to be one of the great events in the history of sharing new information in child neuropsychiatry and neurodevelopment. At least one child in every class is socially excluded – and at least two more children in that same class struggle with one or more learning difficulties.”

“As we continue to learn more about the human brain, and about challenging aspects of our increasingly complex society, the numbers of people needing help for social interaction problems and/or learning difficulties will continue to grow. At the same time too few are being effectively identified and supported.”

“If left undiagnosed or untreated, social interaction problems and/or learning difficulties will become the biggest public health issue of our time.”

Indeed the importance of early intervention was the overall theme and take home message from the two day conference. The concept and consequential acronym ESSENCE – Early Symptomatic Syndromes Eliciting Neurodevelopmental Clinical Examinations – was officially introduced in a keynote lecture by Christopher Gillberg, in which he urged the audience to look at look at early symptoms in a new light. It is vital monitor at the bigger picture, he said, especially during the first five years of a child’s life, rather than lock into a specific diagnose too early.

At least 5% of children under six years of age present with some form of ESSENCE related problems, and the outcome for these children is not good unless we react and act early.

‘ESSENCE, Christopher Gillberg said, is a new acronym for a very old problem.

Lorna Wing, OBE, shared her new views on



social instinct and autism.

“There is no doubt, she said, that problems affecting the social brain are of supreme importance in the case of autistic disorders, but, she continued, the nature of this particular brain dysfunction remains a fascinating puzzle. A lot more research is needed Lorna Wing stated, before we fully understand autism.

Simon Baron Cohen put forward the fascinating theory that high testosterone in utero may

be associated with autistic traits in the offspring.

The importance of the Default Network was discussed and it was thought that it is within the Default Network that we shall be looking for answers in the future, certainly concerning autism.

The gap between male and female prevalence will be closing, Professor Gillberg remarked, but not down to 1:1 he believes.

There were some 48 other speakers to listen to, Eric Taylor, Francesca Happé, Brian Neville, Jonathan Seckl and Anne O’Hare to name a but a few, all sharing the very latest within their specific field, but the most basic facts still remain and that is that understanding is key and that collaboration across the board is essential if we are going to stem this big public health problem of our time.

No Mind Left Behind – Social Brain 3 is available in Virtual mode at a cost of £75 in total. The entire conference was recorded and the very flexible software provides a search mechanism which allows you to use the information/lectures to suit your particular purpose and interest. Simply type in your password and away you go.

For more information on No Mind Left Behind Virtual please go to www.mindroom.org

Would you like to write a short report for ACNR?

If so, please contact Rachael@acnr.co.uk or call Rachael on 01747 860168 for more information.

15th Annual Conference in Recent Advances in Brain Injury Rehabilitation

**Homerton University Hospital,
Wednesday 26th October 2011 • Cost £110**

This conference is aimed at Medical Doctors, Psychologists, Nurses, Physiotherapists, OTs, Speech & Language Therapists, Researchers, Academics, Social Workers and all who work with brain injured people.

Speakers to be confirmed

Presentations made in previous conferences have included:

The aware mind in the still body: fMRI of the vegetative state
Dr Martin Monti, Postdoctoral Researcher, University of Cambridge

What human neuroimaging can teach us about motor control
Marie-Helene Boudrias, Institute of Neurosciences, London

Self-esteem as a predictor of psychological distress after brain injury

Dr Sam Cooper-Evans, Consultant Clinical Psychologist

Families and Carers after Brain Injury

Professor Mike Oddy, Brain Injury Research Trust

For further details and application enquiries please contact
Lauretta Price, Conference Organiser
Email Lauretta.price@homerton.nhs.uk
Tel 020 8510 7970

Bringing together experience and education in multiple sclerosis

19-20 September 2011

*Professor Neil Scolding and Bayer Healthcare are
delighted to invite you to attend the MS Masterclass
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For more information and to register your interest in attending the meeting please go to www.msclass-brisol.co.uk/event

MS Masterclass is a faculty led medical educational programme funded and facilitated by Bayer Healthcare

This invitation is open to members of the medical profession only and no provision can be made for partner attendance. The arrangements for and contents of this meeting are in accordance with the ABPI Code of Practice



Job code: UK.PH.H&N.BET.2011.029

Date preparation: June 2011

22nd international symposium on ALS/MND


Sydney 2011

Sydney, Australia
30 Nov - 2 Dec 2011

The International Symposium on ALS/MND is a unique annual event which brings together leading international researchers, clinicians and healthcare professionals to present and debate key innovations in their respective fields

Scientific meeting

Platform session themes

- Pathobiology of ALS/MND
- Cell stress mechanisms
- RNA and protein processing
- Lessons from other neurodegenerative diseases
- New aspects of the BMAA hypothesis
- Genetics
- In vivo models
- Target pathways and therapeutic strategies

Clinical meeting

Platform session themes

- Holistic care and quality of life
- Translating evidence into practice
- Cognitive change
- Epidemiology
- International perspectives on care practice
- Surrogate markers
- Neuroimaging
- Respiratory and nutritional management
- Clinical trials and trial design

For more information and to register, contact the conference team by email symposium@mndassociation.org or register online at www.mndassociation.org/symposium.

Registered Charity No 294354



Fourth Practical Cognition Course

20-21 October 2011

Research Beehive, Newcastle University

A course is for consultants and trainees in neurology, psychiatry, neuropsychology and rehabilitation medicine who want to develop their practical expertise in cognitive assessment and relate this to clinically relevant neuroscience. This year's programme will cover disorders of language, consciousness, parietal lobe function and social cognition. The course is organized by neurologists Tim Griffiths (Newcastle) and Chris Butler (Oxford), sponsored by the Guarantors of Brain and accredited for CME points.

EARLY BIRD RATE £150

For more information and to register visit
www.practicalcognition.com

Contact for enquiries:

Laura Pereira,
0191 222 8320,

laura.pereira@ncl.ac.uk



One Day Meeting on 21st Century Review of Complex Parkinson's at Downing College, Cambridge

Conference details: 27 May, 2011, Downing College, Cambridge. *Reviewed by:* Alexandra Rizos and Ines Koch, EUROPAR, King's College Hospital, London.



On 27 May, a one day meeting addressing therapies for complex Parkinson's disease (PD) was held at Downing College in Cambridge. The meeting was organised by the research section of the Parkinson's Disease Non Motor Group, formerly PDNMG, now called EUROPAR, endorsed by Parkinson's UK and European Parkinson's Disease Association, with an unrestricted grant from Genus Pharmaceuticals Ltd and attracting 6 CPD points. The meeting hosted an international faculty of key opinion leaders and was chaired by Professor K Ray-Chaudhuri from the National Parkinson Foundation (NPF) Centre of Excellence at King's College Hospital. Over 80 delegates attended including those from Germany and Sweden and comprised of a range of specialities, including neurologists, nurse specialists, therapists, geriatricians and psychiatrists.

The first talk was given by Dr Nin Bajaj from the NPF Centre of Excellence at Nottingham, who reviewed options for managing complex Parkinson's, including deep brain stimulation (DBS), intrajejunal levodopa infusion as well as apomorphine infusion. He outlined the potential of apomorphine as an acute rescue medication for off periods or as continuous

infusion for fluctuations and alluded to the anti-dyskinetic effect of apomorphine. Dr Bajaj also touched upon the potential for the use of apomorphine in patients with oral drug induced hallucinations as has been previously reported by Ellis et al. in 1997 and more recently by van Laar and colleagues.

