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ADVANCES IN CLINICAL NEUROSCIENCE & REHABILITATION

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WCN 2011 – Neurologists from all over the world to meet in magical Marrakesh – P31

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Make a lasting impression...

The 24-hour clinical effect of once-daily Azilect gives patients improved motor control first thing in the morning, even before their first dose of levodopa – an effect that was not seen with multi-dose entacapone.[1,2]

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Azilect ® 1mg tablets
Prescribing information (Please refer to the Summary of Product Characteristics (SmPC) before prescribing) **Presentation:** Tablets containing 1mg rasagiline (as the mesilate). **Indication:** Treatment of idiopathic Parkinson's disease as monotherapy or as adjunct to levodopa in patients with end of dose fluctuations. **Dosage and administration:** Oral, 1mg once daily taken with or without food and with or without levodopa. Elderly: No change in dosage required. Children and adolescents (<18 years): Not recommended. Patients with renal impairment: No change in dosage required. Patients with hepatic impairment: Predominant hepatic metabolism. Do not use in patients with severe impairment. Avoid use in patients with moderate impairment. Use with caution in patients with mild impairment and stop if progresses to moderate. Overdose: Symptoms reported following rasagiline overdose (3-100mg) included dysphoria, hypomania, hypertensive crisis and serotonin syndrome. **Contraindications:** Hypersensitivity to the active substance or to any of the excipients. Do not use in patients with severe hepatic impairment. Co-administration of other monoamine oxidase (MAO) inhibitors is contraindicated due to risk of hypertensive crises. Concomitant pethidine treatment is contraindicated. Allow at least 14 days off rasagiline before using other MAO inhibitors or pethidine. **Special warnings and precautions:** Administer antidepressants with caution as serious adverse reactions have been reported with concomitant use of selective serotonin reuptake inhibitors (SSRIs), serotonin noradrenaline reuptake inhibitors (SNRIs), tricyclic and tetracyclic antidepressants, and MAO inhibitors. Cases of serotonin syndrome have been reported post-marketing in patients treated concomitantly with antidepressants/SNRIs and rasagiline. Avoid concomitant use with fluoxetine or fluvoxamine. Leave at least five weeks between discontinuation of fluoxetine and initiation of treatment with rasagiline. Leave at least 14 days between discontinuation of rasagiline and initiation of treatment with fluoxetine or fluvoxamine. Administer potent CYP1A2 inhibitors with caution. Co-administration with dextromethorphan or sympathomimetics not recommended. Avoid use in patients with moderate hepatic impairment. Use caution in patients with mild hepatic impairment. Use with caution in pregnancy or lactation. There is an increased risk of skin cancer in Parkinson's disease, not associated with any particular drug. Suspicious skin lesions require specialist evaluation. Cases of elevated blood pressure have been reported in the post-marketing period, including rare cases of hypertensive crisis associated with the ingestion of unknown amounts of tyramine. **Undesirable effects in clinical trials:** Monotherapy: >1%: headache, influenza, skin carcinoma, leucopenia, allergy, depression, hallucinations, conjunctivitis, vertigo, angina pectoris, rhinitis, flatulence, dermatitis, musculoskeletal pain, neck pain, arthritis, urinary urgency, fever, malaise. <1%: decreased appetite, cerebrovascular accident, myocardial infarction, vesiculobullous rash. Adjunct therapy: >1%: dyskinesia, decreased appetite, hallucinations, abnormal dreams, dystonia, carpal tunnel syndrome, balance disorder, orthostatic hypotension, abdominal pain, constipation, nausea and vomiting, dry mouth, rash, arthralgia, neck pain, decreased weight, fall. <1%: skin melanoma, confusion, cerebrovascular accident, angina pectoris. Please refer to the SmPC for the rates of adverse events. **Basic NHS Price:** Azilect® (tablets) 1mg x 28 £70.72 **Legal category:** POM **Marketing Authorisation Number:** 1mg tablets (28 pack size) EU/1/04/304/003 **Marketing Authorisation Holder:** Teva Pharma GmbH, Kandelstr 10, D-79199 Kirchzarten Germany **Date last revised:** September 2010. **Further information available from:** Lundbeck Limited, Lundbeck House, Caldecotte Lake Business Park, Caldecotte, Milton Keynes, MK7 8LG

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.

References:
1. Azilect Summary of Product Characteristics. October 2010.
2. Stocchi F, Brooks DJ, Melamed E et al. Effects of rasagiline on severity of OFF in Parkinson's disease. Poster presented at the 58th American Academy of Neurology Annual Meeting, San Diego, California, USA. 2006.

Job No. UK/AZI/1107/0152 AZT/0711/0024
Date of preparation: July 2011

TEVA Teva Pharmaceuticals Ltd

Lundbeck

Alzheimer's Society supporter Sir Terry Pratchett recognised as a Champion of Alzheimer's disease

Award-winning author and Alzheimer's Society supporter, Sir Terry Pratchett, has been named Health Champion of the Year by the UK's leading health experts and journalists. The award, presented at the Medical Journalists' Association (MJA) Summer Awards, acknowledges Sir Terry's tireless campaigning and awareness-raising of dementia-related issues.
Sir Terry, who has a rare form of dementia called Posterior Cortical Atrophy (PCA), said of his award: "I am, of course, very pleased to have won this award but must point out that all I had to do, some years ago, was find out that I had this wretched disease. It took no courage to freely talk about it in public, indeed, it would have taken more courage to do nothing." In addition to Sir Terry's award, Alzheimer's Society's national media team beat off strong competition to be presented with the 'Health Charity of the Year' award.

Alzheimer's Society's Chief Executive, Jeremy Hughes, said: "These two awards are a testament to the hard work of everyone involved. They demonstrate just how far we have come in terms of public awareness of dementia. There are 750,000 people with dementia in the UK, and it is a condition that is likely to affect all of us in some way. We now need to ensure the spotlight is kept on dementia-related issues.'

For more information contact: press@alzheimers.org.uk

Awards for Innovation and Inspiration in Acquired Brain Injury 2011

The United Kingdom Acquired Brain Injury Forum Awards for Innovation and Inspiration 2011 in the field of acquired brain injury are now open and this year there are new categories to extend the range of work which needs to be recognised in the sector. This years categories are:
Innovation by a lawyer/law firm in the field of ABI
Innovation by a clinician in the field of ABI
Innovation by a care provider in the field of ABI
Innovation by a social care worker in the field of ABI
Innovation by a educational person or provider in the field of ABI
Innovation by a voluntary sector provider or registered charity in the field of ABI
The Stephen McAleese Award for Inspiration by an individual in the field of ABI

The awards were launched last year and the judging panel were overwhelmed by the quality and quantity of entries. 'It goes to show that although you may think that you know what is happening in the sector, there is a tremendous amount which is not shared – and we hope that these awards remedy that.' said Professor Mike Barnes, UKABIF Chair.

Nominations may be made by those involved in or benefiting from a project or piece of work. There is an application form which must be completed with each nomination and the deadline for submission is 30th September 2011. The awards will be presented at the UKABIF Annual Conference which takes place on 10th November 2011 at The National Motorcycle Museum in Birmingham and shortlisted entrants will be offered a free place at this event.

Full details and application forms are available on the UKABIF website. – see http://www.ukabif.org.uk/news/3-newsflash/167-ukabif-awards-for-innovation-and-inspiration-2011-

Prof Ray Dolan nominated for 2012 Santiago Grisolia Chair Award

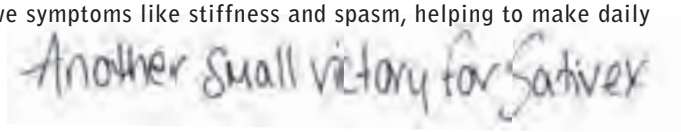
Professor Ray Dolan, Director of the Wellcome Trust Centre for Neuroimaging has been nominated by the Cátedra Santiago Grisolía for the 2012 Prize Santiago Grisolía Chair. The Santiago Grisolía Chair is awarded to outstanding researchers and scientists in the field of Biomedicine and Neuroscience. Professor Ray Dolan will give three lectures on a topic related to the neurobiology of cognition, emotion and behaviour and be awarded a silver medal in the presence of the Highest Authorities of the Valencian Community in Spain next year. Professor Dolan said upon receiving the prize: "I am delighted to receive this prestigious award, and all the more so in light of the illustrious prior recipients."

Bayer

Image by: Peter Fraser

Now if I don't tidy up,
it's because I've got better
things to do.

MS can make simple, everyday tasks difficult or impossible. Adding Sativex to existing spasticity treatment can improve symptoms like stiffness and spasm, helping to make daily life easier for people with MS.



Instead of leaving the Sativex prescribing information at the foot of the page, we've put it where you can't miss it. Please take a look. After all, these are the crucial details that will help you decide if Sativex can help your MS patients.

Sativex® Oromucosal Spray Prescribing Information (refer to full Summary of Product Characteristics (SmPC) before prescribing). Presentation: 1mL contains: 38-44mg and 35-42mg of two extracts from *Cannabis sativa* L., (Cannabis leaf and flower) corresponding to 27mg delta-9-tetrahydrocannabinol (THC) and 25mg cannabidiol (CBD). Each 100 microlitre spray contains: 2.7mg THC and 2.5mg CBD. **Indication(s):** as add-on treatment, for symptom improvement in patients with moderate to severe spasticity due to multiple sclerosis (MS) who have not responded adequately to other anti-spasticity medication and who demonstrate clinically significant improvement in spasticity related symptoms during an initial trial of therapy. **Posology and method of administration:** oromucosal use only. Treatment must be initiated and supervised by a physician with specialist expertise in MS. Direct spray at different sites on the oromucosal surface, changing site for each use of product. May take up to 2 weeks to find optimal dose, review response after 4 weeks of treatment. Re-evaluate long term treatment periodically.

Adults*:** titration period necessary; number/timing of sprays will vary between patients. Number of sprays increased daily according to SmPC table, up to maximum of 12 sprays per day with minimum 15 minutes between sprays. ***Children and adolescents*:** not recommended. ***Elderly: no specific studies but CNS side effects may be more likely (see Warnings and precautions) ***Significant hepatic or renal impairment:*** no specific studies but effects of Sativex may be exaggerated or prolonged. Frequent clinical evaluation recommended. **Contra-indications:** hypersensitivity to cannabinoids or excipients. Breast feeding. Known/suspected history or family history of schizophrenia/other psychotic illness. History of severe personality disorder/other significant psychiatric disorder other than depression due to underlying condition. **Warnings and precautions:** not recommended in patients with serious cardiovascular disease. Caution in patients with history of epilepsy/recurrent seizures. THC and CBD are metabolised in the liver. Several THC metabolites may be psychoactive. Contains approx. 50% v/v ethanol. Risk of falls if spasticity/muscle strength no longer sufficient to maintain posture/gait. CNS side effects e.g. dizziness, somnolence could impact personal safety, e.g. hot food and drink preparation. Theoretical risk of additive effect with muscle-relaxing agents, not seen in clinical trials but warn patients risk of falls may increase. No effect seen on fertility but cannabinoids shown to affect spermatogenesis in animals. Female patients of child-bearing potential/male patients with a partner of child-bearing potential should use reliable contraception. Patients with a history of substance abuse may be more prone to abuse Sativex. Withdrawal symptoms following abrupt withdrawal of long-term Sativex are likely to be limited to transient disturbances of sleep, emotion or appetite. No increase in daily dosage observed in long-term use; self-reported levels of 'intoxication' low; dependence on Sativex unlikely. **Interactions:** no clinically apparent drug-drug interactions seen. Co-administration with food results in mean increase in C_{max}, AUC and half-life (increase less than between-subject variability in these parameters). Concomitant ketoconazole increases C_{max} and AUC of THC (and primary metabolite) and CBD. Increase less than between-subject variability. Risk of additive sedation and muscle relaxing effects with hypnotics, sedatives and drugs with sedating effects. **Pregnancy and lactation:** do not use in pregnancy unless benefit outweighs potential risks. Do not use if breast feeding. Insufficient experience of effects on reproduction - use reliable contraception during therapy and for 3 months after discontinuation. **Effects on ability to drive and use machines:** do not drive, operate machinery or engage in any hazardous activity if experiencing significant CNS side effects; warn patients may cause loss of consciousness. **Side effects:** very common – dizziness, fatigue; common – anorexia, decreased or increased appetite, depression, disorientation, dissociation, euphoria, amnesia, balance disorder, disturbance in attention, dysarthria, dysgeusia, lethargy, memory impairment, somnolence, blurred vision, vertigo, constipation, diarrhoea, dry mouth, glossodynia, mouth ulceration, nausea, oral discomfort/pain, vomiting, application site pain, asthenia, feeling abnormal/drunk, malaise, fall; uncommon – hallucination, illusion, paranoia, suicidal ideation, delusional perception, syncope, palpitations, tachycardia, hypertension, pharyngitis, throat irritation, upper abdominal pain, oral mucosal disorders e.g. discolouration, exfoliation, stomatitis, tooth discolouration, application site irritation; unknown frequency – psychiatric symptoms e.g. anxiety and mood changes, transient psychotic reactions, possible leukoplakia (unconfirmed): inspect oral mucosa regularly in long term use.

Prescribers should consult the SmPC for further information on side effects. **Overdose:** symptomatic and supportive treatment required. **Special precautions for storage:** refrigerate (2 to 8°C); once opened refrigeration is unnecessary but do not store above 25°C. **Legal Category:** POM **Package quantities and basic NHS costs:** 3 x 10mL £375.00. **MA holder:** GW Pharma Ltd, Porton Down Science Park, Salisbury, Wiltshire SP4 0JQ **MA number(s):** PL 18024/0009 **Further information available from:** Bayer Schering Pharma, Bayer plc, Bayer House, Strawberry Hill, Newbury, Berkshire RG14 1JA United Kingdom. Telephone: 01635 563000. **Date of preparation:** March 2010.

Adverse events should be reported. Reporting forms and information can be found at www.yellowcard.gov.uk. Adverse events should also be reported to GW Pharma Ltd. Tel: 01353 616636, Fax: 01353 616638

SATIVEX®

delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD)

UK.PH.SM.SAT.2011.05. February 2011.

Roger Barker, Co-Editor.

In a very stimulating article, Boris Kotchoubey and colleagues discuss disorders of consciousness and how concepts about this have changed with the advent of better diagnostic procedures using functional imaging and evoked potentials. They argue that the presence or absence of higher cognitive functions should not be seen as the only definition for human consciousness, because lower order systems exist which can remain intact even in the absence of these higher order functions. Furthermore these lower order systems will still allow a level of communication to be established and used and as such we may be missing ways to better treat patients in minimally conscious states.

The power of Genome Wide Association Studies (GWAS) to better define the players involved in complex genetic disorders is now being realised and in their article Hanne Harbo and Maria Ban discuss this with respect to MS. They show how international collaborations have managed to find the major genetic risk factors for MS with the latest instalment in this story being published in the August issue of Nature this year. This impressive work has highlighted those critical aspects of the immune system that have a role in MS, although as the authors comment, the next challenge for the consortia is to find the missing hereditability that is still out there.

You know that feeling of not being able to quite remember something followed by moments of anxiety that this is the harbinger of a dementing process? In his contribution to the 'Clinical Dilemmas in Neuropsychiatry', Alex Mitchell discusses this topic of subjective memory complaints and its relationship to mild cognitive impairment and dementia. This is a very helpful distillation of a somewhat under-researched area but generally gives me comfort.

You know that feeling of not being able...sorry.

One of the common misconceptions in the world of medicine is that raised blood pressure causes headaches, or at least that is what many of my patients tell me. In the article from the Norwegian team of Lars Jacob Stovner, Knut Hagen and Erling Tronvik we learn a lot about how higher blood pressures seem to be associated with less pain and what may underlie this relationship.

Neurobehavioural disability (NBD) following head injury is common and often hard to manage. Nick Alderman describes his experiences of managing such patients based on his huge expertise through his work at the National Brain Injury Centre. In his article he not only describes the nature of NBD and its destructive force at the individual, family and society level but also how it can best be assessed and managed.

In the Motor Control Series, Leonardo Fogassi and Francesca Roda discuss mirror neurons - neurons that were originally described because of their capacity to not only discharge when an animal performs a motor act but also when they observe that same act being performed by another animal. The discovery of these cells has generated much debate and in this article we have an excellent overview of how this field has developed by a team that has contributed much to this fascinating area of neurobiology.

Heather Angus-Leppan in the ABN section takes us through what may happen if primary care had direct access to MRI for the investigation of headache as well as discussing the problems of taking on acute neurology with the current number of UK neurologists. This short article not only highlights the problems but also suggests some solutions.

We have our usual collection of journal, book and conference reviews - the latter containing a particularly interesting account by Dr Rosemary Fricker of a recent meeting discussing the different animal models of Parkinson's Disease. ◆

Roger Barker, Co-Editor,
Email. Rachael@acnr.co.uk

It's hard to live life to the full if part of you is always expecting the next seizure. VIMPAT® is an anti-epileptic drug with an innovative mode of action.[1,2] In clinical trials, VIMPAT® has shown improved seizure control when added to first and second generation AEDs.[3] Prescribe VIMPAT® when you want your patients to look forward with the confidence of additional seizure control.[1,3]

VIMPAT®
lacosamide

Confidence, when monotherapy is not enough

PRESCRIBING INFORMATION (Please consult the Summary of Product Characteristics (SPC) before prescribing). **Vimpat® Lacosamide Active Ingredient:** *Tablets:* lacosamide 50 mg, 100 mg, 150 mg and 200 mg. *Syrup:* lacosamide 15 mg/ml. *Solution for infusion:* lacosamide 10 mg/ml. **Indication:** Vimpat is indicated as adjunctive therapy in the treatment of partial-onset seizures with or without secondary generalisation in patients with epilepsy aged 16 years and older. **Dosage and Administration:** *Adults and adolescents from 16 years:* Recommended starting dose is 50 mg twice a day which should be increased to an initial therapeutic dose of 100 mg twice a day after 1 week. Maximum daily dose of 400 mg (in two 200 mg doses). For *solution for infusion:* Infused over a period of 15 to 60 minutes twice daily. Can be administered i.v. without further dilution. *Elderly:* No dose reduction necessary. Age associated decreased renal clearance with an increase in AUC levels should be considered. *Paediatric patients:* Not recommended. *Patients with renal impairment:* No dose adjustment necessary in mild and moderate renal impairment. Dose adjustment is recommended for patients with severe renal impairment and patients with end-stage renal disease (see SPC). Dose titration should be performed with caution. *Patients with hepatic impairment:* No dose adjustment needed in mild to moderate impairment. In accordance with current clinical practice, if Vimpat has to be discontinued, it is recommended this be done gradually (e.g. taper the daily dose by 200 mg/week). **Contraindications, Warnings, etc:** *Contraindications:* Hypersensitivity to lacosamide or to any of the excipients. Known second- or third-degree atrioventricular block. *Precautions:* Lacosamide has been associated with dizziness. Use with caution in patients with known conduction problems, severe cardiac disease or in elderly. Second degree or higher AV block has been reported 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.

ucb CNS
Innovation, Inspired by patients.

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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zonegran® x²
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Beyond efficacy

Zonegran is indicated as adjunctive therapy in the treatment of adult patients with partial seizures, with or without secondary generalisation.

PRESCRIBING INFORMATION
Zonegran® (zonisamide)
Please refer to the SPC before prescribing.
Presentation: Hard capsules: 25 mg, 50 mg, 100 mg zonisamide. ***Indication:*** Adjunctive therapy in adult patients with partial seizures, with or without secondary generalisation. ***Dose and administration: Adults:*** Starting dose is 50 mg in two divided doses. After one week, increase to 100 mg daily. Then increase at one weekly intervals in 100 mg increments. Can be taken once or twice daily after titration. In renal or hepatic impairment and patients not receiving CYP3A4-inducing agents consider two weekly intervals. Withdraw gradually. ***Elderly and patients with renal or hepatic impairment:*** Caution. Not recommended in severe hepatic impairment. ***Children and adolescents under 18 years:*** Not recommended. ***Contra-indications:*** Hypersensitivity to zonisamide, sulphonamide or any excipient. ***Pregnancy:*** Do not use during pregnancy unless potential benefits justify the risks. Women of childbearing potential must use contraception during treatment and for one month after discontinuation. ***Lactation:*** Excreted into breast milk. Either discontinue Zonegran or stop breast-feeding. ***Warnings and precautions:*** Serious rashes occur, including cases of Stevens-Johnson syndrome. Contains a sulphonamide group which is associated with serious immune-based adverse reactions. Closely supervise and consider discontinuation in patients with unexplained rash. Cases of agranulocytosis, thrombocytopenia, leukopenia, aplastic anaemia, pancytopenia and leucocytosis have been reported. Monitor for signs of suicidal ideation and behaviours and consider appropriate treatment. Use with caution in patients with risk factors for nephrolithiasis, including prior stone formation, family history of nephrolithiasis and hypercalcuria. Evaluate and monitor serum bicarbonate levels in patients who are at risk of metabolic acidosis. If metabolic acidosis develops and persists, consider reducing Zonegran dose, discontinuing Zonegran treatment or adding alkali treatment with Zonegran as osteopenia may develop. Use with caution in patients treated with carbonic anhydrase inhibitors, e.g. topiramate. Decreased sweating, elevated body temperature and heat stroke have been reported. Patients should maintain hydration and avoid excessive temperatures. Monitor pancreatic lipase and amylase levels in patients taking Zonegran who develop clinical signs and symptoms of pancreatitis, consider discontinuation. In cases of severe muscle pain/weakness with or without fever, assess markers of muscle damage and consider discontinuation. Zonegran 100 mg capsules contain E110. Caution in patients less than 40 kg. In patients with weight loss consider dietary supplement, increased food intake or discontinuation. ***Drug interactions:*** No clinically relevant pharmacokinetic effects on carbamazepine, lamotrigine, phenytoin, sodium valproate, oral contraceptives (ethinylestradiol or norethisterone). Insufficient data with carbonic anhydrase inhibitors, e.g. topiramate. Zonegran was not affected by lamotrigine or CYP3A4 inhibitors. Caution with drugs which are P-gp substrates. Avoid concomitant administration with drugs causing urolithiasis. Zonisamide is metabolised partly by CYP3A4, N-acetyl-transferases and conjugation with glucuronic acid; therefore caution with substances that can induce or inhibit these enzymes. ***Side effects:*** Most common adverse reactions in controlled adjunctive therapy studies were somnolence, dizziness and anorexia. Refer to SPC for all side effects. Very common effects (≥1/10): anorexia, agitation, irritability, confusional state, depression, ataxia, dizziness, memory impairment, somnolence, diplopia, decreased bicarbonate. Common effects (≥1/100, <1/10): ecchymosis, hypersensitivity, affect lability, anxiety, insomnia, psychotic disorder, bradyphrenia, disturbance in attention, nystagmus, paraesthesia, speech disorder, tremor, abdominal pain, constipation, diarrhoea, dyspepsia, nausea, rash, nephrolithiasis, fatigue, influenza-like illness, pyrexia, weight decreased. Serious effects: pneumonia, suicidal attempt, convulsion, cholecystitis, urinary calculus. Isolated cases of Sudden Unexplained Death in Epilepsy Patients (SUDEP). Post-marketing data suggests patients aged ≥65 years report a higher frequency of Stevens-Johnson syndrome and Drug Induced Hypersensitivity syndrome. ***Legal Category:*** POM. ***Basic UK NHS cost:*** Zonegran 25 mg: packs of 14 £8.82, Zonegran 50 mg: packs of 56 £47.04, Zonegran 100 mg: packs of 56 £62.72. ***Irish price to wholesaler:*** Zonegran 25 mg: packs of 14 €9.20, Zonegran 50 mg: packs of 56 €48.78, Zonegran 100 mg: packs of 56 €65.18. ***Marketing authorisation numbers:*** Zonegran 25 mg 14 capsules: EU/1/04/307/001, Zonegran 50 mg 56 capsules: EU/1/04/307/003, Zonegran 100 mg 56 capsules: EU/1/04/307/004. ***Marketing authorisation holder:*** Eisai Ltd. ***Further information from/marketed by:*** Eisai Ltd, European Knowledge Centre, Mosquito Way, Hatfield, Hertfordshire, AL10 9SN. ***Date of preparation:*** July 2011.

Adverse events should be reported. Reporting forms and Information can be found at www.yellowcard.gov.uk. Adverse events should also be reported to Eisai Ltd on 0208 600 1400/ 0845 676 1400 or Lmedinfo@eisai.net

Date of Preparation: July 2011 Zonegran-UK2395

On the Way to the Deep Layers of Consciousness

Boris Kotchoubey, Prof, PhD, studied medicine (Moscow, 1969-75) and psychology (Moscow, 1979-83), PhD in Psychology (Russian Academy of Educational Sciences, Moscow), later worked in the Institute of Psychology of the USSR Academy of Sciences. Alexander von Humbolt Fellow at the University of Ulm 1992-94, Research Assistant at the Medical University of Lübeck (1994-95), later Assistant Professor and since 2006 Full Professor at the University of Tübingen.

Tao Yu, Master of Psychology (University of Bielefeld, 2008). Presently PhD student in Tübingen. His main research interest is in evaluating brain function in patients with disorders of consciousness using neuroimaging techniques.

Alexandra Markl, MD, was born and grew up near Stuttgart in Germany. Between 2001-08, she studied medicine at the University of Tubingen. In 2010 she completed her doctoral dissertation on the topic dopamine metabolism in alcohol addiction. Since 2008, she works as assistant neurologist at Schoen Clinics of Neurorehabilitation, Bad Aibling (Bavaria).

Dominik Vogel, MD (Munich, 2009), presently neurology registrar at the Schoen Clinics for Neurorehabilitation, Bad Aibling (Bavaria). Main research interests concern using fMRI for the study of perception (including pain perception) in neurological patients.

Friedemann Müller, MD, Master of Psychology, studied psychology (Tübingen, 1975-1984) and medicine (Tübingen, 1980-1986), after which worked at the University Hospital for Neurology (1986-87; 1989-93) and Psychiatry (1993-94), University of Tübingen, and the Department of Neurology, University of Wisconsin (1988-89). Since 1994 at the Schoen Clinics for Neurorehabilitation, Bad Aibling (Bavaria), since 2006 Senior Consultant and Representative of Medical Director of the Clinics.

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Assessment of severe disorders of consciousness (DoC) remains very difficult. The rate of misdiagnosis is exceptionally high and does not decrease across time. These facts have led to the idea of using paraclinical methods (EEG, PET, fMRI) in addition to the clinical methods of the diagnosis of DoC including vegetative state (VS).

In 2006, Owen et al. demonstrated, using an fMRI mental imagery paradigm, the ability to follow a complex verbal instruction (and thus the presence of lucid awareness) in a patient clinically diagnosed as VS. However, an analysis of Owen's method indicates its high false negative rate, that is, even fully conscious patients can fail in Owen's test. This is because the test is well-designed to check for clear awareness but not for deeper layers of subjective experience such as pleasant-unpleasant, pain, or elementary sensation.

In the present article a hierarchical procedure for assessment of several levels of consciousness is proposed based on several fMRI stimulation paradigms. Preliminary data indicate that pre-linguistic, sensory and emotional experience can be preserved in many VS patients lacking all cognitive aspects of consciousness.

What is consciousness?

Is it a unity that can be either present or absent? Or are there several distinct kinds or levels of consciousness? The issue worried philosophers for centuries. For example, Descartes, and more recently logical positivists, regarded consciousness as a unitary domain. In contrast, Husserl and his pupils (among them, Heidegger and Merleau-Ponty) stressed the existence of distinct levels of consciousness. In the recent time, the unitary concept is best presented in Baars'[1] common working space theory, which states that cognitive processes are conscious when they are accessible for all other processing modules. On the other hand, numerous neuroscientists (e.g., [2]) and philosophers (e.g., [3]) emphasise qualitative difference between various subtypes of consciousness, even though they may largely disagree about what is the demarcation between these subtypes. In more general terms, lower-level consciousness (LOC) describes simple experiences like 'seeing red', 'feeling pain', or 'enjoying the taste of wine'. It is assumed to be non-transitive (e.g., it is just to be in pain, not to be in some relation to pain), language-independent and phenomenal (that is, there is something 'what it is like to be in pain'), and common for humans and many nonhuman animals (e.g., [2-5]). In contrast, high-level consciousness (HOC) is transitive (i.e., it is always 'of', or 'about' something, includes a relation to something), requires language, presumes an access of the individual to the content of his/her conscious states, and is specific for humans (although its components might, as exception, be observed in very complex animals such as apes) (e.g., [3, 6-8]). Some authors emphasise sensory[9] and affective[10] character of LOC, thus opposing it to the largely cognitive HOC. Panksepp et al.[11] further suggest that 'raw emotional feelings' can survive even a very severe brain injury, which leads to the complete loss of cognitive awareness. Therefore, investigations of patients with disorders of consciousness (DoC) may shed light on this old controversy.

There are three major kinds of severe DoC: coma, VS, and minimally conscious state (MCS). Coma is characterised by a complete loss of wakefulness and reactivity. VS patients, in contrast, are awake, and their reflexes to simple stimuli such as pain, sounds or flashes are preserved. However, there is no sign of conscious awareness, language understanding, or intentional behavior. If a patient shows weak and unstable signs of consciousness, but the communication is still impossible, the diagnosis is MCS.[12]

The diagnosis of coma usually presents no problem and the main difficulties concern aetiology and, particularly,

Sex/age	Aetiology	Months since accident	Imagery paradigm results	Language paradigm results	Trace conditioning paradigm results	"Empathy" paradigm results	Pain paradigm results
M56	anoxia	38	1	0	2	3	2(s)
M47	vascular	64	1	0	0	1	3
F56	vascular	33	0	0	0	2(s)	3
M29	anoxia	34	1	2	0	1	3
M54	vascular	60	0	no data	0	2(a)	0
F54	anoxia	93	1	0	2	3	2(s)
F62	vascular	66	1	1	2	1	1
F45	anoxia	287	0	0	0	0	0
M59	anoxia	88	0	0	0	2(s)	1
F16	anoxia	20	2	1	0	2(s)	3
F38	anoxia	2	no data	no data	0	0	1
M35	vascular	3	1	1	2	0	1
F64	anoxia	104	0	2	2	2(a)	3
F69	vascular	39	1	0	0	3	1
F71	vascular	2	1	0	0	2(s)	3
M75	vascular	20	2	1	0	3	3
M19	anoxia	4	1	no data	0	1	1
F62	anoxia	4	2	no data	2	1	2(s)
F30	anoxia	1	1	2	2	2(s)	3
M44	herpes	50	0	1	0	1	1
M47	anoxia	18	0	0	2	2(s)	1

Notes: M, male; F, female. The results patterns are coded as follows: 0 = no significant activation; 1 = random activations in unexpected brain areas; 2 = activation of a part of the network expected on the basis of the literature or the own experiments with healthy individuals; 3 = activation in the entire network, comparable with typical activation patterns of healthy individuals; (s) = activations primarily in the sensory portion of the pain matrix (e.g., thalamus, primary sensorymotor cortex); (a) = activations primarily in the affective portion of the pain matrix (e.g., insula, anterior cingulate cortex).

prognosis of the outcome. In contrast, in VS and MCS the diagnosis is very difficult, as it requires the subtle differentiation between simple reflex movements and voluntary actions. The former are compatible with both VS and MCS, the latter contradict the diagnosis of VS in any case, and to the diagnosis MCS if they occur systematically.

Both subjective experience and conscious intention are first-person phenomena that cannot be checked for in a completely objective way. Not surprising, therefore, the rate of diagnostic errors is about 40%, and, even worse, this rate has not decreased for at least fifteen years despite considerable progress in the development of assessment techniques[13 15]. The majority of these errors are the confusion between VS and MCS; however, a proportion of them are also erroneous diagnosis of DoC in patients who are fully conscious. Patients with severe paralysis, global aphasia, vision disorders (i.e., lacking a response to light), and in particular with a combination of these disorders are in danger of being labelled as VS or MCS while they are conscious.[14]

Apparently, the high diagnostic error rate does not simply result from insufficient qualification or limited practice of the neurologists, but is deeply rooted in the impossibility of judging the state of consciousness on the basis of behaviour. This gave rise to the idea that the diagnostics might be improved if, in addition to behavioural assessment, techniques of modern neuroscience are applied to "look into the patient's brain". At the transition of the millenia, two such techniques were actively used: event-related brain potentials[16,17] and positron-emission tomography.[18,19] The two methods are as different as they could be. The former is characterised by perfect temporal but poor spatial resolution, which additionally decreases with the depth of the source; the latter has a good spatial resolution and can represent subcortical activity, but its temporal resolution is bad. Yet the results of the two approaches were similar: in many VS patients neural activities exist that indicate complex cognitive processing of various stimulus qualities including word meaning.

Since, however, the DoC are defined in terms of the lack (VS) or limitation (MCS) of consciousness, the question arises whether the observed cognitive processes can be regarded as indicators of consciousness. The answer is rather negative, because there is vast evidence that each function, including semantic processing, can also be performed without conscious awareness. The obtained brain information processing operations can be necessary for conscious perception or action, but they may not be sufficient.

At this point the research stagnated for a while, but then Owen et al.[20] made a breakthrough. The researches asked a young patient who exactly fulfilled the clinical criteria for VS after a head injury to imagine either playing tennis or navigation in their own apartment. In accord with the instructions, the two tasks elicited two distinct patterns of brain activity (as measured using functional magnetic resonance imaging, fMRI), quite similar to the patterns obtained in healthy individuals with the same instructions.