Thereafter Dr Tove Henriksen from Bispebjerg Hospital in Copenhagen, Denmark, spoke on the effects and side effects of DBS, intrajejunal levodopa as well as apomorphine infusion highlighting its remarkable effect on provoked off periods, an effect similar to levodopa, while outlining issues relating to side effects such as skin nodules, nausea as well as the need to monitor using Coombs test. She highlighted that with good nurse specialist backup, these side effects very rarely lead to discontinuation of infusion therapy.

Professor Per Odin from the Universities of Lund in Sweden and Bremerhaven in Germany, outlined the history of development of therapies for advanced PD focussing on apomorphine. It was interesting to note that apomorphine was developed in the 19th century long before levodopa was discovered, but its clinical use for PD, as pioneered by Andrew Lees and his team as well as K Ray-Chaudhuri and colleagues from

London, could only be developed after the use of domperidone was described by Corsini et al. in 1979. Professor Odin outlined the refining of the apomorphine delivery process.

The second session was started by Professor Regina Katzenschlager from Vienna, Austria, who presented results of an interesting study highlighting the efficacy of apomorphine as an anti-dyskinetic agent, especially when used as 24 hour continuous therapy or in monotherapy. She also outlined that the tolerability for monotherapy is often underestimated and can be more widely adopted as the effects are similar to those described with subthalamic deep brain stimulation (DBS) and intrajejunal levodopa infusion, although direct head to head studies are lacking.

This talk was followed by "hands on" tips on practical management of advanced Parkinson's Disease with infusion therapies by Anne Martin, PD nurse specialist from King's College, London / nurse representative in EUROPAR and Jane Mills, Advocacy Nurse Manager from Genus Pharmaceuticals. They highlighted the importance of patient selection for apomorphine therapies and emphasised that good selection of cases is the key to successful therapy with apomorphine. Potential

pitfalls such as difficulties with the challenge test owing to first-dose-related postural hypotension or nausea, both of which can be helped by use of domperidone, and the development of troublesome skin nodules were discussed. Anne Martin emphasised the need for good hygiene at infusion sites and the daily rotation of chosen sites across the body, including the scapula, as well as tips for nodule management with ultrasound and silicone gel therapies.

Professor Pablo Martinez-Martin from Madrid, Spain, discussed some new EUROPAR data related to beneficial effects on a range of non motor symptoms while using apomorphine infusion, levodopa gel infusion and rotigotine. These data, which have been reported in abstract forms in several international meetings recently, suggest that these long acting therapies have a beneficial effect on non-motor symptoms. For example, infu-

sion of apomorphine has a significantly beneficial effect on aspects of sleep quality and refreshment, mood, non-motor fluctuations and some gastrointestinal symptoms. The overall effect on improvement of quality of life with the infusion appears in these studies to live up to the other non oral therapies in advanced PD.

Professor Ruediger Hilker from Frankfurt, Germany, presented data on recent studies of subthalamic DBS in PD compared to medial pallidal stimulation, as well as to pump-therapies. Motor- and non-motor effects were discussed, as well as potential problematic side effects such as the growing concern of cognitive problems and apathy in patients undergoing DBS. The role of DBS in the treatment of patients with impulse control disorders was also touched upon.

The final sessions were delivered by Professor K Ray-Chaudhuri and Dr Prashant

Reddy, research fellow in movement disorders from King's. Professor Ray-Chaudhuri summarised the current therapeutic strategies for advanced PD and also updated the audience on some recent data from "real life" comparative studies between intrajugal levodopa infusion and subcutaneous apomorphine infusion in PD. Subsequently, Dr Reddy outlined a new initiative which is focussed on developing a patient related outcome measure specific to PD. The day concluded with a collection of video cases illustrating the role of different therapies for advanced PD.

The day was complete with frequent audience interaction and informative question and answer as well as panel discussion sessions. The feedback from the delegates has been extremely positive and a similar one day meeting is planned for 2012. Final dates will be announced nearer to the time. ♦

Annual Cambridge Centre for Brain Repair Spring School

Details: 30 March-1 April, Cambridge, UK. **Reviewed by:** Sean Dyson and Romina Vuono, Cambridge Centre for Brain Repair.

The 15th annual Cambridge Centre for Brain Repair Spring School meeting was held from the 30th March to the 1st of April in Cambridge. This year's meeting, titled 'Restructuring the Deconstructing Brain: Neurodegeneration and its Repair', focussed upon our increasing understanding of the mechanisms of neurodegeneration and potential future therapeutic approaches that arise from such insights. Talks focussed mainly upon three degenerative disorders: Amyotrophic lateral sclerosis, Huntington's disease and Parkinson's disease, with the approaches of individual speakers spanning from biochemistry and molecular biology through to genome wide association studies and clinical neuroimaging.

Following opening remarks by Dr Roger Barker, Dr Julie Williams began the meeting by discussing genetic risk factors in the development of Alzheimer's disease. Findings from a recent three staged genome wide association study led by Dr Williams were presented demonstrating common variants at MS4A6A/MS4A4E, EPHA1, ABCA7, CD33 and CD2AP as being associated with AD. Dr Williams went on to discuss the fact that the loci identified in this most recent and the earlier association studies in AD point towards a potential role of endocytosis and the immune system in the pathology of AD.

Dr Magdalena Sastre next extended the discussion of immune involvement in AD by

highlighting the role of inflammation in the progression of AD. The basis of microglial activation early in the disease was discussed as a possible attempt to reduce β -amyloid load prior to senile plaque formation, and that progression of the disease may be linked to a gradual decrease in the ability of microglia to phagocytose A β . Dr Sastre discussed the failure of non steroidal anti-inflammatory drugs to decrease A β levels and plaque formation in AD clinical trials despite promising results from animal models. The failure of these trials was hypothesised to be as a result of the recruitment of overly advanced patients and insufficient amounts of anti-inflammatory drugs being delivered to the brain.

Inflammation in AD was further discussed by Professor Maria Grazia Spillantini who described results from her group demonstrating that although Ibuprofen can delay the onset of pathology in P301S tau transgenic mice it cannot prevent neurodegeneration. Professor Spillantini next discussed progressive death of superficial cortical neurons in the P301S tau model of AD and the neuroprotective effect conferred by the transplantation of neuronal precursor cells. Astrocytic maturation resulting in the secretion of undetermined neurotrophic factors, rather than neural replacement, was presented as a potential mechanism underlying the therapeutic effect of transplantation in this instance.

The meetings first day was brought to a

close by Dr Rick Livesey who explained his group's generation of monolayer cultures mimicking corticogenesis from human pluripotent stem cells. The use of this culture system as a model to probe cortical circuit formation and neurodevelopmental pathologies was discussed, including work focusing upon the cortical pathologies of Down's syndrome.

Following a PD case presentation by Dr Barker the second day of the meeting began with a talk by Professor John Hardy describing genetic analysis of sporadic neurodegenerative disease. The contribution of genetic variability at high risk loci, such as MAPT, to neurodegeneration was discussed, together with findings of low risk loci from genome wide association studies with PD and AD patients.

Dr Serge Przedborski spoke on the pathogenic processes underlying PD focussing on findings from studies utilising toxic and genetic animal models of the disease. These models highlight the contributions of distinct genetic mutations to features of degeneration in PD; for example, LRRK2 mutations have been shown to result in axonopathy whereas Parkin/PINK1 mutations are linked to mitochondrial dysfunction. The message to be taken from such findings, Dr Przedborski argued, is that PD may well be the result of the interaction of various pathological mechanisms, both cell autonomous and non-cell autonomous.

Dr James Rowe's talk discussed insights obtained into neurodegeneration from neuroimaging. The application of techniques such as functional MRI, VBM and Magnetoencephalography (MEG) in investigating structural and functional correlates of cognitive deficits in PD and Progressive Supranuclear Palsy (PSP) were described. He also discussed the use of brain network models and the potential for compensation or plasticity in these diseases.

Dr Roger Barker next spoke on the topic of fetal midbrain transplantation for the treatment of PD. The reported failure of two NIH funded double blind placebo controlled trials opened the talk and Dr Barker went on to discuss methodological issues that may have impacted upon the success of these trials. These included the amount of tissue transplanted per patient, the variable use of immunosuppressive therapy and differing primary outcome measures between the two trials. Dr Barker continued by discussing the presence of a subset of patients (generally young with less advanced disease) in these trials who responded well to transplantation, and in whom continual improvement has been reported for now over 10 years. Discussion of TRANSEURO, a European collaborative project aiming to define protocols for fetal tissue preparation, transplantation and patient assessment in the context of PD grafting closed Dr Barker's talk.

The possible prion-like nature of polyglutamine peptides was the focus of Dr Ron Kopito's talk. Experiments were presented which demonstrated that cultured mammalian cells are able to internalise labelled fibrillar polyglutamine aggregates, which upon internalisation become

sequestered in aggresomes alongside proteins of the ubiquitin-proteasome system. More interestingly, these internalised aggregates are able to recruit endogenous proteins with homologous amyloidogenic sequences. These data, Dr Kopito argued, give weight to the idea that cell to cell transfer of pathology may be a feature of polyglutamine diseases.

Further discussion of prion-like mechanisms in neurodegenerative disease, this time amyotrophic lateral sclerosis (ALS), was provided by Dr Anne Bertolotti. Mutations in the superoxidase dismutase (SOD1) gene have been demonstrated to result in aggregation of the protein in some familial forms of ALS. Dr Bertolotti described experiments which demonstrate that purified mutant SOD1 can enter cells via macropinocytosis followed by exit from the produced vesicle into the cytosol. Upon entry into the cytosol these mutant proteins initiate the aggregation of endogenous soluble SOD1 protein. Furthermore, it was shown that mutant SOD1 aggregates can transfer between cells through extracellular release of the aggregates.

Accumulation of misfolded proteins in characteristic brain lesions or inclusions is a highly characteristic feature of neurodegenerative diseases. Professor Manuela Neumann's talk was based on understanding the basic biology of TDP-43 and FUS/TLS in the brain and the pathological mechanisms leading to inclusion body formation, neurodegeneration and cell death in neurodegenerative diseases. The RNA-binding protein TDP-43 is a pathological protein in the majority of frontotemporal dementias (FTD) and most amyotrophic lateral sclerosis (ALS) cases. Very recently it was demonstrated that a second RNA-binding

protein named FUS/TLS plays another important role in the pathogenesis of a subset of FTD and ALS, thereby providing strong evidence that alterations in RNA processing might be a key event in the pathogenesis of these conditions.

Dr Emanuele Buratti next spoke more about TDP-43 and FUS/TLS and their involvement in ALS, FTD and in a variety of other neurodegenerative diseases. Dr Buratti discussed the wide influence of these proteins on the cell through their ability to act upon various cellular processes (such as DNA transcription, pre-mRNA splicing, mRNA export/import). The talk focused upon some of the novel functions that have recently been uncovered, such as a role in miRNA synthesis, regulation of transcript levels, potential autoregulatory mechanisms, and the basis that such findings provide for understanding the pathological role of TDP-43 and FUS/TLS in disease.

Dr Matthew Wood gave the final talk of the meeting by describing the potential of gene therapy in the treatment of neurodegenerative disease. Dr Wood began by discussing gene therapy in the context of Duchenne muscular dystrophy focussing upon the development of antisense oligonucleotide mediated exon skipping, and its ability to promote the formation of functional dystrophin in individuals with out of frame mutations. In the context of neurodegenerative disease, Dr Wood highlighted the difficulty of delivering gene therapy agents to the CNS. Recent work from Dr Wood's group was then discussed in which siRNA was delivered specifically to the brains of mice using exosomes expressing the membrane protein Lamp2b fused with the neuron specific RVG-peptide. ♦

PREVIEW: MS Trust Annual Conference 2011

Now in its 15th year, the MS Trust Annual Conference 2011 (13th-15th November) is the only multiple sclerosis event aimed specifically at specialist nurses, allied health professionals, and social care professionals. The world of MS is changing rapidly and "personal career development" remains a challenge.

Attending this key event provides opportunities to acquire the latest knowledge to enable health professionals to provide the best service for their patients in a cost effective manner. Evidence will be presented as to how "MS the disease" may be changing, along with developments in diagnosis as well as latest treatments and management strategies.

The conference is a popular event, a highlight on the MS professionals' educational calendar, and very well regarded as an opportunity to network with professional colleagues. Speakers from as far away as Canada will be

present and delegates from across the world are expected.

Plenary lectures include:

Professor D Miller, The National Hospital, London will discuss "The diagnostic process – what is changing?"

Professor H Tremlett, University of British Columbia on "The epidemiology of MS – and their implications".

Dr Eli Silber, Kings College Hospital London will present "Drug treatments for MS – how to decide."

The Hon. Sarah Joiner, London
"It's my future as well".

Many seminars are arranged including:

"Setting up a fingolimod service". "Pregnancy, childbirth and parenting in MS". "Service development – the specialist as a manager". "Palliative care – a team approach".

"Identifying and managing risk in MS".

There will be a whole morning looking at the critical topic of cognitive deficits in MS; designed specifically for therapists and recognising that, in over 50% of people with MS, cognitive issues can be a cause of job losses and failure to correctly follow HP guidance.

As well as a very comprehensive Exhibition Area the conference now offers an "MS Infozone" which has proved hugely popular with delegates. Here is a place to find practical support and information on a wide variety of topics including: MS services available outside the NHS and personal professional development information. ♦

For full programme and registration options, visit:
www.msstrust.org.uk/conference



Jane Haley

is the Scientific Coordinator for Edinburgh Neuroscience, University of Edinburgh. She has a research background in electrophysiology, a technique she has used to investigate

the mechanisms underlying chronic pain, long term potentiation, potassium channel modulation and neurodegeneration. Currently she fosters communication, collaboration and community spirit amongst the neuroscience researchers in Edinburgh.



Joanna Wardlaw

is Professor of Applied Neuroimaging at the University of Edinburgh and Director of the Brain Research Imaging Centre. Her main research interests are in the pathophysiological changes in the brain that occur during

stroke, the causes and treatment of cerebral microvascular disease and developing new methods for evaluating the accuracy of imaging tests. In 2011 she was elected a Fellow of the Royal Society of Edinburgh.



Burkhard Schafer

is Professor of Computational Legal Theory at the School of Law, University of Edinburgh. His main field of interest is the interaction between law, science and

computer technology; How can law, understood as a system, communicate with systems external to it, be it the law of other countries (comparative law and its methodology) or science (evidence, proof and trial process).



Peter Sanderecock

Is Professor of Medical Neurology, and Director of Edinburgh Neuroscience, University of Edinburgh. He is an academic clinical neurologist who

combines clinical practice in stroke medicine with research on the treatment and prevention of stroke. His chief research interests are in evaluating interventions for the treatment, prevention or rehabilitation of stroke.