However, an analysis of Owen's method indicates its high false negative rate. The authors demonstrated in several control experiments that a positive finding in such a test would prove the patient's awareness (i.e., the ability to understand and follow a verbal instruction) independently of behavior. However, a negative finding would not prove anything. There is both theoretical and empirical evidence that even fully conscious patients with neurological diseases can fail in Owen's test.[21] This is because the test aims at the higher-order language-related awareness. If there are (see the first paragraph) other, language-unrelated layers of subjective experience such as pleasant-unpleasant, pain, or elementary sensations, these layers are not addressed.

However, just these elementary aspects of consciousness are of vital importance from the practical point of view. Not the ability to think clearly or problem solving decides whether the patient is a human person or just a mindless body, but the ability to experience

pain and suffer. Furthermore, only a small portion of the diagnostic errors concerned the patients who were in full possession of HOC. Therefore, a method capable of assessing the full-blown, 'normal' awareness would only moderately decrease the error rate.

Thus, the aim of the present project was the development of a set of stimulation paradigms designed to investigate different levels of conscious experience without the patient's ability to demonstrate overt behavior. Like Owen et al., we use fMRI as the recording technique whose relative slowness (as compared to the EEG) is more than compensated for by its ability to reveal the activity of various brain structures including those related to "primary" emotional processes.

The battery needed to fulfil several criteria. Firstly, it should address the different levels of cognitive functions that could possibly remain. Secondly, these functions should be related to consciousness, which is not trivial given that even very complex cognitive processes (e.g., learning) can run unconsciously. Thirdly, the patients' ability to appropriately respond to the stimuli should be manifested in their fMRI responses. Last but not least, the overall examination time should be limited because DoC patients quickly become tired, and the probability of severe movement artefacts increases with time of testing.

For this reason, our project included the following hierarchical procedure.

1. The mental imagery paradigm was an exact replication of[20] and addressed HOC including its important components, selective attention and working memory.[22]
2. Patients who cannot follow verbal instructions can nevertheless understand language. In the language paradigm short correct (e.g., May is the month that follows April) and incorrect sentences (e.g., March is the month that follows April) were presented. The paradigm was based on the idea that whereas semantic associations (e.g., cat-dog) can be processed adequately at an automatic level, the understanding of the factual correctness of sentence requires its conscious apprehension. On the basis of the literature, we expected a larger activation in the classical language areas to false than correct sentences as a neurophysiological sign of sentence understanding.
3. Patients who do not understand language can nevertheless retain the ability to consciously learn. The simplest form of conscious learning is trace conditioning.[23] We used a trace conditioning procedure in which two tones were randomly presented 30 times each. One of them (a conditional stimulus, CS) was followed 15 times by a weak electric shock (unconditional stimulus), whose intensity twice exceeded the average pain threshold in a comparable control group. The interval between the CS and the shock was 3 s. The BOLD-contrast was that between the CS not followed by the shock and the other tone, which was never accompanied by a shock.
4. Patients who lost the ability to build new explicit associations can nevertheless retain emotional responses to affective stimuli. Whereas the processes depicted above are learning-related and probably belong to HOC, at least some kinds of emotional experience might be speculated to be inborn and to belong to LOC (of course, we do not know exactly which kind of consciousness is simpler than another kind, because the criteria of simplicity /complexity are highly controversial in this respect). Brain responses to exclamations (screams) expressing pain and suffering were compared with the responses to other sounds of human voice, both positive (e.g., laughing) and negative (e.g., snoring). In healthy individuals, such pain-related sounds elicit activation of the whole pain matrix of the brain even though they are not nociceptive.[24]
5. Finally, the fifth paradigm was simply the presentation of nociceptive stimuli, i.e., electrical shocks to the index finger. Here, again, the activation of the pain matrix (as compared with rest) was expected. It is also worth noticing that while several components of this matrix (e.g., the somatosensory cortex) are mainly related to sensory aspects of pain, other components (e.g., the insula and the cingulate gyrus) are closely related to its subjective, emotional aspects.

To avoid the unnecessary patient transportation, two different Siemens MRT devices (1.5 T and 3 T) were used for examinations. In the former, in which fourteen patients were examined, T2* weighted MR signal was measured using a gradient echo-planar imaging sequence (TR = 3.41 s, TE = 50 ms, FoV = 192 mm, flip angle = 90°, 64 x 64, 36 slices covering the whole brain, slice thickness 3mm, no gap, voxel size 3x3x3mm). In the latter (seven patients), the corresponding parameters were TR = 2.38 s, TE = 25 ms, FoV = 210mm, 40 slices, voxel size 3.3x3.3x3mm. Individual T1 weighted anatomical images served as an underlay for the activation pictures. The data were processed using SPM8.

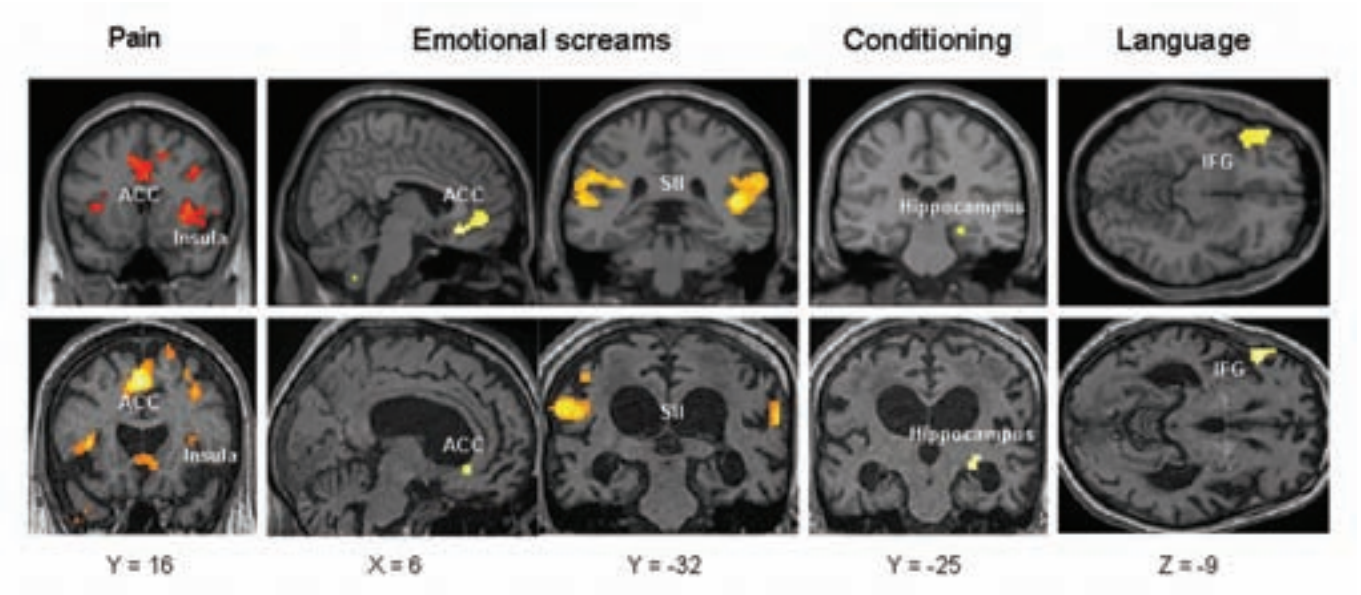

Figure 1. Top row: group average brain activation patterns in healthy participants. Bottom row: examples of brain activations in selected VS patients. For a better comparison, the same slice is shown for patients and controls. Leftmost column: the contrast between pain stimulation and rest. Note the activation in the structures (i.e., ACC and insula) related to the emotional rather than sensory aspects of pain. Middle left column: empathy paradigm, the contrast between pain-related and pain-unrelated sounds of human voice. Middle right column: trace conditioning paradigm, the contrast between CS+ and CS-. Rightmost column: language paradigm, the contrast between correct and wrong sentences. According to [26], the activation threshold for individual patients ($p<.005$, at least ten contiguous voxels) was selected so that to balance the probabilities of Type I and Type II errors. ACC, anterior cingulate cortex; SII, secondary somatosensory cortex; IFG, inferior frontal gyrus; CS+, a tone that had previously been followed by a pain stimulus; CS-, a tone that had never been followed by pain. All the patients whose data are presented in the Figure had VS following a hypoxic brain damage for at least five months.

A total of twenty-one patients (aged 16-75; 11 females) carefully diagnosed as VS took part in the study after the approval of the Ethics Commission of the University of Tübingen and the informed consent of each patient's legal representative. The characteristics of the patients are described in the Table above.

In the imagery paradigm, three of the 21 patients showed responses similar to those of control individuals. In the language paradigm, activations in some of the expected brain structures were found in three of 17 patients (the language paradigm was not performed in four patients with a different mother tongue). In trace conditioning, similar positive findings were obtained in eight patients. However, none of the patients displayed a pattern of activity that would entirely correspond to that of healthy individuals in any of these paradigm.

Different results were obtained in the other two paradigms. In response to emotional sounds, four patients demonstrated significant activations of the entire pain matrix of the brain including both sensory and affective components, nine patients showed activity in several (but not all) regions of this network, and eight patients showed no response or responses inconsistent with the expected ones. During pain stimulation, eight patients demonstrated activations in the entire pain matrix, practically identical to the responses of healthy controls, and three further patients showed a widespread activity in the components of this matrix related to sensory aspects of pain (thalamus, putamen, cerebellum, somatosensory cortex).

Clearly, these data do not strongly prove the patients' real experience of negative emotions related to pain and emotional cries. However, the opposite thesis that an unresponsive patient has no subjective experience at all is difficult to defend when significant activity is observed in the entire brain network, or even a considerable part of it, which is known to strongly correlate with such subjective experience. Also, the exact quantitative data reported above should be treated with caution. There are numerous reasons as to why a particular fMRI test may yield a negative result even if the corresponding function in the given patient is preserved. However, the general qualitative trend in the data is unequivocal. Whereas neural correlates of cognitive (presumably conscious) processes are rare findings in VS, correlates of emotional processes are well expressed in many patients. This is in line with the hypothesis[11] that emotional consciousness can remain even despite the nearly complete loss of cognitive awareness. It is furthermore worth noting, that our previous experiment[25] has indicated that patients in acute non-traumatic coma can consistently respond to emotional screams like those used in the paradigm 4 of the present study.

From a theoretical viewpoint, the data indicate that the essential cognitive functions constituting our everyday awareness, such as explicit learning ability, biographical memory and language comprehension, do not make the whole of human subjectivity. There may be even more basic and probably simpler functions, which include not only feeling pain and pleasure, but also feeling pain (and perhaps pleasure) of others. However simple, these functions importantly contribute to being human. From a practical viewpoint, the data suggest that emotional contact with caregivers (e.g., using affective prosodic cues, music as affective stimulus, or touch) can be established even in patients with a complete loss of all major cognitive functions. People having pets, and parents of young children, know that the lack of HOC does not completely preclude communication. For many patients fulfilling the diagnostic criteria of VS the same may hold true as well. ◆

Emotional contact with caregivers (e.g., using affective prosodic cues, music, or touch) can probably be established even in patients with a complete loss of all major cognitive functions

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From GWAS to Molecules in MS

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Multiple sclerosis (MS) is one of the most frequent causes of neurological disability in young adults in western countries. Despite extensive efforts, little is known about events that trigger the disease or factors that control its highly variable course and severity.

Given its unpredictable nature, alongside the accumulation of significant disability in a large proportion of patients, MS is a feared disease, often leading to a severe impact on patients and their families as well as a large cost for society. The established immune modulation MS therapies are only indicated for the relapsing remitting forms of MS and are often only partly effective, some with serious side effects. The development of more successful treatments is limited by our poor understanding of pathogenesis and disease mechanisms. Through genetic and molecular studies of MS, guidance to 'personalised medicine' and establishment of new therapies can hopefully be achieved.

Familial clustering is a firmly established feature in MS, with 15-20% of affected individuals having a family history of the disease, epidemiological studies showing this is primarily a result of shared genes rather than a shared environment.[1] The importance of genetic factors in determining susceptibility to the disease prompted efforts towards identifying responsible genes in the expectation that this knowledge will provide invaluable information about pathogenesis and inform future research into effective treatments.

Candidate gene studies identified the importance of HLA genes in MS

Early genetic research efforts quickly established association with the human leukocyte antigen (HLA) region in the major histocompatibility complex (MHC) on chromosome 6p21.[2] Subsequent research efforts have refined this association and confirmed that in virtually every population tested, risk is primarily determined by the class II allele HLA-DRB1*15:01.[3] Carriers of this risk allele typically have a three-fold increased risk of developing MS, making this the largest genetic factor predisposing an individual to MS yet identified. Considerable progress in fine mapping and dissecting this important signal has provided growing evidence supporting the involvement of genes within the class I region with MS, independent of the 15:01 association.[4] Much work still needs to be undertaken to completely understand the role of this complex region in the development of MS.

In the years following the HLA discovery, despite the heritable nature of susceptibility to MS, candidate gene studies made remarkably little progress in identifying the genes involved in MS. The invariable use of inadequate sample sizes coupled with the limited probability that a relevant gene might be selected for study have been prominent amongst the reasons for the limited success of this approach.

Genome screening identified the first non-HLA gene associations in MS

As such the momentum shifted towards screening the genome, an advantageous method as no prior knowledge of the pathogenesis of disease is required as genetic variants are screened throughout the genome in the hope that they will be correlated with the disease causing allele. The first genome screens were performed by linkage analysis genotyping microsatellite markers in affected sib-pair families in the mid-1990s in the UK[5], US[6] and Canadian[7] population and have since been completed in several other populations. Disappointingly no region of genome wide significance was identified in any study and little overlap in the results between studies was found. In 2005, a definitive linkage screen was completed by the International Multiple Sclerosis Genetics Consortium (IMSGC), by whom 4506 single nucleotide polymorphisms (SNPs) were typed in 730 multiplex families.[8] While the only region to reach genome wide significance was the already established HLA region, this linkage study did establish that outside the HLA region, common susceptibility alleles (frequency >10%) are unlikely to increase the risk of disease by a factor of more than two and therefore association screening is a more powerful method to establish these small genetic effects in MS.

It was only as the understanding of the nature and extent of human genetic variation increased and the technology to screen hundreds of thousands of single nucleotide polymorphisms (SNPs) in the human genome in a cost and time efficient manner become available, that the ability to complete genome-wide association screens (GWAS) was made possible. The first high-density genome wide association screen in MS was published in 2007.[9] Close to 1000 trio families (an affected individual and both of their parents) were screened for over 300,000 SNPs and implicated the IL7RA and IL2RA genes in MS susceptibility, which was successfully replicated and confirmed in other populations.[10] Since then more than 10 GWAS and meta-analysis studies have been completed and alongside replication studies have confirmed a growing list of genes involved in MS susceptibility (see Figure 1).[9,20] These are the first genuine associations to be identified in multiple sclerosis since the long established association within the HLA region. As indicated by the MS linkage studies,[9] no other MS loci have been identified with a higher risk than the HLA region, reflected in odds ratios typically around 1.2 for the now established non-HLA MS risk loci (Figure 1).

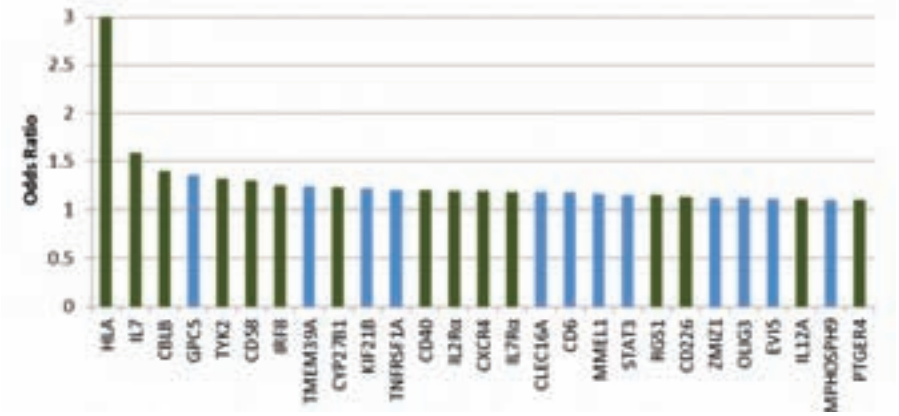
Interestingly these associations have uncovered a growing overlap in susceptibility loci between MS

and other autoimmune diseases, including for example the IL7R, IL2RA, CLEC16A and CD226 genes.[11, 21] This result is not surprising as epidemiological studies have identified an increased frequency of autoimmune disease in the family members of MS patients, suggesting shared disease mechanisms based on a common genetic background.

Acknowledging the crucial importance of the sample size for well-powered genetic studies, the IMSGC decided to perform the largest and most well powered MS GWAS. In collaboration with the Wellcome Trust Case Control Consortium 2 (WTCCC2) close to 10,000 MS samples and 20,000 controls were analysed using a 660K SNP chip, providing one of the largest and statistically most complex GWAS studies performed both due to the number of samples included as well as the large number of populations represented in the screen. This screen will identify an additional list of MS associated loci.[22] The results from this screen will be published in the near future.