Correspondence to:

Dr Jane Haley,
Edinburgh Neuroscience Scientific Co-ordinator,
University of Edinburgh,
1 George Square, Edinburgh EH8 9JZ, UK.
Tel: 0131 650 3522
Email: edinburgh.neuroscience@ed.ac.uk
www.edinburghneuroscience.ed.ac.uk

Neuroscience in Fashion

An Encounter at Inspace

14th April 2011, Edinburgh

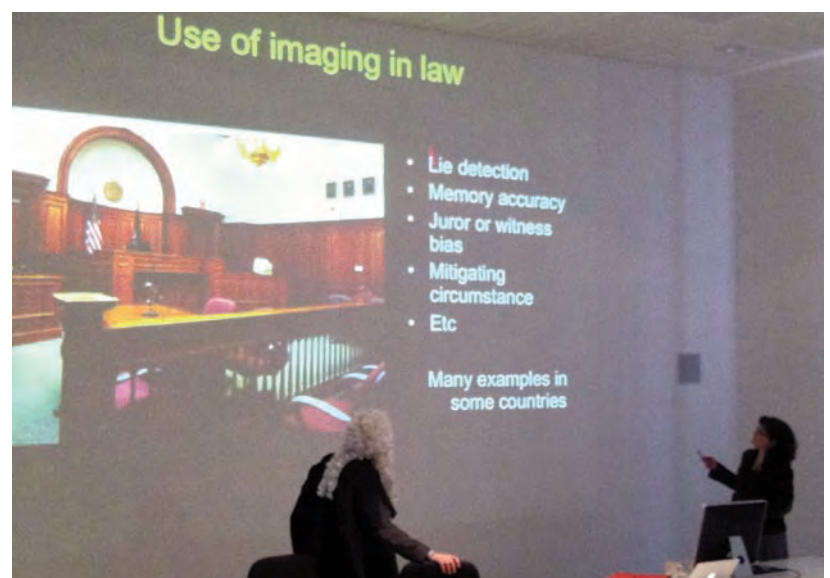
"You are an expert – you have to help me!"

This desperate cry came from a lawyer and was addressed to a neuroimaging expert. While defending a client, our lawyer was faced with a prosecution team who wanted to use functional brain imaging to prove that his client was lying. What should he do? He didn't know anything about brain imaging – "a series of pretty pictures, which always look convincing" was how he described his very limited experience of this technology. His colleagues didn't have any experience of it either, so couldn't advise him. What he needed was expert advice, but the prosecution were being advised by an expert who ran a company that sold imaging services so this use of the technology must be appropriate, mustn't it?

In fact although this 'encounter' was a staged one, and it took place during an event as part of the Edinburgh International Science Festival in April, it did mirror real life. The lawyer was Burkhard Schafer, Professor of Computational Legal Theory and the neuroimaging expert was Joanna Wardlaw, Professor of Applied Neuroimaging, both from the University of Edinburgh. The event was one of a series of interdisciplinary 'Encounters' put on for the public at the Inspace venue (which hosts a variety of events to promote public engagement with science). These two experts have been working together throughout 2010, stimulating debate about

the use of brain imaging technology outside the medical arena. Science, it seems, is also subject to the whims of fashion trends, just as any other sector of society, and brain imaging technology appears to be reaching a crossroads. Since the introduction of magnetic resonance imaging in 1980s this technology has been the domain of clinicians and researchers but now the technology is escaping beyond the areas for which it was intended and spreading its wings. With more than 50 MRI scanners currently in use in Scotland and over 100,000 scans taking place there annually, naturally we are excited that this technique is leaving home, but perhaps we should also be asking whether it has grown up enough first? So, is brain imaging "the new black"?

Encounters: Neuroscience in Fashion was an event for the public, which arose from a series of considered debates with experts that took place throughout 2010 at the Scottish Universities Insight Institute. This event highlighted some of the areas that should be considered when using this technology in new settings. Employing brain scans in a court of law to prove if someone is lying may seem far-fetched, but brain imaging has already been introduced as evidence in over 100 court cases worldwide so far. Whilst this has not happened in the UK yet (to our knowledge), attempts have repeatedly been



made to introduce the brain imaging lie detector test in the USA (including in death row cases)¹ and in India it has led to a woman being imprisoned for murder². Surely though, a reliable lie detector is the nirvana of the legal world, and if this technology provides a solid reliable test then we should be delighted that it has found a second home in the courts? Well, as with most things, it isn't as simple as that.

There is no doubt that the advent of MRI has had a huge, beneficial, effect on medical diagnosis but this has resulted from the use of structural MRI where gross changes in the structure and integrity of the brain can be observed. More recently the development of functional MRI³ has allowed us to superimpose information about local increases in brain blood flow (making the assumption that this relates directly to neural activity) on a structural scan. And this is where the amazing power of this technique and the potential problems really start. For researchers this unlocks a Pandora's box of possibilities as it allows us to observe the brain in action as a person thinks. But can 'mind reading' in a controlled research environment really be translated to other areas, such as the legal system? One of the most interesting (and very surprising) issues to come out of the expert debates was the realisation by the lawyers that functional brain scans are not 100% accurate

and, similarly, the researchers were shocked to realise that the lawyers thought that they might be! The power of a colourful image is seductive, but functional brain images are not simply photographs of the brain in action: instead they result from the complex post scan processing of groups of subjects and subsequent pseudo-colouring of the images. Crucially, it is the averaging of data from groups of subjects that allows researchers to form conclusions with any reliability and even then it requires an understanding of the underlying assumptions built into the system to reach a 70%+ accuracy level. The big difference with lie detection, in addition to the somewhat artificial setting in which it would be applied, is that you have, by necessity, only one subject. This inescapable problem is one reason why this technology is currently not appropriate for legal use – would you want your future to be resting on a test that was not 100% reliable?

If this use of imaging technology doesn't worry you (and many law-abiding citizens may not be bothered by what happens in the courts), then how about compulsory brain imaging by insurance companies to find out if you have a higher than average likelihood of developing a disorder such as schizophrenia or Alzheimer's before they will issue you with health or life insurance?⁴ Still not bothered? Then what about pre-employment screening

by companies looking to see if you have the correct qualities for the job you are applying for⁵ – it may not matter what you say in the interview, as your brain may tell a different story. Feeling a bit uneasy now? When we suggested that brain imaging was "the new black" you thought we meant fashionable, didn't you? ♦

REFERENCES

1. Hughes V. *Science in Court: Head Case*. Nature 2010;464:340-2.
2. Girdharadas A. *India's Novel Use of Brain Scans in Courts Is Debated*. New York Times (2008) 15th September, page A10.
3. Belliveau JW et al. *Functional mapping of the human visual cortex by magnetic resonance imaging*. Science 1991;254:716-19.
4. Sample 1. *Secrets of the mind must remain private property, says scientist*. Guardian (2003) 20th November, <http://www.guardian.co.uk/uk/2003/nov/20/health.businessresearch>
5. *Haier Gray matter correlates of cognitive ability tests used for vocational guidance*. BMC Res Notes (2010) 3:206.