Moving into the post GWAS area of molecular characterisation in MS

Much work still remains to understand the full genetic architecture of susceptibly to MS. As the variants typed in a GWAS are only a small fraction of variants that co-segregate, causal variants for disease will only occasionally be directly typed in GWAS. Fine mapping studies, in which the regions that are found to be associated with disease in GWAS are followed up and extensively mapped to identify the causal variants, are essential and are currently being completed. These studies will further define the causative associations, and lead to molecular studies aimed at characterising the functional effects of the identified MS associated loci.



The figure shows the MS associated risk loci as identified from published GWAS and replication studies in MS (references 9-20) and the odds ratios for the risk variants identified at each loci. A large proportion of the associated genes in MS are identified as being involved in immune system processes (as identified from the Gene Ontology database) and are shown in green in the figure, while those not involved in immune system processes are shown in blue.

Analyses of cellular pathways as well as gene-gene and gene-environment interaction studies of the established MS loci are further needed to fully comprehend the mechanisms of disease.

So far, there does not appear to be a genetic difference between the different clinical subgroups of MS. This may merely be a reflection of the lack of clearly defined subgroups. Careful genotype-phenotype studies, comparing the clinical and paraclinical expression of the disease (for example as evaluated by detailed MRI examinations), are needed in order to define if the mechanisms of disease development varies between different MS patient groups.

Future of genetic analysis in MS

Despite the success of the recent GWAS in MS, the variations associated with MS to date account for only a moderate proportion of the inheritable risk of MS. This "missing heritability" is a feature not only in MS but also other complex genetic diseases. Factors that can contribute to this missing heritability include missed or rare genetic variants, allelic heterogeneity (where more than one allele at a single locus is associated with disease) and epigenetic effects. Identification of the missing heritability is one of the next challenges in MS genetics.

In conclusion, genetic studies have the potential to identify molecules of importance to MS aetiology through systematic well powered scientific studies, most successfully applied by recent GWAS studies made possible by large international collaborative projects. Genetic research of MS susceptibility is therefore now quickly moving into another phase, characterising the full genomic architecture of disease susceptibility alleles as well as focusing on characterisation of the molecules involved in MS development. ◆

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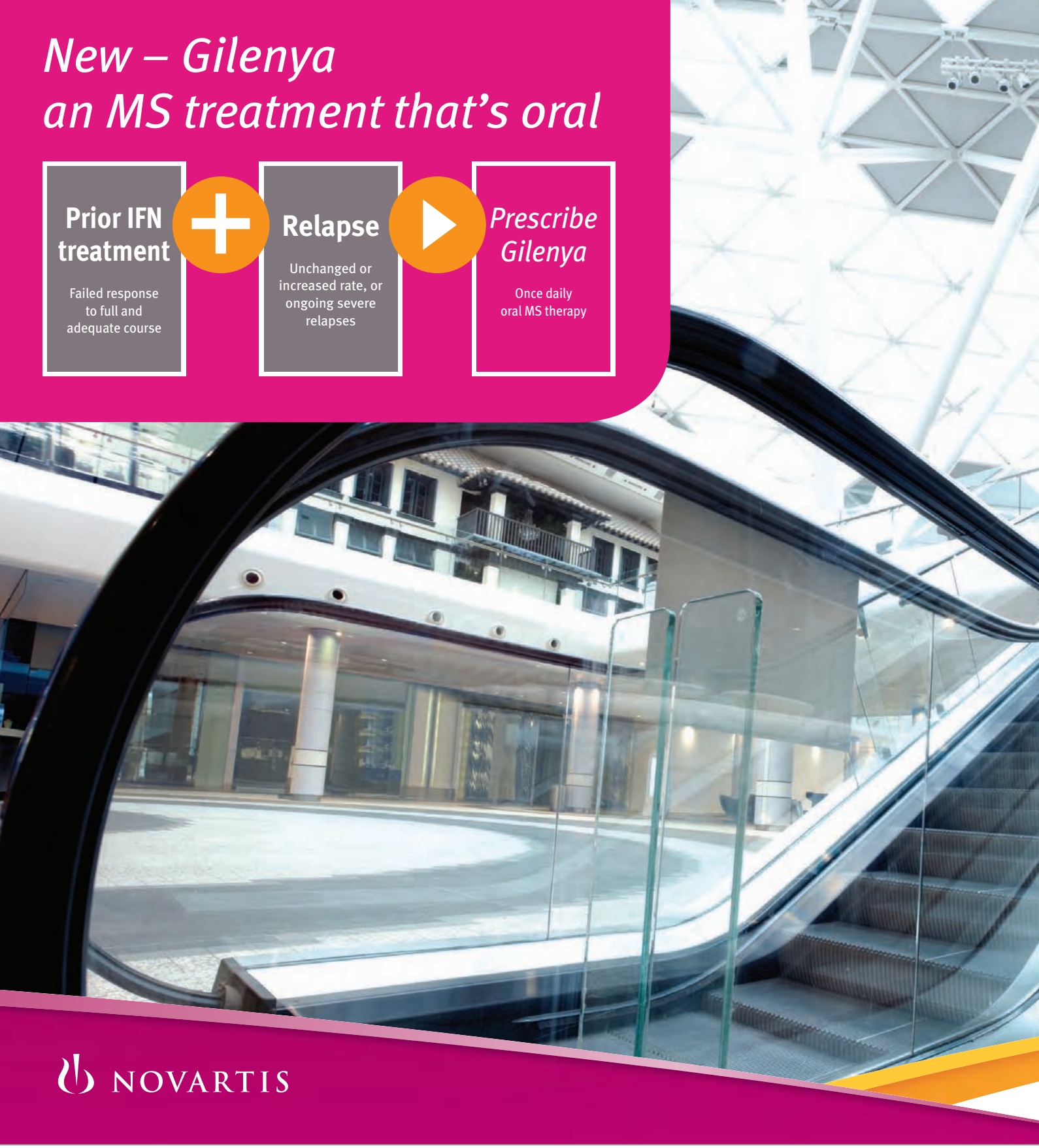

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A new perspective in MS

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tPA for Stroke

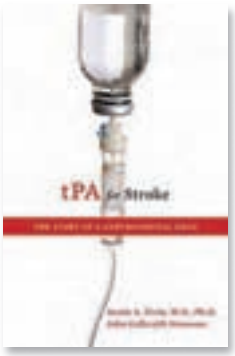
As a neurology trainee, I was extremely keen to read this book, because thrombolysis for the management of stroke has had an immense impact on my training years. As a trainee at St George's Hospital, London, the on calls were quiet when I first started as a research registrar in 2002.

The change with 24 hour thrombolysis service in 2007 was huge (we became resident neurologists on call) and this has become even busier with the advent of HASUs (Hyper Acute Stroke Units). So did this book explain how this drug has changed the face of stroke and hence neurology from a predominantly outpatient non-acute service to that of an emergency? Yes!

The book takes you on a journey – the first section, "Discovery", being on the product itself (tPA – tissue plasminogen activator) - from discovery in 1947 to the publication of the pivotal NINDS study in 1995 in the New England Journal of Medicine, to the granting of FDA approval and EU approval in 1996 and 2002 respectively) and the second section on how it eventually affected practice, "Change, Resistance and Transition". Throughout the book, cases were used to highlight the issues and personalise the experience. The most interesting section of the book for me was the controversy surrounding the acceptance or otherwise of tPA. The authors dissected why tPA was met with such scepticism in 1996 for such a prolonged period. They do not mince their words and one of the reasons given was "due to the makeup of the specialty (neurology) and the people in it". I have always wondered why tPA in stroke was not taken up by A&E (emergency) doctors, unlike its use in the cardiac world. This book discussed the issues surrounding this.

tPA for Stroke was Eminently readable but a timeline would have been helpful for orientation. The other potential weakness for a UK reader is that it is mainly about the drug's US history. However, its use in Europe is discussed, including how the UK is alone in having developed a public health strategy (Act F.A.S.T.) to address awareness. The chapter "Deer in the Headlights" highlighted the number of legal cases regarding, not the misuse of tPA, but the lack of its use. These cases in the US may be considered as useful lessons encouraging us to move away from the historical pessimism that surrounds stroke management to active and swift consideration for thrombolysis. That chapter concluded that "if a service cannot meet that standard, it should arrange for patients to bypass their hospital and go directly to others that are prepared to treat strokes as the emergencies they truly are". This is indeed what happens in the UK since the creation of HASUs in 2010.

The aim of the book, according to the authors, was to raise awareness of tPA and, at the end, one does feel convinced of its status as a revolutionary neurological drug. This book is an interesting read for those of us who are stroke enthusiasts, and for those who are not; I recommend it wholeheartedly to both groups! ◆



Authors: Justin A Zivin, John Galbraith Simmons
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Price: £17.99
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Reviewed by:
Arani Nitkunan, Department of Neurology, St George's Hospital, London.

Medical Neurobiology

Medical Neurobiology by Peggy Mason is a large volume text reviewing the neurosciences and their relevance in clinical practice. The book aims to bridge a perceived void between science and clinical practice by presenting the neurobiology without losing sight of the 'bigger picture' of a physician's day-to-day work.

The structure of the book is split into two halves. A straighforward but comprehensive first chapter introduces the components of the nervous system and very much achieves its goal of encouraging the reader to read on and delve deeper. This section includes overviews of neurons and glia and the embryological development of the nervous system before describing the physiology of neural communication and gross neuroanatomy.

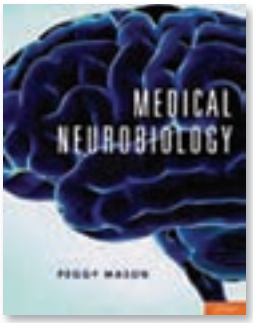
The latter half of the book deals initially with sensory perception, specifically visual, auditory and somatosensory perception. Following this, motor outputs are explored. These sections are beautifully written and explained in a systematic and logical manner, which is where this book really shines when compared to its peers. Particular highlights include the chapters on visual perception and gaze control. The book successfully explains the physiology of each major system in the context of the relevant anatomy. The later chapters are particularly effective if read while the preceding basic sciences chapters are fresh in the mind.

Perhaps the greatest strength of this book and, incidentally, the most enjoyable sections to read, are those where the newly acquired knowledge is applied to scenarios in clinical practice. The book is certainly not a clinical text, but it does explain key anatomical or physiological principles as clinical 'gems' presented in boxes throughout. For example, why does hemiballism result from a subthalamic nucleus lesion? How does the consumption of alcohol cause vertigo via its influence on the cupula? What is the relevance of 'chunking' in patients with Obsessive Compulsive Disorder? The author promises to deliver many 'ahhh…so that's how it works' moments of clarity to the undergraduate (or inner undergraduate).

Considering its target audience, there are no major criticisms of this text. One area of basic neurosciences which has seen great advances in recent years, that of neuroimmunology, is not included. However, this may be reasonably considered beyond the remit of a text that aims to introduce normal neurobiology.

Speaking as products of a 'modern' medical curriculum, featuring the 'Problem Based Learning (PBL)' approach, this text would seem to have great appeal for the medical undergraduate with an interest in neurology and for junior trainees keen to review this fascinating field of medicine. The method of learning in PBL is to consider all relevant areas from anatomy and physiology, through to clinical diagnosis and treatment within a 'module'. For clinicians brought up on this medical diet, Mason's book represents an excellent neurology review. For those with fond memories of 'Martini' or 'Tortoura' and their usefulness in rapidly getting to grips with a topic during their early years of medical school, this book could be seen as an extension.

Highly recommended for the target readers, undergraduates and junior trainees. ◆



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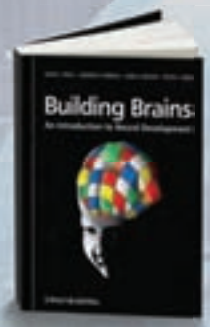

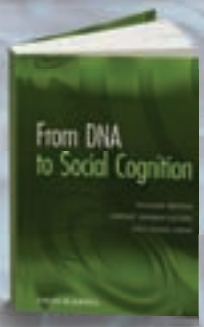

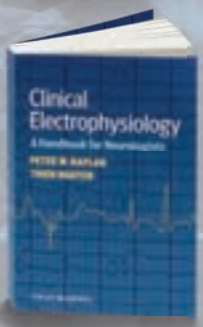

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Welcome to the eighth in a series of articles in *ACNR* exploring clinical dilemmas in neuropsychiatry. In this series of articles we have asked neurologists and psychiatrists working at the interface of those two specialties to write short pieces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

Alex J Mitchell

is consultant in liaison psychiatry at Leicestershire Partnership Trust and honorary senior lecturer in psycho-oncology at the University of Leicester. In 2004 he authored "Neuropsychiatry & Behavioural Neurology Explained" and in 2009 was co-editor of "Screening for Depression: An Evidence based Approach." His research interests include the scientific approach to clinical diagnosis and improving quality of mental health care. He maintains the website www.psycho-oncology.info

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Are People with Subjective but no Objective Memory Complaints at Increased Risk of Dementia?

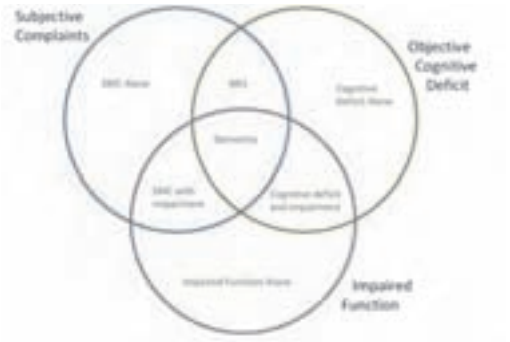
Case

A 55-year-old teacher who lives alone seeks help for memory complaints. She reports forgetting the names of students and losing items around the house but has minimal evidence of functional impairment, no difficulty driving and no history of mental or physical illness. She has a history of hypertension but is otherwise well. She has previously been tested on the MMSE which revealed a score of 29/30. Testing on the CAMCOG and ACE suggest she is on the 90th percentile for her age with no appreciable objective cognitive decline. She is worried about the risk of future dementia.

Should this patient be concerned about the risk of dementia? For younger people with minimal risk factors is the MMSE sufficient as a screening test? At this stage are further investigations indicated and in the absence of a formal diagnosis can anything be done to help?

Subjective memory complaints (SMCs) are everyday memory and related cognitive concerns expressed by people who may or may not have deficits on objective testing. SMC are of course common in people with mild cognitive impairment (MCI) and dementia and depending of how they are defined may occur in up to 50% of the healthy elderly population although after exclusion of depression a rate of around 20-30% is more typical.[1,2] The rate of complaints in those under 55 years is very poorly studied but Commissaris and colleagues (1998) found that 39% of people with a mean age of 33.9 answered positively to the question "Do you consider yourself forgetful?",[3] suggesting perceived deficits are probably more common than thought.

One important issue when trying to elicit SMC is that awareness of deficits generally decreases as severity of cognitive impairment increases (particularly in the most severe stages). Moreover many people who suspect cognitive problems may be reticent about disclosing them and in many cases are reluctant to undergo formal testing. For this reason informant report is strongly recommended where available, and is independently predictive of diagnosis and decline.[4] Although definitions of SMC have not been operationalised numerous several self-report questionnaires have been developed and can be used simply in clinical practice. Examples of validated tools are the Everyday Memory Questionnaire – Revised (EMQ-R) and the Short Memory Questionnaire (SMQ). It is now recognised that the presence of SMC is associated with



distress and reduced quality of life.[5] Causes of SMC without objective complaints are diverse but conceptually it may be helpful to try and separate those with no evidence of cognitive impairment from those with subclinical cognitive change and those with mild cognitive impairment. A simple classification based on these three domains is illustrated (Figure 1 above).

Indeed psychological factors such as depression influence expression of memory complaints. Therefore perceived forgetfulness is not always a sinister irreversible finding and even when examined cross-sectionally most purely subjective memory complaints do not interfere with daily function.[6,8] Practically anyone with memory complaints should also be asked about symptoms of depression, and ideally screened with a severity questionnaire such as the Patient Health Questionnaire (PHQ9).

The prognostic significance of SMC is important but until recently poorly studied. A review identified only seven studies published up to 2000 that considered dementia longitudinally and of these five studies found an association between baseline SMC and dementia after two years or more.[9] However these

studies were all in the elderly population and also did not account for baseline MCI and/or objective neuropsychological impairment. Two recent studies have been informative. Wang et al (2004) examined 1,883 subjects without dementia or objective cognitive impairment (they scored 91 or higher on the 100- point Cognitive Ability Screening Instrument).[10] 126 developed dementia during five years of follow-up. For subjects who reported SMCs at baseline ages of 70, 75 and 80 years, the hazard ratios of developing dementia were 6.0, 3.2 and 1.6 respectively. That is, risk was most elevated in younger groups. Additionally, a subset of people with baseline normal cognition who reported a high level of subjective deterioration had a higher risk for developing dementia (OR = 2.7; CI 95%, 1.45–4.98). In a small study Gallassi et al (2010) followed 92 SMC patients for four years stratified into those with SMC alone and those with MCI. During the follow-up, 45.5% of SMC remained unchanged, 13.9% were diagnosed as MCI and only one progressed to dementia. Of the MCI patients, 32.3% remained stable, 18.4% developed dementia and 4% reverted to SMC alone. Visual attention, behavioural memory, long-term verbal memory, apathy and caregiver distress were independent predictors of progression to dementia.[11] This preliminary data suggests a modest but significant risk of decline in older people with purely subjective complaints but no data has been forthcoming in younger adults. Our group recently conducted a meta-analysis of conversion studies. Compared to those without SMC the relative risk of progression (SMC vs healthy elderly) from these studies was 2.18 (1.48 – 3.20). More informative perhaps the annual conversion rate for those with SMC was 2.7% (95% CI 2.0% to 3.6%). A major modifying variable in determining risk in those with subjective but no objective decline is function (activities of daily living). Unfortunately this is one area that is often inadequately tested in routine clinical care, leading to the assumption that function was always normal in MCI and SMC. Whilst gross function impairment is uncommon, new research suggests an important subset are subtly impaired. Data from the Spanish Neurological Diseases in Central Spain study (NEDICES) cohort involving 1,073 participants reported SMC questions this assumption. Of 730 with pure SMC, 18.1% had significantly impaired function and 9.5% had severely impaired function measured by the Pfeffer scale.[12] It is likely, that those with SMC and impaired function are at increased risk of dementia even when symptoms present under 65 years. Clinically this means that everyone reporting SMC should also be tested for impaired function and whilst this can be done clinically it can also be useful to use an objective scale.

The clinical approach to people with possible early dementia or MCI has been extensively described elsewhere.[13,14] I would recommend putting clinically worrying SMC in that category. Clinically worrying SMC would include SMC with evidence of objective cognitive or functional decline, informant concern, evidence for early progression as well individuals with concomitant risk factors for dementia (such as concurrent vascular disease). A reasonable work up would include physical and neurological examination, neuropsychological testing and neuroimaging focussing on a standardized tests for dementia and MCI. Focal atrophy on magnetic resonance imaging (MRI) of the medial temporal region and decreased metabolism in this area as well as parietal lobes on 18F-fluorodeoxyglucose-positron-emission tomography (FDG-PET) has been shown to predict the conversion from mild cognitive impairment to Alzheimer's disease.[15] However imaging, in particular PET, is not widely available and CSF biomarkers may offer an alternative.[16] However no method has excellent accuracy in the earliest stages. In this case the preliminary MMSE of 29/30 is probably insufficient if there is any clinical reason for concern. The MMSE, although popular, has been found to have insufficient accuracy in the diagnosis of MCI (sensitivity 62.7%; specificity 63.3%).[17] The accuracy of other cognitive tools is under active investigation but the reported 90th percentile score on the ACE certainly seems to rule out appreciable objective decline. Nevertheless a remaining question in this case is whether any formal intervention can be recommended. Although there is extensive data on the treatment of early dementia and modest data on treatment of MCI, there is a paucity of RCT evidence for those with memory complaints alone.[18] Work involving the asymptomatic elderly and observation of cohorts is currently inconclusive and doesn't appear to strongly support the use of donepezil, ginkgo biloba, NSAIDs, COX-2 inhibitors, vitamin E, vitamin B_6, vitamin B_{12}, statins, hormone replacement therapy, or omega-3 fatty acids to delay progression to dementia.[19 21] Therefore whilst it is important to remember that pure SMC is not an entirely benign condition, the risk of dementia in working age adults remains to be clarified[22] and no good preventative strategies other than correcting obvious risk factors and sensible lifestyle advice currently exist.

Clearly there are many areas of uncertainty when it comes to subjective without objective complaints and it is difficult indeed potentially misleading to give too rigid a forecast at baseline. Nevertheless in the absence of functional decline although the risk is elevated in absolute terms it is still modest (about 3% per year). This risk can not be assumed to be constant but should be re-evaluated with annual examinations. For younger people under 55 years without functional decline or cognitive impairment on neuropsychological tests (not simply the MMSE alone which is insufficient) then neuroimaging and CSF testing can be considering useful but not yet essential. A careful psychiatric history is certainly essential. Whilst we await strong evidence for preventive strategies monitoring in the form of serial bi-annual testing with a convenient battery such as the CAMCOG is recommended along with robust treatment of vascular risk factors such as hypertension. ◆

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Avoiding VOMITs and Improving Care

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British neurology is under pressure to meet new demands in our outpatient and inpatient work. The two are closely linked and the Association of British Neurologists (ABN) is working hard to influence changes in both areas.

Outpatient neurology, open access MRI and real efficiency

Cancer targets have infiltrated all areas of medicine, including neurology. In particular, headache is seen as a potential area of change. The potential 'solution' of direct access MRI scanning for GPs for all new headache patients (trialled locally in some areas already) won't solve any problems, will create new ones and at the end of it all, won't get rid of the patient's headache. Instead of more scans, the ABN suggests increasing partnership with primary care, working to increase awareness and utilisation of current headache management guidelines such as BASH (The British Association for the Study of Headache), Map of Medicine, and other locally produced guidelines.

Eliminating cancer as the underlying cause is only a very small part of neurological practice, and can usually be done clinically in the case of headache. Headache makes up a huge chunk of neurology referrals, and, as an isolated symptom, is almost never the consequence of a brain tumour. With the large number of patients with migraine and other headaches, many scans would be requested if direct access was implemented. Given the limited number of MRI scanners available, this will compromise the availability of scans in patients for whom the scan will have a greater role in diagnosis and management.

Given that migraine occurs in 5% to 10% of the population (at least), and may resist treatment for over a month and sometimes much longer, it would be unnecessary and costly to arrange MRI brain scans on everyone with chronic migraine. Patients with chronic migraine rarely require an MRI scan. Furthermore, a scan does not cure their headache, and up to 6% will have an incidental or false positive finding such as a small aneurysm. This creates unnecessary and enormous anxiety, as well as potentially leading to more investigations with added costs and occasional risks, and even to surgery with very serious risks. This figure does not include the findings of VOMITs, UBOs, and with increasing age, white matter hyperintensities and microbleeds. Incidental findings generate a huge need for specialist referrals to settle anxiety, and explain findings. Indiscriminate MRI scanning would be enormously expensive over and above the cost of the scan itself.

Access to scanning is not the most important issue for patients with headache, and will not solve their pain. Education and empowerment of GPs to treat migraine earlier and more could have a significant impact on improving their care.

Making a difference at the coal-face

A joint report from the ABN and Royal College of Physicians (RCP) "Local adult neurology services for the next decade" has just been launched and is available on the RCP website. It is staggering that the UK is one of the few places in the world where neurologists are not acutely involved in neurological emergencies. They are common, making up 10% of emergency medical admissions (and many more with stroke). Services for patients admitted to hospital with an acute neurological illness are particularly concerning because they are rarely provided by neurologists, in contrast to those for stroke and other acute medical specialties, which may result in patients not receiving the best possible care available. Neurology remains a shortage specialty, with appointments mainly to the regional neurosciences centres and an inequality of more than three to one in numbers of neurologists in different parts of the UK.

Neurology services in the UK are organised around large regional neurosciences centres with an emphasis on research and academic excellence. These are crucial and should not be threatened, or we will lose the heart of what is needed to maintain excellence. They have produced world class research and new treatments for patients. But district general hospital services remain under-resourced because of a lack of local neurologists, in contrast to the USA and Europe with more neurologists per head of the population (1:40,000 versus 1:125,000). The lack of local neurologists in the DGH has resulted in poor local services exacerbated by an increase in outpatient demand driven by waiting time targets, inadequate resources and sometimes poorly structured services networked across health providers.

Long-term care of neurology patients also require big improvements. Patients need a range of neurology services at different stages of their illness - acute admission, outpatient care and long-term care. However, these are currently badly integrated, leaving many patients unable to access the right specialist at the right time and often far from home. They include such a variety of conditions that more than one model is needed for good care. For the patient, and their families, they need to be able to move between services, without fights or delays in provisions.

To solve these problems, the report recommends better integrated primary, secondary and tertiary resources to achieve a neurology network that is easily accessible, provides local care where appropriate and, as needed, at the regional neurosciences centre. The report proposes changes to cover acute neurology services, outpatient care, care for patients with long-term neurological conditions, the relationship between local services and the regional centres, commissioning, workforce planning and training.

What can we do?

We don't want the new report to grow dusty on the shelf. It is clear that both large and small scale changes are needed to improve acute and long-term care of neurology patients.

Improvements have been, and can be, made at local level and we really would like to hear about more of these, as models of good care.

The neurological charities support our calls for improvements in services for patients, both acutely and in the long term, and it is clear that central changes are needed. It is also clear that some of the changes will require more money. The resources required for direct access MRI would be much better spent on implementation of the RCP-ABN report, and we are making this crucial point to the Department of Health. ◆

The Premotor Cortex and Mirror Neurons

In 1991, Nature rejected the first report on mirror neurons for its 'lack of general interest'. Undeterred, the research team managed to publish a report the following year, and mirror neurons have been in the news ever since. Indeed, claims that mirror neurons underpin such functions as language acquisition, theory of mind and empathy have been made. Here, Fogassi (one of the authors of the original report) and Rodà present an account of mirror neurons and motor control.

Martyn Bracewell, Series editor

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Several neurophysiological studies in monkeys demonstrated that neurons of the agranular frontal cortex code goal-related motor acts, such as reaching an object, grasping it, etc., rather than simple movements. In particular, single neurons of ventral premotor area F5 (Figure 1) code the motor goal at an abstract level, discharging when a monkey grasps an object independent of whether this act is performed with the hand, the mouth or even with a tool.[1] This "internal motor knowledge" is then exploited, through reciprocal anatomical connections between parietal and premotor cortex, by the incoming sensory information, constituting a system matching the sensory input onto specific motor representations. This system enables individuals to attribute a "motor meaning" to the sensory input. One of the best examples of this matching process is provided by mirror neurons.

Mirror neurons in the monkey

Mirror neurons, originally described in monkey area F5, are visuomotor neurons discharging both when a monkey performs a hand or mouth goal-directed motor act (e.g. grasping, biting, or manipulating an object) and when it observes the same or a similar act performed by another individual (Figure 2). A sub-class of mirror neurons respond not only during execution and observation of a motor act, but also to the sound of noisy motor acts such as peanut breaking.[1] Although mirror neurons are generally not influenced by many details of the observed motor acts, recently it has been demonstrated that a consistent number of them can be modulated by the visual perspective (egocentric or third person view) from which a motor act is observed[2] or by the distance at which the observed act is performed.[3] Thus these neurons, beyond encoding the goal of the observed motor acts, can also contribute to recognize some details of it, probably through feedback connections between ventral premotor cortex and posterior, high order visual areas.

The idea that mirror neurons have a crucial role in the understanding of motor acts has been supported by further neurophysiological investigations. In one of these[4] it has been demonstrated that mirror neurons discharge also when the hand-target interaction is hidden behind a screen, thus showing that the motor representation of the observed motor act is retrieved even in absence of its full visual description.

The presence of mirror neurons has been demonstrated also in the inferior parietal cortex, in a cytoarchitectonic area (PFG) strictly linked with the F5 "mirror" sector. Thus, these two areas, together with STS (containing visual neurons responding to the

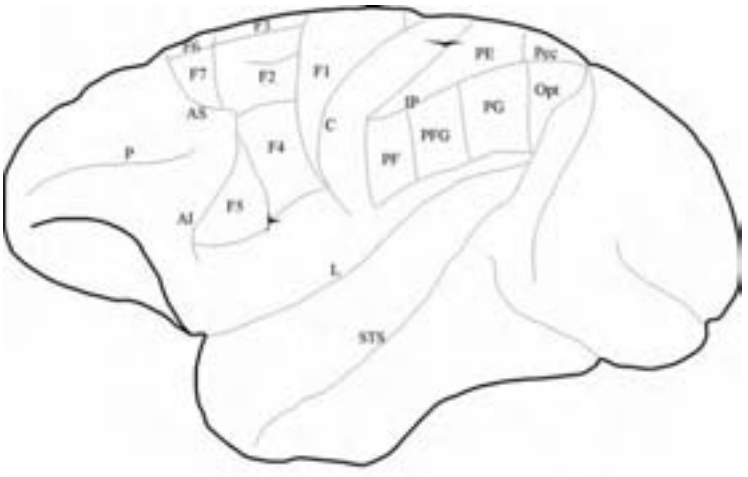

Figure 1: Lateral View of the monkey brain showing the parcellation of the agranular frontal and posterior parietal cortices. Motor areas are indicated with the letter F followed by a number. The areas forming the posterior parietal cortex are indicated with the letter P, followed by another letter, except the most posterior part of the inferior parietal cortex (Opt). Abbreviations: AI, inferior arcuate sulcus; AS, superior arcuate sulcus; C, central sulcus; IP, intraparietal sulcus; L, lateral fissure; P, principal sulcus; STS, superior temporal sulcus.

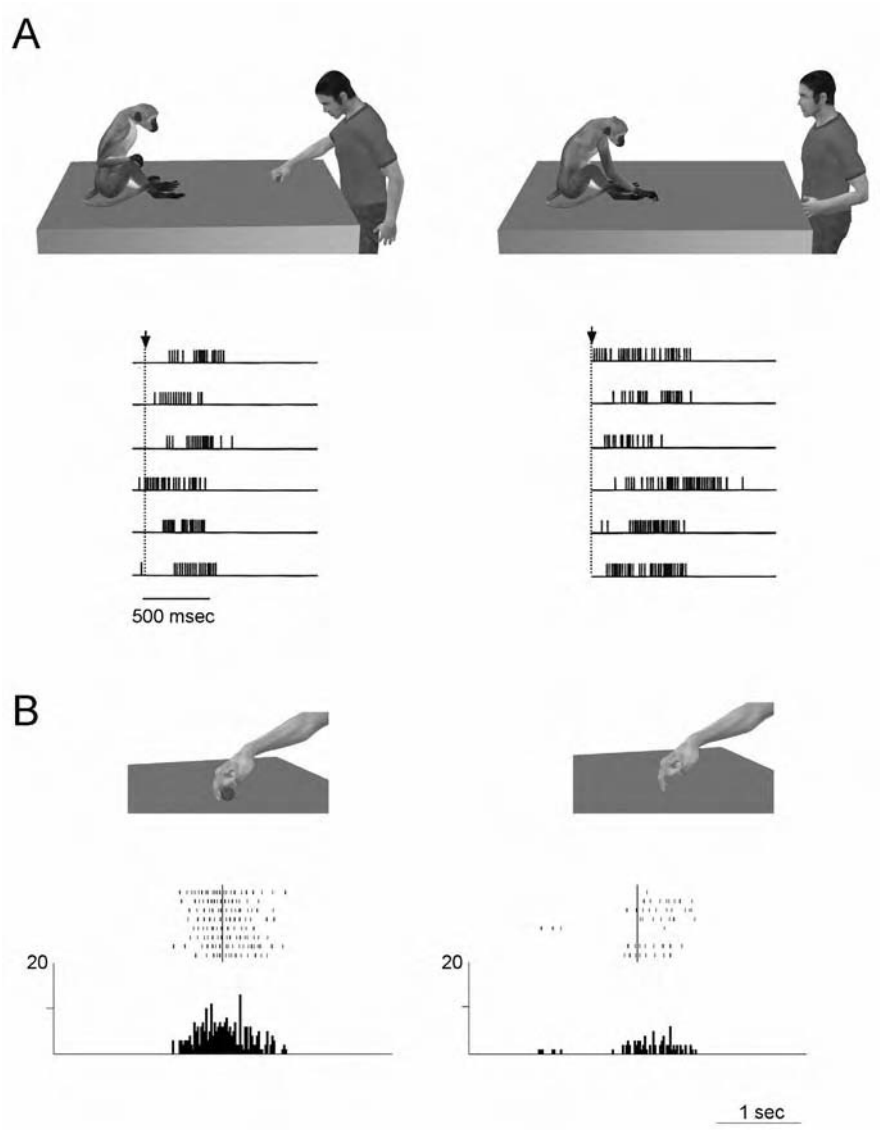

Figure 2: Example of two mirror neurons responding during observation and execution of hand motor acts. A. Top. Illustration of the experimental condition. Left. The monkey observes the experimenter grasping a piece of food. Right. The monkey grasps a piece of food. Bottom. Neuronal discharge recorded in six trials for each condition. The arrows indicate the experimenter's (left) and the monkey's (right) onset of grasping. B. Top Illustration of the experimental condition. The monkey observes a specific goal-directed motor act (digging out of an object- left) compared to a mimicking of the same motor act (right) without the target. Bottom. Rasters (10 trials) and histograms illustrating the mirror neuron discharge in the two conditions. Note that the discharge is much stronger during observation of the goal-directed act. Abscissae: time. Bin width: 20 msec. Ordinates: Number of spikes/bin. Modified from (3).

observation of biological motion,[3] constitute the functional circuit involved in transforming the visual description of a motor act in its motor representation (see Figure 1).