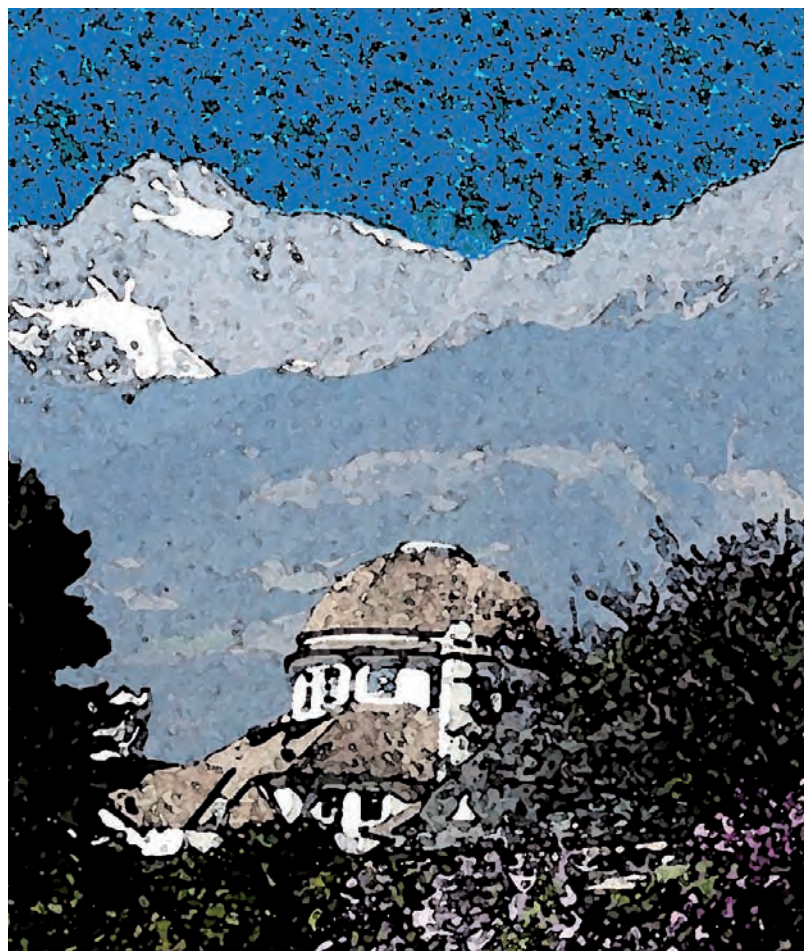
FURTHER READING

What are you thinking? Who has the right to know? Brain Imaging and Its Impact on Society. Report from the 2010 debates:

<http://www.scottishinsight.ac.uk/Programmes/Pastprogrammes/BrainImaging.aspx>

A Judges Guide to Neuroscience: A Concise Introduction Produced by the MacArthur Foundation supported Law and Neuroscience Project, USA.

<http://www.sagecenter.ucsb.edu/news/sage-center-and-law-and-neuroscience-project-publish-judges-guide-neuroscience>



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Jane Alty

is a neurology SpR in Leeds and BMA Liaison Representative for the Association of British Neurologists Trainees' Committee.



Biba Stanton

Biba Stanton is a neurology SpR in London and Chair of the Association of British Neurologists Trainees' Committee.

Correspondence to:

Jane Alty,
E floor, Martin Wing,
Leeds General Infirmary,
Leeds, LS1 3EX, UK.
Email: altyjane@doctors.org.uk

KEY DOCUMENTS IF YOU WANT TO KNOW MORE...

Department of Health (2010). Equity and excellence: Liberating the NHS
http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_117353

Department of Health (2011). Liberating the NHS: Developing the Healthcare Workforce
http://www.dh.gov.uk/en/Consultations/Liveconsultations/DH_122590

BMA response to Liberating the NHS: Developing the Healthcare Workforce consultation 31 March 2011
http://www.bma.org.uk/images/thefutureofmedicaleducationtrainingandworkforceplanning_tcm41-205198.pdf

Royal College of Physicians. Liberating the NHS: Developing the Healthcare Workforce Consultation Response. 29 March 2011
<http://www.rcplondon.ac.uk/policy/responding-nhs-reform/other-government-proposals>

BMA submission to the NHS Future Forum May 2011
http://www.bma.org.uk/healthcare_policy/nhs_white_paper/listeningresponse.jsp

How might my training be affected by the proposed NHS reforms?

By the time you read this the Government's response to its "listening exercise" on the NHS reforms will probably have been announced; but at the time of going to press it has yet to be seen whether the proposed reforms will be withdrawn or amended in view of the strength of opposition by groups such as the BMA, RCP, RCGP, RCN, Unite, Unison and patient groups. This article addresses how training, education and workforce planning might be affected if the current proposed reforms are implemented.

Timeline

The Government first published its plans to reform the NHS in the white paper 'Equity and Excellence: Liberating the NHS' in July 2010. Several months of consultation occurred before 'Liberating the NHS: Legislative Framework and Next Steps' was published in December 2010 – this explained how the consultation had shaped the Health and Social Care Bill and reaffirmed the Government's commitment to reforming the NHS. A few days later a consultation paper 'Liberating the NHS: Developing the Healthcare Workforce' was published; this included proposals for the removal of many bodies that commission, deliver and quality manage training and suggestions for replacing them with a single national body called Health Education England (HEE) and numerous employer-led local 'skills networks.' The Royal College of Physicians responded, "We are greatly concerned that the proposals set out in Developing the Healthcare Workforce do not fully recognise the complexity of medical education and training, nor the potential damage to the long term sustainability of the health service" and "it seems to us irresponsible that it is proposed to dismantle the well-tried organisation of postgraduate medical education and training, with little assurance that the proposed new system will function safely".

The proposed NHS reforms have since been set out in the Health and Social Care Bill that was introduced into Parliament in January 2011. In April 2011, Health Secretary Andrew Lansley announced that the Government had "paused" the Health and Social Care Bill to run a 'listening exercise' and set up a panel of clinicians, patients representatives and stakeholders – the NHS Future Forum – to report back to the Government by the end of May. The BMA has since published its official submission calling for the Health and Social Care Bill to either be withdrawn or undergo major changes. The NHS Future Forum is due to publish its recommendations in early June 2011 and the Government will respond a few weeks afterwards.

The English doctor

A key point to highlight is that the proposed reforms will only affect England and not Scotland, Wales or Northern Ireland. Hence, there are concerns about the potential for variation in the standard of training across the four nations of the UK, which could have consequences for patient care and lead to a less mobile medical workforce.

The demise of deaneries?

The reforms propose that Strategic Health Authorities (SHA) in England will be abolished by April 2012 and, as deaneries currently reside within SHA, there is the threat that they will be dissolved too. It has been proposed that the responsibility for education, training and workforce planning will pass to 'skills networks' that will be led by local healthcare providers, i.e. Trusts, and overseen by the new body Health Education England (HEE).

The BMA, RCP and RCGP are particularly concerned about the lack of detail and clarity in the proposals about how and where the SHA roles in education, and the various deanery functions, will be undertaken once SHAs are abolished. There are also few details about how the new 'skills networks' will operate and the RCP have stated that "We do not believe that the proposed local skills networks will have either the skills or the long-term vision to allow optimal workforce training, or that they will have the impartiality to ensure the delivery of education and training of a consistent high quality". It is also unclear who will take on other roles of the deanery such as supporting trainees in difficulty, organising annual assessments and coordinating out of programme experience. The deaneries have been instrumental in supporting less than full time training, which is an essential part of promoting equality of opportunity for women in medicine and yet the consultation document completely neglects to consider how less than full time training could be managed in the new system.

Education and training

Currently deaneries have an important quality management role, positioned regionally to overview and support local training programmes, with additional national oversight. The BMA is particularly concerned that devolution of medical education and training to local levels will result in individual training programmes no longer being equitable or transferrable across the UK and the RCP states "There is a real risk that the reform of the whole health service will divert from important developments and improvements in education and training". Furthermore, it is unclear how skills networks could coordinate the governance of

training schemes when these usually involve a number of different trusts.

The proposals also suggest that training of all health care professionals would be organised through HEE and local skills networks, with no specific arrangements in place for doctors. This model fails to recognise that doctors may be a "special case" due to the length and complexity of their training, and that doctors' experience of multi-professional approaches to training has not always been positive. Indeed, the RCP states, "Postgraduate medical training has been subject to three to four large organisational changes in the last ten years, with the advent and demise of educational consortia and workforce development confederations. It is vital that proposals for any further changes are developed from a clear evidence base" and "there is little evidential base for the changes proposed".

Research

There are no specific proposals about the development of medical research and moreover medical research is not mentioned at all in the workforce consultation paper. There is real concern that if services shift to the private sector, there may be a removal of research facilities as a means of reducing costs and increasing profits.

Private sector

The proposed increased use of the private sector is likely to have a major impact on

juniors' training. It is generally accepted that the private sector is unlikely to want to take on newly qualified doctors, and to effectively want a predominantly consultant based service. Similarly, concern has been raised that trusts, or at least departments within trusts, may follow suit, choosing not to operate as training units when competition between providers is introduced. If this were to occur the worry is that trainees may find there are far fewer job opportunities open to them, not to mention the longer term knock-on effect on workforce planning.

Recruitment and workforce planning

Medical workforce planning is a complex process with the length of training schemes resulting in a lag of several years between decisions being made and the results being seen. Deaneries play a crucial role in the recruitment of junior doctors to training programmes but the government's proposals suggest that Trusts should have greater responsibility for planning and developing the workforce. However, the BMA believes that "individual employers are unlikely to have the expertise, insight or incentives to undertake effective workforce planning and training for the service as a whole in the long-term" and specifically want the medical recruitment mechanisms which have been successfully developed over the last four years to be retained. If careful planning is not

coordinated there may be short term disruption to service delivery as training posts go unfilled and long term disruption to workforce supply due to irregular output of trained specialists.

Conclusions

Whether there is really any pressing need for radical re-organisation of training is highly questionable: UK postgraduate training remains highly regarded worldwide, and has already been through significant upheavals in recent years. The consultation document seems focussed on applying an ideology of localism rather than seeking to address specific aspects of the current system which may indeed benefit from improvements. As trainees, we have probably all had moments of frustration in our dealings with deaneries, but it is far from certain that 'local skills networks' would be more efficient or less bureaucratic. Indeed, many are worried that fragmentation of the organisation of training is likely to create new difficulties for trainees in navigating the system. Discussion of the Government's proposed health reforms has tended to be dominated by GP commissioning, with many trainees not even aware of these proposals. We would argue they should be a matter of grave concern to all of us. At the time of writing, it remains to be seen whether the Government really intends to listen to the profession. Watch this space. ♦

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Photo courtesy of Richard Bryant

EDITOR'S CHOICE

Slimy uptake of an anti-convulsant

We all use Valproate. We use it to treat epilepsy (partial and generalised), bipolar disorder and migraine, making valproate one of the most highly prescribed medications in the neurology clinic. Its use as a potential treatment for seizures was discovered almost 40 years ago, having been used as an organic solvent for the previous 80 years. Within 4 years, valproate had become an approved (and highly effective) treatment. Moreover, we know that for many idiopathic primary generalised epilepsies, valproate is the treatment of choice with dramatic effectiveness. Despite this widespread familiarity, how many readers would be able to explain how valproate enters cells and its precise mechanism of action?

To help us, we need to turn to a recent article by Terbach et al. in the *Journal of Cell Science*. Knowing that the method of valproate uptake into cells was unknown, Terbach et al. set out to identify the mechanism by first studying valproate uptake in the slime mould, *Dictyostelium*. By carefully using a number of basic biochemical techniques, Terbach et al. were able to establish that Valproate was actively taken up into cells against an electrochemical gradient, was protein-mediated and depended on a proton gradient. The researchers then used a mutant *Dictyostelium* screen to look for resistance to the growth-inhibitory actions of valproate. By using this approach, the membrane bicarbonate transporter, Slc4, was proposed as the membrane protein involved in active valproate uptake. Further experiments showed that by inhibiting this transporter with known specific pharmacological agents, valproate uptake was blocked. The mode of valproate uptake was

conserved in zebrafish (*Danio rerio*) and *Xenopus*, and biochemical manipulation was shown to prevent valproate-induced developmental defects. Furthermore, the SCL4 family of bicarbonate transporters are also found in mammalian cells and are homologous to *Dictyostelium* Slc4 and have been implicated in fatty acid transport across membranes.

Is this clinically relevant? The valproate concentration in rat brain required to exert an anticonvulsant effect is around 0.1% of the necessary serum concentration. This relatively high serum concentration is required due to the low permeability of the blood-brain barrier to the drug. In addition to its valuable therapeutic properties, we are all aware of valproate's adverse effects in patients, including teratogenicity, and that this is likely to be serum dose-related. By identifying the uptake mechanism, this may be the first step in regulating the concentration of valproate in specific tissues leading to greater efficacy and minimising adverse effects. Key questions remain, however, including those related to valproate's precise mechanism of action.

This work demonstrates again the importance of laboratory-based experiments using basic biological models to answer key questions. It is a good example of 'translational research', whichever way the term is defined.

– *Dr Rhys Roberts, Honorary Consultant Neurologist, Addenbrooke's Hospital, Cambridge.*

Terbach N, et al. Identifying An Uptake Mechanism For The Antiepileptic And Bipolar Disorder Treatment Valproic Acid Using The Simple Biomedical Model *Dictyostelium*. J CELL SCI. 2011, 124(Pt 13):2267-76.

Long-term outcome in Parkinson's patients with DBS

There are several studies describing the long-term outcome of idiopathic Parkinson's disease e.g. the Sydney Multicentre Study, CamPaIGN (a population-based epidemiological study in Cambridgeshire), and outcome of patients with deep brain stimulation (DBS). This study reports very long-term data (>30 years from disease onset) in IPD patients with subthalamic nucleus (STN) DBS. The aim of the study was to ascertain whether certain clinical factors (gender, phenotype i.e. tremor-dominant vs. akinetic rigid, and age at onset) influenced outcome (time to develop complications), but the study was small with only 19 patients (and no power calculations, with long-term data available from 14 patients). The study did not compare DBS patients with control IPD patients. The cohort was slightly different to others studied (e.g. the Sydney cohort) in that the patients were very young (mean age 38.63 years). The authors found a progressive worsening of motor symptoms in both medication and stimulation ON conditions, and cognition. The majority of patients developed non-motor (non-levodopa responsive) symptoms, the hallmark of advanced IPD, at long term follow up. The percentage of patients developing these symptoms was lower than other similar studies perhaps because of the younger age at onset in this cohort and possible inclusion of genetic cases. It is known that younger patients have slower disease progression but tend to reach the

same advanced-IPD milestones at the same age as older onset patients, with most patients in their 70s having such complications. Thus if this cohort had been followed up for even longer, the rates of complications may have been higher. Perhaps surprisingly, younger tremor-dominant patients while less likely to develop freezing of gait did not differ in the development of falls, postural instability, dysphagia, autonomic symptoms and dementia (although this may be a reflection of the small number of patients studied). Thus, this study adds to the literature on IPD outcome, with the main contribution being length of follow-up, but it does have some limitations.

– *Dr Wendy Phillips, Consultant Neurologist, Addenbrooke's Hospital and Princess Alexandra Hospital, Harlow.*

Merola A, et al. Parkinson's disease progression at 30 years: a study of subthalamic deep brain-stimulated patients. BRAIN 2011. Epub.