The mirror system in humans

Several electrophysiological and neuroimaging studies demonstrated the presence of a mirror system also in humans.[3] TMS stimulation of the motor cortex of subjects observing a grasping motor act elicits a specific enhancement of motor evoked potentials (MEPs) of the same muscles used to execute the same observed motor act. PET and fMRI studies demonstrated that observation of motor acts activate three main areas, likely homologous of the monkey areas activated in the same task, namely STS, supramarginal gyrus and the posterior sector of the inferior frontal gyrus (IFG), plus the anterior intraparietal area (AIP) and, in some cases, the superior parietal lobule.[1,3] Interestingly, observation of goal-related motor acts performed with different effectors (i.e. mouth, hand and leg) determines a somatotopic activation, with some degree of overlap, of frontal and parietal cortices,[1] indicating that observation of a motor act performed with a specific effector activates the corresponding motor representation.

More recent studies demonstrated that in humans, like in monkeys, the mirror system can be activated during observation of motor acts performed with a non-biological effector, such as different types of tools and/or a robot arm.[5,6] However, by comparing human and monkey brain activation during tool action observation Peeters and coworkers[6] showed that only in humans is there is an extra area of the supramarginal gyrus exclusively activated by tool observation.

Intention understanding

A series of experiments in monkeys investigated F5 and PFG neuronal activity while monkeys executed or observed different actions (eating or placing) containing the same motor act (grasping)[7,8] The results showed that a high percentage of both purely motor and mirror neurons in both areas discharged differentially during both execution and observation of the grasping act, depending on the final goal of the action in which the act was embedded. Thus, the modulation of grasping neurons reflects the action goal, that is the motor intention of the agent. Furthermore, when monkeys had to perform more complex actions the activity of grasping neurons was modulated since its early phases, suggesting that this activity could depend from a neural mechanism, probably located in the prefrontal cortex, that allows one to select actions on the basis of the context.

A mechanism similar to that described in monkeys might play a role in understanding others' intentions also in humans. An fMRI study by Iacoboni and coworkers[9] showed that when the context in which a motor act was observed suggested to observing subjects the intention underlying it, there was a differential activation of the right IFG compared with control conditions in which only the context or only the motor act were shown.

Altogether, monkey and human studies indicate that the parieto-frontal mirror network subserves the automatic understanding of motor intentions underlying the actions of others, through a process of retrieval of action representations. It is possible, however, that in cases in which the interpretation of others' behavior requires reasoning, beyond the 'mirror' network other cortical areas, considered to be part of a 'mentalistic network,[10] are involved.

Plasticity of the mirror system

The presence of mirror neurons responding also to tool actions[11] strongly suggests a plasticity of the mirror system. Examples of this plasticity have been reported also in humans. For instance, Cross et al[12] demonstrated that the ventral premotor (PMv) and inferior parietal (IPL) activity of expert dancers can be modulated during the observation of new complex whole-body dance sequences only if they are rehearsed.

In an fMRI study, Gazzola and coworkers[13] found that the observation of hand motor acts in aplasic subjects (born without arms or hands), produced an activation of the mirror system that, in the frontal cortex, included the mouth and foot representations. This suggests a recruitment of cortical representations involved in the execution of motor acts that achieve similar goals using different effectors.

In another fMRI study, Ricciardi and coworkers[14] showed that in congenitally blind patients listening to the sound of actions there was an activation of the mirror system, as in the normally sighted controls observing and listening to the same actions.

The reorganisation of the motor representa-

tions shown by these studies prompts the possibility to exploit this plasticity for rehabilitative purposes. For instance, Ertelt and coworkers[15] employed a three weeks action observation therapy on stroke patients with mild paretic hand. A group of them, who had to observe and reproduce motor acts of increasing complexity, showed a motor improvement (evaluated with functional scales), when compared to the control group observing videos showing non motor-related material, and then performing the same motor acts as the first group. Moreover, an fMRI study on the investigated patients showed that during execution of an object manipulation task, the first group, after the therapy, presented a greater activation of areas belonging to the mirror network than the second group.

In agreement with these findings, a recent pilot study based on Virtual Reality Neurorehabilitation[16] proved that acute stroke patients had particular benefits, as compared to control patients, on recovery of proximal movements and on the ability to perform functional daily life activities after adding, to a standard rehabilitation, exercises (Rehabilitation Gaming System) requiring the execution and observation (through virtual reality) of motor acts such as hitting, grasping or placing a spherical object.

Conclusions

The discovery of the mirror system prompted its investigation in many social cognitive functions in healthy and pathological subjects. One example is represented by the autistic spectrum disorder, characterised by a deficit in intersubjective relations, in which a decrease in the function of the mirror circuit has been proposed. Interestingly, EMG and behavioural studies showed that autistic children lack the typical fluidity that characterise the organization of intentional actions and they are not able to understand intentions when they can rely only on pragmatic information.[1] ◆

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Effectiveness of Neurobehavioural Rehabilitation for Young People and Adults with Traumatic Brain Injury and Challenging Behaviour

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Traumatic brain injury (TBI) can happen to anyone at any time. Very young children, young men and older people are particularly at risk. TBI is often caused by road traffic accidents, falls, violence and sport. It has been described as the 'silent epidemic': a conservative estimate is 295 new cases per 100,000 in the UK which equates to approximately 180,000 people each year presenting with head injury at hospital. Improved medical services mean more people survive but the long term effects can be devastating. These include a wide range of physical, cognitive, sensory, functional and emotional impairments, disabilities and handicaps which can be long-term. Despite high prevalence and the proven effectiveness of neurorehabilitation, brain injury has been regarded as a 'Cinderella' condition for many years with treatment and care provided to survivors being patchy, under-resourced and of variable quality.

Neurobehavioural disability and outcome

Neurobehavioural disability (NBD) and social handicap arising from this has a major impact on long-term outcome. NBD comprises a complex, subtle, pervasive constellation of cognitive-behavioural changes that typify post-acute TBI. This undermines social independence and is associated with poor prognosis. Emotional difficulties and challenging behaviour are characteristic of NBD. Relatives frequently describe their family member as having undergone a personality change. In some cases, aggression and sexually inappropriate behaviour are evident. Stress and burden on family members are immense. It has been estimated that one new TBI case per 300,000 people each year in the UK has severe, persistent behaviour problems that exclude them from mainstream services.[1] As a consequence, at least 200 people per year gravitate to care homes, prison and mental health units that are unable to meet their complex needs.

Neurobehavioural rehabilitation

The National Brain Injury Centre (NBIC) was the UK's first provider to offer rehabilitation to people with TBI and other types of acquired brain injury who also presented with challenging behaviour. Part of St Andrew's Healthcare, the UK's largest not-for-profit mental health care charity, NBIC admitted its first six patients in January 1979. Thirty years later, the service has grown to over 100 beds with separate care pathways for young people, men and women, units that cater for those with very challenging behaviour, and others that offer slow-stream, long-stay rehabilitation, both within a hospital setting and the community. Patients are typically referred because they present with challenging behaviour of such severity to preclude them from mainstream neurorehabilitation services, and often from the communities in which they live.

The treatment model is psychosocial and NBIC was the first service to evolve what is now termed 'neurobehavioural rehabilitation'.[2] This approach acknowledges that challenging behaviour is primarily a product of physical damage to the brain, but recognises this is further shaped by the environment. This can help sustain challenging behaviour, which can be unwittingly maintained by those people charged with the care of a person with a brain injury. This clinical population is not popular with rehabilitation professionals because of their irritating, threatening, and embarrassing behaviour, as well as their general lack of motivation.[3] Consequently, patients with brain injuries may be avoided by staff and carers, and become socially isolated. Unfortunately, while challenging behaviour may be primarily attributable to damaged neural systems, it can be reinforced by environments in which there are limited opportunities for appropriate social behaviour. Under conditions in which people are habitually ignored for long periods, it is possible their only social contact is when staff intervene when managing challenging behaviour. This can inadvertently reinforce and maintain it.

Whilst the environment can unwittingly maintain NBD and social handicap, it can also be manipulated to benefit rehabilitation. Neurobehavioural rehabilitation services attempt to reduce NBD and social handicap by creating an environment in which people are re-taught skills they have lost through brain injury, which are then encouraged and reinforced in the context of everyday behaviour. Treatment interventions work primarily to reverse contingencies that previously maintained challenging behaviour, first by requiring staff to interact with patients who may previously have been ignored, and second, by ensuring social reinforcement is directed at desirable, rather than challenging behaviour.[4] In this way, interventions based on operant learning theory create enriched environments that change the behaviour of people working with challenging brain-injured patients and encourage development of a positive social climate that promotes therapeutic relationships. Provision of these interventions within a highly structured environment encourages new learning, skill acquisition, and promotion of independence, giving patients more choice, control, and freedom as they progress.

The multidisciplinary team

In addition to challenging behaviour, patients admitted to neurobehavioural services invariably have a range of complex needs that are potentially amenable to rehabilitation. For this reason, a wide range of clinical specialists is drawn together to form a multidisciplinary team who work with the patients including neurology, neuropsychiatry, neuropsychology, nursing, occupational therapy, physiotherapy, speech and language therapy, education and dietetics. Following a period of assessment, individual programmes are implemented whose goals are to reduce challenging behaviour to enable patients to benefit from the clinical specialties they had been unable to access previously. All members of the multidisciplinary teams implement these programmes: role blurring and effective communication ensure they are delivered all the time, not just in formal therapy sessions.

Evidence base

Because neurobehavioural rehabilitation was completely new, a great deal of research regarding its effectiveness has been undertaken. In NBIC a diverse research programme that underpins clinical effectiveness and seeks to find new, innovative ways of helping patients has been a characteristic of the service since it opened, much of which is conducted in partnership with universities and other academic centres of excellence. In 1985 the first study that examined outcomes achieved by the initial 24 service users to pass though the NBIC programme was published.[5] Results demonstrated that more than two thirds of this very challenging group had benefited, and a fifth continued to make further gains after discharge.

A very recent review paper has been published which confirms the evidence base and efficacy of the different types of interventions used in neurobehavioural services to help patients manage challenging behaviour.[6] Other studies have demonstrated functional and fiscal benefits of neurobehavioural rehabilitation, including savings to be made in providing care in the medium-to-long term.[7,9]

Assessing individual outcome: SASNOS

A range of bespoke behaviour rating scales and other outcome measures conceptualised for use with people with ABI have been designed by clinicians within NBIC. Most recently, a four year project carried out in collaboration with Swansea University has resulted in publication of the 'St Andrew's-Swansea Neurobehavioural Outcomes Scale.[10] (SASNOS). This new measure fills a gap in the market by providing a global measure of symptoms of NBD and social handicap that has known, robust psychometric properties. Patients are rated by clinical teams on 49 items which measure five major domains of NBD, each of which has 2-3 sub-domains. Standardised scores are computed so domains can be compared. Initial ratings can be used as a baseline to track progress in rehabilitation. They can also be compared with those of neurologically healthy people to help clinicians with setting goals.

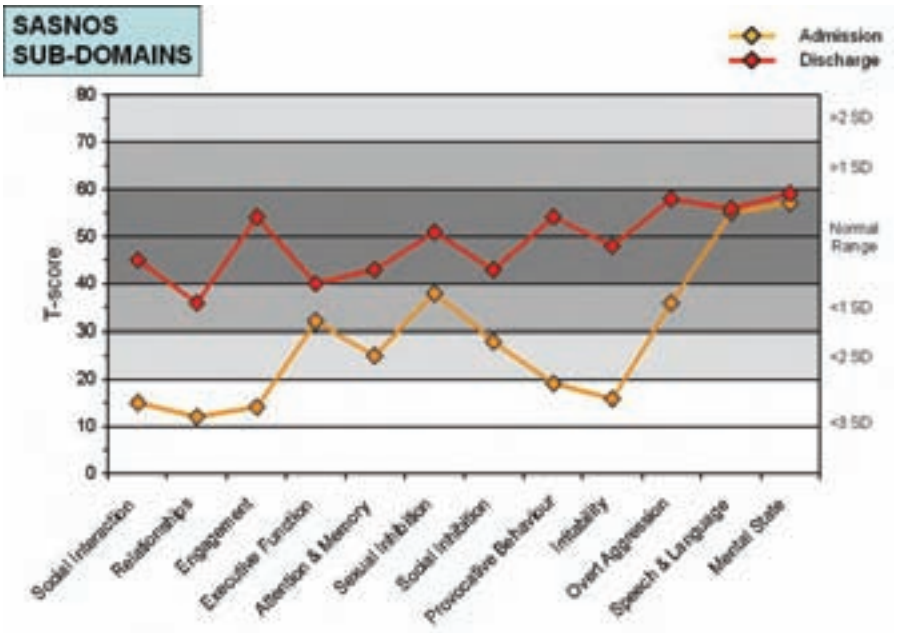

Figure 1: Change in SASNOS ratings in response to participation in neurobehavioural rehabilitation.

Figure 1 illustrates how SASNOS was used to reflect an individual patient's (KJ) response to neurobehavioural rehabilitation. The standardised score plot of symptoms of NBD observed and rated by members of the clinical team during the first two weeks of admission suggested that social handicap was underpinned by difficulties in interpersonal relationships, cognitive function and sexual inhibition and aggression. This plot assisted clinicians to determine KJ's strengths-weaknesses profile, determine the priority of his rehabilitation goals, and design neurobehavioural rehabilitation interventions. A second set of ratings made at discharge show the substantial improvement in these target areas, with symptoms for most sub-domains being rated at levels comparable with the neurologically healthy population.

Conclusion

Finally, it has been independently acknowledged in the literature that it is a mistake to believe that people with acquired brain injury and challenging behaviour can be effectively managed in non-specialist services.[1] Opinion and evidence indicates that admission to specialised neurobehavioural rehabilitation units is required in such cases, and in addition to the clinical benefits this provides the most cost-effective solution. Use of appropriate outcome measures will help determine individual response to rehabilitation, and assist commissioners to benchmark services against one another. SASNOS is free to download and use from the St Andrew's Healthcare website at www.stah.org/services/brain-injury/sasnos.aspx.

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The Relationship Between BP and Pain:

The Nord-Trøndelag Health Survey

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Chronic pain conditions, including headache, constitute large public health problems in most societies, but relatively little is known about their origins. During the last three decades, scientific evidence has accumulated about a relationship between pain and blood pressure (BP), showing that increased BP is related to lower pain sensitivity (so-called hypertension-associated hypalgesia). Most of this evidence stems from experimental studies on animals, in which the effect of BP manipulations on pain behaviour has been investigated, but there are also studies on humans where pain sensitivity has been related to BP levels.

HUNT studies

Relatively little has been known about the relevance of this phenomenon for the most prevalent pain conditions, but in the Nord-Trøndelag Health Survey (the Norwegian acronym is HUNT), where the whole population above 20 years of age in the Nord-Trøndelag county in Middle Norway was invited to participate (approximately 92,000), it has been possible to study the relation between BP and pain on a population level. Three HUNT surveys have been performed till now, in 1984-86, 1995-97, and 2006-08 (HUNT 1, 2 and 3), and the two last surveys in particular included a wide range of health-related questions, in addition to measurements (BP, weight, height and others) and blood and urine samples. In the last two surveys, there was also a study among adolescents (HUNT Youth), covering the age group 13-19 years. The analysis of HUNT 3, when the data were released in 2009, has recently begun, whereas the HUNT 2 data have been thoroughly analysed.

Headache and BP

One of our early publications from the HUNT 2 was performed to test (or rather to disprove) the commonly held notion that headache was related to increased BP. In this paper, we looked prospectively at BP in HUNT 1 as a risk factor for developing headache 11 years later (HUNT 2).[1] In HUNT 1, there was no data on headache, but more than 59,000 respondents had answered questions about painkillers, and we assumed that 41,000 subjects never using such medication had a negligible amount of headache. Of the 41,000, almost 23,000 participated in HUNT 2 eleven years later. As expected, there was no positive association between BP and prevalence of headache. This was, however, not very surprising, since there had already been a consensus agreement expressed by the diagnostic classification of the International Headache Society that moderate to mild hypertension did not induce headache.[2]

It was surprising, however, that the prevalence of headache in general was 30% lower in the group with systolic BP> 150 mmHg compared to those with BP ≤140. Similar, but less clear findings were made in the cross-sectional analysis where

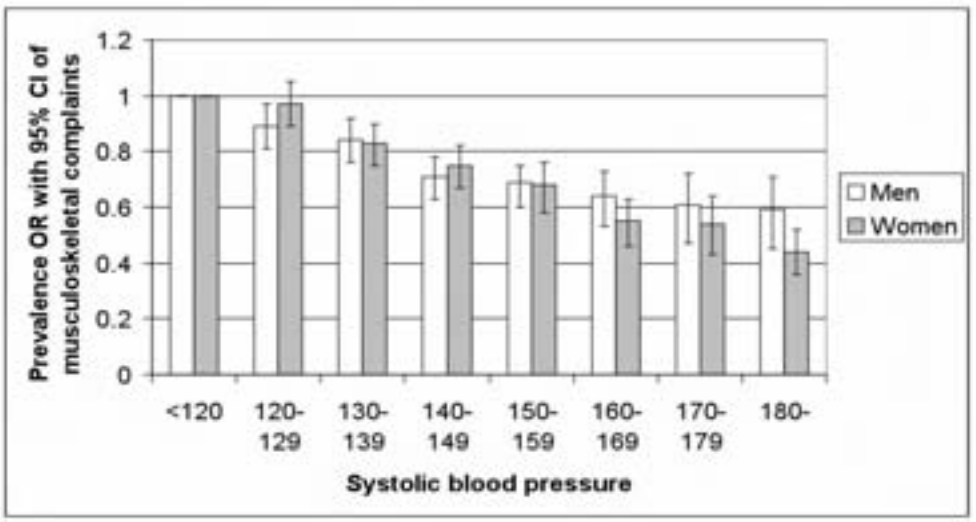

Figure: One-year prevalence of chronic musculoskeletal pain related to systolic BP level among 66140 men and women (From the HUNT study, [2]published with permission from Blackwell Publishing Ltd).