The Wisdom of Age?

"The frail elderly are our market" was the rather arresting statement that I retained from another fruitless meeting with our local health commissioners. The needs of younger adults with complex disability tend to be addressed very much according to where one happens to live rather than one's needs. Many specialist rehabilitation services apply upper age limits in a sometimes seemingly arbitrary fashion that effectively implies that older individuals with complex needs may not gain as much benefit from labour-

intensive multi-disciplinary rehabilitation as their younger counterparts. Is there any evidence for this assumption? As individuals with chronic neurological disease live longer, what will this mean for those of us charged with meeting their health needs? One would assume, rather bleakly, that increasing age coupled with physical or psychological disability could only mean an even greater demand for already scarce resources in the future. This Canadian study, however, would suggest not. The health service utilisation levels of a large retrospective cohort (part of the National Population Health Survey) in terms of GP attendances, specialist review, hospital admissions and home care services were assessed to evaluate the relative and combined effects of increasing age and disability. There were two competing hypotheses up for grabs; "double jeopardy" (age and disability will have a synergistic effect producing greater utilisation of health resources) and "age-as-leveller" (the social disadvantages of disability will be less important with increasing age leading to utilisation of health resources that would be less than the sum of the effects of age and disability). A number of other factors were used to create a multivariate model including demographic variables, individual impairments and activity levels.

Unfortunately, as the study was retrospective, the measures of "disability" were fairly crude self-reported items. The objective value of defining this cohort is, therefore, somewhat limited. Nevertheless, disability was found to be a much stronger predictor of health service utilisation than age. The surprising finding that age and disability seem to cancel one another out as predictors of health care utilisation with increasing age suggests that the "age-as-leveller" hypothesis is more viable than the "double jeopardy" hypothesis. Of course, there are any number of potential explanations behind this, but the suggestion that the health needs of younger adults with complex disabilities may actually diminish with increasing age is intriguing and worthy of further exploration.

– *Dr Lloyd Bradley, Consultant in Rehabilitation Medicine, Western Sussex Hospitals.*

McColl MA, Shortt S, Gignac M, Lam M. Disentangling the Effects of Disability and Age on Health Service Utilisation. DISABILITY AND REHABILITATION, 2011;33(13-14):1253-61.

Italy) and Sanders (Duke, NC, USA) publish the largest cohort study to date, on this group of myasthenia. Data from two independent, large and well-characterised groups of patients studied in two well-respected myasthenia centres looked at 110 patients (70 from Rome, 40 from Duke) followed up for an average of 11 years (Rome) and 5.3 years (Duke) (range, 0.5 to 33 years). Data from all MG patients (n=919) seen at Duke University and from a pooled group of 1582 AChR-antibody positive patients were used as comparative cohorts. Duke University had almost an equal proportion of African-Americans and Caucasians, whereas all patients from Rome were Caucasians.

The incidence of MuSK antibodies in AChR-antibody negative patients ranged from 39-49%, confirming earlier reports. 85% of MuSK patients were females and the mean symptom onset was in the fourth decade (range 6-68 years), at least a decade later than in the AChR-positive patients. Pure ocular presentation at onset was comparatively less common in the MuSK patients (36%) compared to all myasthenics (60%). Moreover, the vast majority of MuSK patients with initial ocular symptoms developed generalised disease between 2-3 weeks of onset. However, there was significantly more number of patients with MuSK myasthenia who had bulbar/neck symptoms or respiratory failure at initial presentation (50% vs 21%).

Repetitive nerve stimulation was abnormal in only approximately 60% of patients as compared to the 97% of patients who had increased jitter in at least one muscle on SFEMG. SFEMG was more likely to be abnormal in the facial muscles (>90%) compared to peripheral limb muscles (<50%). Only 57% patients improved on treatment with cholinesterase inhibitors which were more prone to produce side-effects (fasciculations, cramps, worsening of myasthenia etc). Plasma exchange was more likely to achieve clinical improvement compared to IVIg (93% vs 61%). Even though most MuSK patients had an acute onset, rapid progression and brittle course early in the disease, the long-term outcome was comparable to the AChR-antibody positive group with remission or improvement occurring in nearly 90% of patients in both groups with appropriate therapy.

In summary, this large study confirms the initial reports that MuSK myasthenia occurs predominantly in females, have frequent early crises and responds poorly to pyridostigmine. Facial muscle SFEMG performed by experienced neurophysiologists remains the most sensitive diagnostic test. Reassuringly, long-term prognosis is comparable, although multiple immunosuppressants may be required.

– *Dr Saiju Jacob, Consultant Neurologist, Queen Elizabeth Neurosciences Centre, Edgbaston, Birmingham.*

Guptill JT, Sanders DB, Evoli A. Anti-musk antibody myasthenia gravis: Clinical findings and response to treatment in two large cohorts. MUSCLE NERVE 2011 Jul;44(1):36-40.

MuSK myasthenia - clinical characteristics and response to treatment

MuSK-antibodies are comparatively rare, which are present in about 5-8% of all myasthenia patients (i.e. in approximately 50% of patients negative for the standard AChR-antibodies). It has been known that this is a predominantly oculo-bulbar condition with relative resistance to treatment using cholinesterase inhibitors or immunosuppression. In the current issue of Muscle and Nerve, Drs Evoli (Rome,

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epilepsy. This year's award for clinical science will be presented on December 10th at the 10th International League Against Epilepsy (ILAE) World Congress on Epilepsy, which will be held in London, UK. The award is associated with the discipline of clinical science and is presented to the author(s) of the paper judged to be the most original and significant contribution to the field of epilepsy. This year's award for clinical science will be presented on December 10th at the 10th International League Against Epilepsy (ILAE) World Congress on Epilepsy, which will be held in London, UK. The award is associated with the discipline of clinical science and is presented to the author(s) of the paper judged to be the most original and significant contribution to the field of epilepsy.

These are no one more deserving of this honour. Tadie has worked hard for children with the symptoms of sudden loss of consciousness. I am very impressed by the energy and passion she has shown in the field of heart rhythm disturbances. Her work has improved the quality of life for many children with this condition.

Guy's Hospital installs Siemens' Aera MRI



Guy's and St Thomas' NHS Foundation Trust, UK, has installed a MAGNETOM® Aera 1.5 Tesla MRI system from Siemens Healthcare at Guy's Hospital. The multi-purpose system is being used for a wide range of examinations such as head imaging, orthopedics and neuroimaging.

The Aera's wide 70cm Open Bore is able to accommodate a variety of patient sizes, allowing many examinations to be completed with the patient's head outside the bore. This improves the clinical environment for claustrophobic or larger patients, helps to reduce sedation rates and minimise stress levels. The system is also equipped with a Tim® Dockable table option. This helps with preparing the patient for scanning outside the room and smoothly wheels and docks onto the MRI scanner when ready.

"The Aera's detachable table is beneficial as it is easier for transferring bed patients, such as those with cord compression and for use in

emergency situations," said Kim Robertson, Head of Radiology Service at Guy's Hospital. "Radiographers are benefiting from the system's ease-of-use and appreciate the integrated coil technology which is making for faster scans without compromising on image quality."

"The Aera is helping to make examinations easier, more comfortable and more efficient," said Malcolm Pickering, Regional Sales Manager at Siemens Healthcare. "The system's advanced technology is designed to streamline workflow and is ideally suited to assist with the high patient throughput at Guy's Hospital."