Table: Chronic musculoskeletal pain reported in HUNT 2 specified at different locations related to high BP in HUNT-1 and HUNT 2*. (Reproduced with permission from the Archives of Internal Medicine 6)

Location of musculoskeletal symptoms	HUNT-1				HUNT-2			
	SBP ≥ 160 mm Hg		DBP ≥ 100 mm Hg		SBP ≥ 160 mm Hg		DBP ≥ 100 mm Hg	
	OR#	*(95% CI)*	*OR#*	*(95% CI)*	*OR#*	*(95% CI)*	*OR#*	*(95% CI)*
Neck (n=9,010)	0.7	(0.6-0.7)	0.7	(0.6-0.8)	0.7	(0.6-0.7)	0.7	(0.7-0.8)
Shoulder (n=10,139)	0.6	(0.6-0.7)	0.7	(0.6-0.8)	0.7	(0.7-0.8)	0.7	(0.7-0.8)
Elbows (n=4,284)	0.6	(0.5-0.6)	0.6	(0.5-0.7)	0.6	(0.5-0.7)	0.7	(0.6-0.8)
Wrist/hands (n=6,357)	0.6	(0.6-0.7)	0.6	(0.5-0.7)	0.6	(0.6-0.7)	0.7	(0.6-0.8)
Chest/abdomen (n=2,477)	0.5	(0.5-0.6)	0.6	(0.5-0.7)	0.6	(0.5-0.7)	0.6	(0.5-0.8)
Upper back (n=4,365)	0.5	(0.5-0.6)	0.6	(0.5-0.7)	0.6	(0.5-0.6)	0.6	(0.6-0.7)
Low back (n=8,182)	0.6	(0.6-0.7)	0.6	(0.5-0.7)	0.6	(0.6-0.7)	0.6	(0.6-0.7)
Hip (n=7,257)	0.6	(0.6-0.7)	0.7	(0.6-0.8)	0.7	(0.6-0.7)	0.7	(0.6-0.7)
Knees (n=7,263)	0.7	(0.6-0.7)	0.8	(0.7-0.9)	0.7	(0.6-0.8)	0.7	(0.6-0.8)
Ankles/feet (n=5,932)	0.7	(0.6-0.7)	0.8	(0.7-0.9)	0.6	(0.6-0.7)	0.7	(0.6-0.8)

§ High BP defined as Systolic BP (SBP) ≥ 160 mm Hg and diastolic BP (DBP) ≥ 100 mm Hg.

Odds ratio (OR) with 95% CI. The reference group (OR=1.0) are individuals with normal BP (SBP < 140 mm Hg, and DBP < 90 mm Hg, respectively). Adjusted for age, gender, education, and use of antihypertensive drug therapy.

data on both headache and BP came from the HUNT 2 study. A later, more thorough analysis of the HUNT data confirmed these results.[3] The most clear cut relation was found for the variable pulse pressure (ie the difference between systolic and diastolic pressure) showing that a large pulse pressure was related to a low prevalence of headache. This was true for both sexes, for both migraine and non-migraineous headache, and in both the prospective and the cross-sectional analyses. It could not be due to some effect of BP medication since the pain-BP-relationship was most marked for those not using antihypertensives in all the analyses.

A similar inverse association between headache and BP on a population level has also been demonstrated by other groups, in Brazil, France and Iceland (for references, see 3). We have also recently confirmed the findings in another HUNT 2 cohort among adolescents (HUNT Youth),[4] although this cohort was smaller (<6000), and the relation more complex to analyse because the headache prevalence increases markedly with age in this age group.

Chronic musculoskeletal complaints and BP

The HUNT 2 also contained data on chronic musculoskeletal complaints (cMSCs) (ie pain in one part of the body lasting more than three months during the last year). CMSCs were found to be comorbid with headache in the sense that such pains occurred almost twice as often among those with either migraine or non-migraineous headache compared to the general population.[5]

For cMSC, the relation to BP was similar to the one found for headache.[6] The Figure shows how the prevalence decreases gradually with increasing systolic BP in this population of more than 66,000 individuals. It could also be demonstrated that those with low BP (systolic < 140 mmHg and diastolic < 90 mmHg) had much higher prevalence rates than those with high BP (systolic ≥160 mmHg or diastolic ≥ 100 mmHg), in all parts of the body (Table). The effects were large, with ORs from 0.4-0.8, i.e. from 20% to 60% lower prevalence rates among those with the highest BP values. As was the case with headache, the effects were more marked in the prospective than in the cross-sectional analyses.

In the literature, there is less epidemiological evidence about a BP-pain relationship for pains other than headache, but it has been found that hypertensive patients experience less intense pain during angina and myocardial infarction then the normotensive patients (for discussion, see7)

Hypertension-associated hypalgesia

This phenomenon is the most likely explanation for the inverse relation between BP levels and prevalence of the pain conditions demonstrated in the HUNT survey. The phenomenon is well known as a part of the "fight or flight reaction", in which BP increases as pain sensitivity decreases, in addition to many other changes (For review, see 7-9). Several studies have shown a diminished perception of painful stimuli in hypertensive animals, independent of the method used to increase BP (by pharmacological means, increasing salt intake, or with surgery to renal arteries) or to deliver nociceptive stimuli. This effect can be abolished by cutting the nerves from the baroreceptors. It is also present in rats with spontaneous hypertension compared to normotensive rats, and in humans, patients with hypertension have been shown to have decreased pain sensitivity to dental pulp stimulation. This phenomenon is also present within the normotensive range, and it seems to be mediated by endogenous opioids as the hypalgesia can be blocked by naloxone.[7]

There is probably a genetic influence on this pain-BP relation, as it is possible to breed rat strains in which the relation is not present. Also, the relation may not be one of simple cause and effect, as it has been shown that in spontaneously hypertensive rat strains, there is hypalgesia at a young age, before the hypertension develops. Similarly, among humans it has been found that pain sensitivity among 14 year olds can be used to predict BP at the age of 22.[10] Importantly, it seems that the pain-BP association can be reduced or abolished by chronic pain.[11] This may explain why the relation was more evident in the prospective HUNT analyses, where BP was measured in pain-free individuals and related to pain conditions 11 years later, than in the cross-sectional analyses where BP was measured among subjects both with and without pain.

As to the mechanisms for hypertension-associated hypalgesia, there is evidence that stimulation of the baroreflex arch due to increased BP may inhibit pain transmission at both spinal and supraspinal levels, possibly due to interactions with brain areas that modulate nociception and cardiovascular reflexes in the brainstem, e.g. the nucleus tractus solitarii, the locus coeruleus and the periaqueductal grey substance, areas known to be involved in the regulation of both pain and BP.

In some analyses we found that the pulse pressure had an even clearer relationship to pain than systolic BP. It has previously been shown that increased pulse pressure in

healthy middle-aged subjects is associated with reduced baroreflex sensitivity, which has been shown to correlate with reduced sensitivity to pain. This accords with a case-control study by our group, demonstrating increased baroreceptor senisitivity among female migraineurs,[12] but another study has shown decreased baroreflex sensitivity in migraine.[13]

Undoubtedly, chronic pain conditions in different body parts may also have "local" causes in various peripheral tissues (muscles, joints, intestines, vessels, meninges etc), and the relative contribution of nociceptive impulses from the periphery and of centrally determined sensitivity to pain may vary. However, according to the HUNT studies, the effect of hypertension-associated hypalgesia on pain in the population is large, the difference between groups with high and low BP being from 20 to 60% in our analyses, both for headache and cMSCs.

Conclusion

The HUNT studies have, with epidemiological methods, convincingly shown that the mechanisms involved in hypertension-associated hypalgesia are operative in the common pain conditions in the population. These mechanisms are not of minor importance but can explain a substantial part of the variation in pain between individuals. We are eager to explore these mechanisms further in the HUNT 3 study, where we have even better prospective data, high quality brain MRI images of a sample of the population, and possibility to do genetical analyses. More knowledge about the precise mechanisms mediating the relation between BP and pain conditions could lead to better prevention and treatment of these prevalent, costly and disabling disorders. ◆

ACKNOWLEDGEMENT

We are grateful to Blackwell publishing Ltd for the permission to reproduce the Figure, and from the Archives of Internal Medicine for permission to reproduce the Table.

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PREVIEW: WCN 2011 – Neurologists from all over the world to meet in magical Marrakesh

With the theme "With Africa, for Africa", the XXth World Congress of Neurology (WCN) 2011 will provide neurologists from Africa and around the globe with a unique opportunity to share knowledge at the world's largest neurology event. The congress will take place on 12-17 November 2011 in Marrakesh, Morocco.

WCN's scientific programme features world-class speakers and a diverse array of neurological topics as well as several teaching courses, with the ultimate aim of finding real solutions to improve the long-term outcomes for patients with neurological disorders.

In addition to the scientific programme, WCN 2011 will feature the dynamic Tournament of the Minds competition and lively social events. Participants will also have the opportunity to take part in tours of beautiful Marrakesh and its surroundings.

"Come to Marrakesh, a cultural, artistic and gastronomical capital," writes Dr. Vladimir Hachinski, President of the World Federation of Neurology, in his invitation to colleagues.

"The speakers at the XXth WCN have been selected not only for their expertise, but because they can convey the advances in their area to neurologists specialising in their field. The Congress provides wonderful updates in all major areas of neurology and many opportunities for interaction."


Marrakesh by Evening, Djemaa el-Fna Square.

Scientific Programme

The scientific programme will feature an impressive line-up of international experts. The bulk of the programme will be made up of main topic sessions, each with a number of lectures under a common theme. Many of the sessions and lectures will focus on the congress theme, "With Africa, for Africa," and will highlight the achievements of African neurologists and the challenges they face. These include "History of Neuroscience in the Maghreb" on Monday, November 14, and "Neurological Care Policy in Africa" on Wednesday, November 16.

Daily plenary sessions will include the following topics: The Mirror Neurons and the Cognitive Brain (Giacomo Rizzolatti, Italy); The Future of DBS in Neurology and Psychiatry (Alim L Benabid, France); Challenges in Adopting International Guidelines Into National Stroke Programmes (Lu Chuanzhenn,China); Neuroaesthetics: Artistic Creativity and the Brain (Sémir Zeki, UK); and Vertigo and Balance (David Zee, USA). Also included under the plenary sessions are the Named Orations: Melvin D Yahr Lecture (presented by Anthony Lang, Canada); the Eddie and Piloo Bharucha Lecture (Elly Katabira, Uganda); Soriano Lecture (Christian Elger, Germany); and the Fulton Symposium Soriano Lecture (Hidehiro Mizusawa, Japan).

Teaching Courses

Teaching courses are another highlight of the rich scientific programme. The courses will run throughout each day of the congress in parallel to the rich and varied scientific programme. Participation in a course will translate into separate CME credits, in addition to the CME credits given for participation in regular congress sessions.

The course content will include a range of clinical and more general topics. The clinical subject matter will include epilepsy, stroke, infection, sleep, pain, child neurology, movement disorders, and dementia, among others. These sessions will feature practical demonstrations, using equipment specific to the condition or disease under discussion, as well as live demonstrations on patients. But there will also be sessions that address broader issues, such as a session on advocacy by the American Academy of Neurology, neurological education, and how to write a scientific paper. Teaching courses will also focus on challenges facing neurologists in low-income countries, such as one titled, Dementia in the Developing World.

The World Stroke Organization will present a free session titled ABC Cardinal Principles of Stroke Management, and other free courses will deal with examining a comatose patient; tremors; diplopia; and myopathy. The International Working Group of Young Neurologists and Trainees will host a workshop for young neurologists.

The choice of subject matter reflects the emergence of new therapies and diagnostic technology, such as Botox, deep-brain stimulation, EEG video, interventional radiology, and neuroimaging, as well as the more refined distinctions between the subspecialties, such as sports medicine, brain injury, neurorehabilitation, and neurocritical care.

The congress secretariat will publish a full syllabus for each course ahead of the congress starting date.

Tournament of the Minds

In addition to enjoying a high-quality scientific programme and a magical host city, participants will be able to exercise their brains in the Tournament of the Minds.

The Tournament of the Minds is a unique opportunity to interact with colleagues, test intellectual tenacity, and demonstrate national pride, all while competing in country teams. As such, the aim of the Tournament of the Minds is to provide an experience that is both educational and entertaining for participants. This is the fourth time the tournament has been organised by the World Federation of Neurology at a World Neurology Congress.

WFN member societies are invited to enter a team of four Neurologists in the Tournament. Teams will compete with each other in a knockout competition, to answer questions on a range of Neurological topics based on clinical cases from around the world; the questions will focus on visual material, videos and stills, with a minimum of text. Tournament judges will award the winning team an attractive prize.

To participate, please contact the president of the relevant local Member Society who is responsible for coordinating national teams.

For more details about WCN 2011, please visit the congress website: www.wcn-neurology.com.

RAatE 2011

Recent Advances in Assistive Technology & Engineering Conference and Exhibition

Monday 28th November

University of Warwick Conference Centre, Coventry

Delegate Registration

RAatE 2011 is the only UK conference focused on the latest innovations and developments in Assistive Technology. This conference will be of interest to everyone who uses, works with, develops or conducts research on Assistive Technologies (AT).

This year's event is run in association with the Health Design & Technology Institute at Coventry University. The HDTI seeks to develop new products and new systems of care provision for the assisted living sector.

The conference program has, over the past years, regularly included new technological developments, service innovations, results of formal research projects, service based research and development and a wide range of other stimulating topics.

Known as a friendly and productive conference, RAatE offers you a chance to meet and share knowledge and experience with other people working in AT.

RAatE 2011 is delighted to announce this year's keynote speaker as Dr. Roger Smith, Fellow of RESNA and Professor of Occupational Science and Technology at the College of Health Sciences and the University of Wisconsin, Milwaukee.

Dr Smith has published and presented in the area of disability access, assistive technology and functional performance measurement and has also secured over $8m of funding for research and projects relating to disability and rehabilitation.

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November 30, 2011, Marbella, Spain

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The European Charcot Foundation is pleased to announce that they will provide an unrestricted educational grant to sponsor a limited number of young investigators with a travel grant of €1500,- to attend the University Classes in Multiple Sclerosis VIII.

Young investigators are invited to apply before October 15, 2011. Conditions for applications are available on our website.

EUROPEAN CHARCOT FOUNDATION
SYMPOSIUM

Towards Personalized Treatment in Multiple Sclerosis

December 1, 2 and 3, 2011, Marbella, Spain

17th European Charcot Foundation Lecture

Prof. X. Montalban

'Towards Treatment of Persons with Multiple Sclerosis: on detour and access'

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- Tools for prognosis
- Treatment heterogeneity, targets and risks
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- Personalized treatment, partnership and disease complexity

For detailed information and registration visit our website www.charcot-ms.eu

Basal Ganglia at the Base of the CN Tower

Conference details: 5-9 June 2011; Movement Disorders Conference, Toronto, Canada. ***Reviewed by:*** Dr Tom Foltynie, Consultant Neurologist, Queen Square, London.

So what's new in Movement Disorders? Of course there's a growing trend to keep new unpublished data to yourself these days, lest your rivals and competitors get wind of your latest breakthrough, but despite this, MDS 15 in Toronto had plenty of novelty.

PD Mechanisms and Pathogenesis

You come all the way to Canada and yet it turns out that one of the star talks of the week hails from Sheffield, UK. I'd not heard Peter Redgrave speak before, but he gave a delightful talk as part of an Obeso/ Brown/ Redgrave basal ganglia trio. He explained the evolutionary existence of the basal ganglia well ahead of the development of the cortex and the fact that it has a clear role in action selection in response to diverse environmental stimuli. He elaborated that we should think of our behaviour as either "goal directed " or "habitual", with distinct anatomical circuits from cortex to basal ganglia. He proposed that Parkinson's disease (PD) patients are trapped in the goal directed behaviour circuit, and have lost the habitual pathways responsible for automatic walking, postural reflexes and sequential motor programmes. There must also be distortion at the point of convergence between these circuits, explaining why even voluntary movements become slower and more effortful.