For more information contact Laura Smith at Siemens Healthcare, T. 01276 696374, E. laura.smith@siemens.com, www.siemens.co.uk/healthcare

European Commission approves inclusion of Anti-JC Virus Antibody Status as a PML risk factor in Tysabri labelling

The European Commission has approved the inclusion of anti-JC virus (JCV) antibody status as an additional factor to aid in stratifying patients at risk for developing progressive multifocal leukoencephalopathy (PML) in the Summary of Product Characteristics (SmPC) for Tysabri® (natalizumab) in the European Union. In addition, as part of a standard review process, the EC concluded the quality, safety and efficacy of Tysabri continue to be adequately demonstrated and renewed the EU five-year Marketing Authorisation.

The new SmPC language states that patients who are anti-JCV antibody positive are at an increased risk of developing PML compared to patients who are anti-JCV antibody negative. Recent studies suggest that irrespective of MS treatment, approximately 55% of MS patients are anti-JCV antibody positive. The SmPC language also states that patients who are anti-JCV antibody positive, have received prior immunosuppressant (IS) therapy, and received treatment with TYSABRI for more than two years have the highest risk of developing PML. The addition of anti-JCV antibody status to previously-established risk factors further stratifies the potential risk of developing PML.

"This label change can help give confidence to physicians and patients by providing additional guidance on stratifying the potential risk for developing PML in Tysabri-treated patients," said Tomas Olsson, Professor of Neurology in the Department of Clinical Neurosciences at the Karolinska Institute in Stockholm, Sweden. "Understanding all factors, including anti-JCV antibody status, is essential, and the Swedish MS Society has established guidelines recommending how this can be put into practice."

Merck Serono and Affectis Pharmaceuticals agreement to develop oral drugs for neurodegenerative diseases

Merck Serono has announced that an exclusive licensing agreement was signed with Affectis Pharmaceuticals AG, Munich, Germany, for the development and commercialisation of oral compounds targeting P2X7 receptors. These receptors are believed to be involved in neuroinflammation observed in some neurodegenerative diseases.

Under the terms of the agreement, Merck Serono will have worldwide exclusive rights to develop and commercialise selected compounds. The contract also includes a research collaboration focusing on P2X7 antagonist optimisation.

"We are pleased to announce this collaboration with Affectis Pharmaceuticals, a company with

robust experience in drug discovery in the central nervous system area," said Dr. Bernhard Kirschbaum, Executive Vice President for Global Research and Development at Merck Serono. "This partnership reflects our long-term commitment to developing innovative treatments for neurodegenerative diseases, where unmet medical need still remains."

Trobalt®▼ (retigabine) for adjunctive treatment of partial onset epilepsy

The National Institute for Health and Clinical Excellence (NICE) has issued a Final Appraisal Determination (FAD), recommending retigabine as an option for the adjunctive (add-on) treatment of partial onset seizures with or without secondary generalisation in adults aged 18 years and older with epilepsy, when previous treatment with other anti-epilepsy drugs (AEDs) has not provided an adequate response, or has not been tolerated. These epilepsy treatments are commonly prescribed as initial

monotherapy or used in combination.

Of those people diagnosed with epilepsy in the UK, around 30 percent do not respond to initial epilepsy treatments and remain uncontrolled. This group is considered refractory and equates to approximately 60,000 people in the UK.

Refractory epilepsy has a negative impact on the quality of the lives of patients with the disorder, is associated with an increased risk of sudden death and significant costs to society and to the healthcare

system. Retigabine is the first in a new class of epilepsy treatments and is currently the only AED to target neuronal potassium channels which are involved in inhibitory mechanisms in the brain, and are thought to have a role in seizure control. The efficacy and safety of retigabine was established in two pivotal multicentre, randomised, double-blind, placebo-controlled, fixed dose studies. The NICE recommendation of retigabine will offer patients and clinicians an additional option for difficult to control epilepsy.



Confidence to take action everyday

COPAXONE® (glatiramer acetate)

PRE-FILLED SYRINGE PRESCRIBING INFORMATION

Presentation – Glatiramer acetate 20mg solution for injection in 1ml Pre-filled Syringe. **Indication** – Treatment of patients who have experienced a well-defined first clinical episode and are determined to be at high risk of developing clinically definite multiple sclerosis (MS). Reduction of frequency of relapses in relapsing-remitting MS in ambulatory patients. In clinical trials this was characterised by at least two attacks of neurological dysfunction over the preceding two-year period. **Dosage and administration** – 20mg of glatiramer acetate (one pre-filled syringe) administered sub-cutaneously once daily. **Children (12 – 18 years)** No specific studies. Limited published data suggest the safety profile of 20mg administered sub-cutaneously once daily is similar to that seen in adults. **Children (<12 years)** Not recommended. **Elderly** No specific data. **Impaired renal function** No specific studies. Monitor renal function during treatment and consider possibility of deposition of immune complexes. **Contra-indications** – Known allergy to glatiramer acetate or mannitol (excipient). **Pregnancy. Special warnings and precautions** – Sub-cutaneous use only. Initiation to be supervised by neurologist or experienced physician. Supervise first self-injection and for 30 minutes after. One or more of vasodilatation, chest pain, dyspnoea, palpitations or tachycardia may occur within minutes after injection. These generally resolve spontaneously after a short time. If severe, treat symptomatically. Caution in patients with pre-existing cardiac disorders and review such patients regularly. Rarely convulsions and/or anaphylactic or

allergic reactions. Rarely, hypersensitivity (bronchospasm, anaphylaxis or urticaria). If severe, treat appropriately and discontinue Copaxone. **Interactions** – No formal evaluation. Increased incidence of injection-site reactions with concurrent corticosteroids. Theoretical potential to affect distribution of protein-bound drugs, therefore concomitant use of these should be monitored. **Pregnancy and lactation** – Not to be used in pregnancy. Consider contraceptive cover. No data on excretion in human milk. **Undesirable effects** – Local injection site reactions (erythema, pain, mass, pruritus, oedema, inflammation, hypersensitivity, injection site atrophy). An immediate post-injection reaction (one or more of vasodilation, chest pain, dyspnoea, palpitation, tachycardia) may occur within minutes, reported at least once by 31% of patients receiving Copaxone compared to 13% of patients receiving placebo. Other undesirable effects more than 2% (>2/100) higher incidence in the Copaxone treatment group than in the placebo group: Nausea, anxiety, rash, back pain, chills, face oedema, vomiting, skin disorder, lymphadenopathy, tremor, eye disorder, vaginal candidiasis, weight increased. Rarely: Anaphylactoid reactions. Please refer to the SPC for a full list of adverse effects. **Overdose** – Monitor, treat symptomatically. **Pharmaceutical Precautions** – Store Copaxone in refrigerator (2°C to 8°C). If the pre-filled syringes cannot be stored in a refrigerator, they can be stored at room temperature (15°C to 25°C) once for up to one month. Do not freeze. **Legal Category** – POM. **Package Quantity and Basic NHS Cost** – 28 pre-filled syringes of Copaxone: £513.95. **Product Licence Number** – 10921/0023.

Further Information – Further medical information available on request from Teva Pharmaceuticals Limited, The Gate House, Gatehouse Way, Aylesbury, Bucks, HP19 8DB. Date of Preparation – December 2009.

Adverse events should be reported.
Reporting forms and information can be found at www.yellowcard.gov.uk.
Adverse events should also be reported to
Teva Pharmaceuticals Ltd on
telephone number: 01296 719768.

Date of Preparation: February 2011

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COPAXONE®
(glatiramer acetate)

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