We have long known about interrelated pathways of proteasomal dysfunction and mitochondrial dysfunction in the neurodegenerative process. It seems that mitochondrial dysfunction and removal (mitophagy) and ongoing replenishment through biogenesis is repeatedly being identified as critical in PD pathogenesis. Serge Przedborksi gave a useful review of the last 20 years progress since MPTP toxicity was first identified, all the way to the recent identification of PGC1α and PARIS (parkin interacting substrate) all with respect to the mitochondrial pathways. To add further detail, David Park reviewed his work on Calpain, cdk-5 and prx-2 that relate oxidative stress mediated by mitochondrial dysfunction with subsequent cell death, while Valina Dawson reviewed some of her unpublished cell biology that has been recently discovered, relating oxidative stress as a cause for mitochondrial dysfunction and subsequent nuclear DNA damage. A key part of this pathway is PARP-1, and PARP-1 inhibitors that cross the blood brain barrier have been identified and shown to be protective in vitro and in animal models of PD. The field has also been greatly advanced by the work of Heidi Macbride who showed real time fission/fusion and budding of mitochondria, and their dynamic movement through the cytosol and into and out of the nucleus. A novel PD gene VPS35 appears to play a role in the process of mitochondrial budding.... watch out for this.

CN Tower, Toronto, Cananda.

Tom Foltynie.

The take home message seems to be that PD pathogenesis undoubtedly involves proteotoxicity, mitochondrial dysfunction and neuroinflammation, all interacting with multiple points for potential therapeutic intervention.

Therapeutics

Carl Clarke presented the evidence regarding treatments for advanced PD. Despite its widespread use, we have little actual "Evidence" to justify the use of Apomorphine, evidence from only small numbers of patients for Duodopa but data from trials involving large numbers of patients undergoing Deep Brain Stimulation (DBS). While experienced clinicians have plenty of their own anecdotal experience to underwrite the use of all three of these agents in appropriate patients, will this evidential thin-ice jeopardise our ability to offer these treatments in these harsh economic times? Dr Clarke predicted that cost effectiveness data that is soon to emerge from the PD surg trial may further jeopardise the availability of these treatments for advanced PD patients – I for one, really do hope not.

Dr Clarke also discussed the plausibility of a randomised trial comparing the efficacy of these three expensive treatments, and pointed out that this is highly unlikely given the need for companies to protect their commercial interests, and the impossibility of effective treatment blinding. Even if financed, such a trial would prove difficult given that different patients and clinicians already have well established prejudices/ preferences regarding these disparate treatments. In my own opinion, I have no doubt that one size does not fit all in advanced PD and an attempt to define choice one, two and three that suits all comers is far too simplistic. Long term improvements in function and quality of life can be highly variable in response to these treatments depending on patient phenotype such as age / severity of motor symptoms / motor phenotype / extent of cognitive impairment / other non motor symptoms.

To complicate the PD therapeutic horizon further, there is no shortage of new and evolving treatments for PD. Olivier Rascol gave a whirlwind tour through these, both dopamine and non-dopaminergic, oral and inhaled (Apomorphine) as well as the surgical (particularly the gene therapy approaches). There is growing interest in the use of the cholinesterase inhibitors or methylphenidate as treatments for dopa refractory falls in PD, and preliminary data needs to be confirmed or refuted in future trials.

I was keen to hear whether there have been further developments in DBS and indeed there were a whole bunch of posters demonstrating the long term benefits of Sub-Thalamic nucleus (STN) DBS in PD, and highlighting its use in Chorea-acanthocytosis, Tourette syndrome and many forms of dystonia. Jerry Vitek reminded us of the possible under-investigated merits of Globus Pallidus externa (GPe) DBS, and Paul Krack reviewed the non-motor issues surrounding the use of DBS. The most innovative talk came from Peter Tass who described a novel way of applying different frequency DBS to adjacent populations of cells to de-synchronise their activity and lead to prolonged normalisation of firing patterns, thus making a huge saving on electrical energy required

and thus battery life. Perhaps DBS might become cheaper after all.... For me though the biggest audience cheer of the week came from the dry humour and razor critique of DBS publications relating to the Pedunculopontine nucleus by my colleague Marwan Hariz. He reminded us that publishing was not the be-all and end–all of science; we should also take time to read, criticise and reflect on new discoveries both as clinicians and most importantly as peer reviewers.

VO Games

Tony Lang and Kapil Sethi, prior to performing their ritual humiliation of the expert panel, explained that the official Olympic committee have opposed the use of the term "Video Olympics" at the MDS, lest it leads to confusion between the real Olympics and our Annual MDS meeting. A needless fear given that cases were all much more straightforward this year, with a clear learning point from each one -

1. Methylmalonic aciduria causing chorea (with the clue being the accompanying progressive renal failure).
2. Presenilin mutation causing an autosomal dominant dementia, but also with ataxia, parkinsonism and extensor plantar responses.
3. MELAS in a monk with unusual (possibly myoclonic) orofacial movements, accompanied by diabetes and gait freezing
4. (For the audience alone) – A young girl voluntarily and repetitively shaking her head – to provoke photosensitive seizures.
5. Alpha mannosidosis causing a progressive myoclonic ataxia with mental retardation and hearing loss – the clue being the accompanying bony deformities.
6. SCA-2 manifesting as an ataxia with oculomotor apraxia.
7. DRPLA with a fairly typical presentation but unusual Iron deposition in the cerebellum seen using gradient echo MRI- possibly related to a previous subdural haemorrhage.
8. Marchiafava Bignami causing acute parkinsonism with characteristic callosal atrophy and white matter change.
9. Kufs disease presenting as autosomal recessive young onset PD and a neuroleptic malignant (type) syndrome following L-dopa administration - diagnosed on axillary skin biopsy - why did they think to do this?
10. Focal seizures in Wilson's disease - not all new problems in Wilson's are related to drug side effects & copper leaching.
11. Alexander's disease presenting with ataxia, and a palatal tremor (once sought), showing the typical "tadpole" sign on MRI.
12. Sepiapterin reductase deficiency presenting with Dopa responsive dystonia (as you'd expect), but with the lesson that serotonergic dysfunction also needs treatment.
13. An ataxia telangiectasia–like disorder in 2 patients that looked pretty similar to myoclonus dystonia, and doesn't always feature telangiectasia.
14. Molybdenum cofactor deficiency – to be added to the short list of causes of lens dislocation, but causing massive swelling and signal change through the basal ganglia with abulia and a complex movement disorder. I didn't get this one...

To summarise, it seems clear that multiple mechanisms of variable relevance in variable pathways are involved in PD pathogenesis. It's not surprising we see a clinically heterogeneous disease. And we must retain our clinical skills – in our sub-specialty we have a huge number of treatable conditions that require accurate diagnoses. See you in Dublin next June. ◆

Models in Parkinson's Research: Are we addressing the right questions?

Conference details: 18 May 2011; London, UK. ***Reviewed by:*** Dr Rosemary Fricker, Senior Lecturer, Keele University, UK.

The Seventh Research Conference of the UK Special Parkinson's Research Interest Group (SPRING) brought together leading scientists and clinicians from across the globe to debate the value of current models of Parkinson's disease (PD). The aim of this one day meeting was to discuss the usefulness of current PD models in broadening our understanding of the disease process, and as a tool to test future therapies.

The first session set the scene by identifying the key features of PD that need to be reproduced in models. Jose Obeso (Navarra Medical School, Spain) and Tamas Revesz (UCL, London) described the complexity of neurodegeneration in PD, which affects many neuron subtypes and not solely the nigrostriatal dopamine neurons, causing a long phase of preclinical pathology, and evolving not only the cardinal motor symptoms but also cognitive impairments and dementia seen in PD. In addition, neuronal pathology appears as Lewy neurites in neuronal processes as well as Lewy bodies within cells, suggesting that problems with neurotransmission may be a key component of the disease process. There was some disagreement as to whether PD pathology is synchronised and multisystemic, or if it spreads in a caudo-rostral fashion from one region to another (the Braak hypothesis). However, both speakers concluded that an ideal animal model should incorporate: age-dependent and focal loss of dopamine neurons with associated motor dysfunction, Lewy body and Lewy neurite pathology, and progressive neurodegeneration that represents the non-motor components of the disease.

The second session focussed more specifically on rodent models of PD. Tim Greenamyre (Pittsburgh University, USA) gave an eloquent overview of the rotenone model developed in his laboratory, highlighting the strengths of this toxin-induced neuron degeneration. Rotenone targets complex 1 in the mitochondria, inhibiting mitochondrial respiration and thus energy metabolism. Greenamyre's group have observed iron deposition in the substantia nigra pars compacta (SNc) following rotenone administration, suggesting that iron may contribute to the pathology of the disease.

Peter Magill (Oxford University) reported work to elucidate the nature of neuronal firing patterns in the basal ganglia circuitry, and how these are affected in PD to cause an increase in bradykinesia and rigidity. Injecting 6-hydroxydopamine into the basal ganglia (the 6-OHDA rat model) causes large changes in the β oscillation firing patterns of basal ganglia neurons, with increased synchrony of pairs of neurons, particularly within the Globus Pallidus (GP). A single GP neuron can innervate neurons in the GP, entopeduncular nucleus, subthalamic nucleus and substantia nigra pars reticulata. Thus, death of SNc dopaminergic neurons may cause whole networks of neurons to undergo changes in rhythm, oscillation and synchrony and, by firing at the wrong time or in the wrong place within the basal ganglia, cause many of the symptoms of PD.

Rosemary Fricker is a Senior Lecturer at Keele University Medical School. Her current research is focussed on identifying novel proteins that influence the differentiation of stem cells to dopamine neurons, for the treatment of Parkinson's disease.

Dysfunction of the proteasome in clearing unwanted proteins from neurons is a candidate pathway that may be involved in the development of idiopathic PD. Dr Lynn Bedford (Parkinson's UK Senior Fellow, Nottingham University) presented her work to develop a genetic mouse model, by conditional deletion of the 26S proteasome in tyrosine hydroxylase positive neurons. Mice with this deletion show progressive neurodegeneration and the formation of Lewy-like inclusions containing α-synuclein, ubiquitinated proteins and mitochondria. However, when these mice were crossed with α-synuclein null mice, lack of α-synuclein had no effect on Lewy body formation, suggesting that it may not be a key player in the process.

The third session of the conference focussed on modelling PD in other animals and human cellular systems. Tilo Kunath (Parkinson's UK Senior Fellow, Edinburgh University) presented research to generate induced pluripotent stem cell lines (iPSCs) from a patient with familial PD caused by triplication of the SNCA gene encoding α-synuclein. These iPSCs were differentiated into midbrain dopamine neurons and were shown to express double the levels of α-synuclein when compared to neurons derived from iPSCs generated from an unaffected family member.

Animals such as zebra fish, *Caenorhabditis elegans* and *Drosophila* have been used to model neurodegenerative disease and offer advantages such as short life cycles, relatively straightforward gene manipulation, simplicity or easier visualisation of neuronal circuitry, and the potential to screen large numbers of animals for pathology or potential therapies. Oliver Bandmann (Sheffield University) described techniques by his group for transient knock down of the PD-related genes *DJ-1, parkin and PINK1* by injecting antisense oligonucleotides into zebrafish embryos at the single cell stage. This morpholino strategy can generate stable lines that display key features of PD such as mitochondrial dysfunction and loss of dopaminergic neurons.

Anton Gartner (Dundee University) presented research to generate PD models in *C.elegans* via *α-synuclein* gene mutation or using the 6-OHDA toxin to induce neurodegeneration. Using the 6-OHDA model to screen for neuroprotective genes, they have found that the membrane protein tetraspanin-17 may have a neuroprotective role for dopamine neurons depending on its specific expression level. Alex Whitworth (Sheffield University), presented data on *Drosophila* models of PD derived by mutating the genes: *PINK1* and *Rhomboid-7*. Their research suggests that aberrant fusion of mitochondria stops their degradation and this may play a role in neuronal death in PD.

The conference ended with an open discussion between the audience and a panel of experts: Paul Bolam, Oxford; Kieran Breen, Parkinson's UK; Jose Obeso, Navarra; Richard Wade-Martins, Oxford; and Rosemary Fricker, Keele. Many issues were raised including: is PD a syndrome rather than a single disease, and should we therefore be developing more complex models, or indeed using humans as models? Which models might be most useful for the pharmaceutical industry, enabling better therapeutics to be developed for early PD? One of the problems discussed was the lack of biomarkers for models, particularly for in vivo imaging of rodents and primates to assess neuron degeneration and repair. The final conclusion? We should continue with both current and new avenues of research, as all models are good but none are yet sufficient. ◆

This editorial is sponsored by Biogen Idec UK Ltd

Evolving Strategies for the Management of Patients with MS

Biogen Idec Nurse Academy 2011

Friday 1st & Saturday 2nd July, Wokingham and Friday 8th & Saturday 9th July, Manchester

The Biogen Idec Nurse Academy returned this year promising to deliver a diverse and challenging programme on a range of topics spanning the MS field. MS nurses from around the United Kingdom gathered in Manchester and Wokingham to hear leading clinicians discuss new data, emerging products and evolving opinion on the management of MS. Some key excerpts from the meeting are presented below.

Research has suggested that 40–60% of patients with MS will develop cognitive impairment. Whilst this may be graded as mild in 80% patients, even mild cognitive impairment can have a significant impact on the patient and their family and friends. It can be extremely frightening, with some patients worrying they are going insane. Dr Anita Rose, Consultant Neuropsychologist at Titleworth Neuro, provided a useful insight into dealing with cognition problems in patients with MS in her presentation 'Am I Mad, Crazy, Stupid or Nuts?'. Cognitive problems can not only cause relationship issues and impact on employment but, in the later stages, can raise concerns around safety, independence and the ability to self care. As a symptom, cognition is often ignored, possibly due to the stigma associated with this type of problem and possibly because it may not be apparent on initial assessment – it frequently remains a 'hidden' symptom. Whilst assessment of cognitive impairment at the point of diagnosis does not routinely occur in patients in the UK – many HCPs believe it should be advocated. Dr Rose pointed out that MS nurses can get involved in this and highlighted that the Montreal Cognitive Assessment (http://www.mocatest.org/) is a useful test which is free, easily accessible and is easy to complete with patients. There are a number of helpful interventions which can be discussed with the patient depending on their symptoms. For example, if a patient mentions that they are suffering with attention problems when trying to complete a task like doing the shopping, advise them to go to the supermarket at a time when it is less busy so that distractions such as noise and crowds of people will be reduced.

> *"Intervention can have a positive impact on quality of life, mood, employment and relationships"*
> *Dr Anita Rose*

Figure 1: The negative cycle of thought, emotion and behaviour (adapted from Kingdon & Turkington, 2005).

Also encourage them to remove distractions they face when at home, for example by turning off the television or radio. If a patient is having trouble with their memory, encourage them to modify their environment by using signposts and labels around the house or encourage the use of memory aids such as post-it notes or diaries. Activities including brain training programmes can also help with keeping the brain active and some research shows this can have a positive effect on cognition. In addition to advising interventions for cognitive problems, it is also important to assess for confounding factors such as depression and stress. It is thought that there is a 50% lifetime risk of suffering from depression if a person has MS. This can have a dramatic impact on cognition and can usually be remedied.

Alongside pharmacological treatments there is also a wealth of non-pharmacological options which offer the potential to help patients with MS. Peter Phiri, a BABCP accredited Cognitive Behavioural Therapist in Southampton, discussed one such option – cognitive behavioural therapy (CBT).

CBT can help patients with MS to manage pain and fatigue, reduce the emotional impact (such as low mood or high stress levels) and reduce depression and anxiety.

It can also improve treatment adherence and help the patient to develop alternative ways of coping with functional problems. As people at the forefront of MS care, there are a number of advantages for MS nurses using CBT with their patients:

- they have already fostered excellent relationships with them
- they are credible and dependable
- they are trained in interviewing skills
- they are aware of other treatments the patient may be receiving
- they often have 1:1 sessions with their patients.

CBT is based on formulating the patients' problems using a cognitive model. It requires a sound therapeutic alliance and structure and involves the participation of both the therapist and patient. The therapy is goal orientated and problem focused with the initial target being the 'here and now'. The aim of CBT is to teach the patient skills they can use when identifying, evaluating and responding to their cognitive biases, beliefs and assumptions. Figure 1 shows how negative thoughts, emotions and behaviours can become cyclical.

CBT change methods which can be used with patients include developing a pleasure-predicting sheet, on which the patient writes down the activities they plan to do and how much pleasure they estimate they will experience. Once the activity is completed the patient writes down how much pleasure they actually experienced and they can then compare the two ratings and consider the reasons they are different/the same. Other change methods might involve use of a thought diary on which the patient can record the situation, their mood and the intensity of the mood. The therapist will help the patient develop a balanced alternative view taking in to account the evidence both for and against that particular thought. The patient then rates how much they actually believe the alternative balanced thought on a scale of 0 (i.e. they don't believe it) to 100 (i.e. they totally believe it). This is followed by the patient re-rating their mood. This form of cognitive restructuring allows for a shift in mood, reducing the intensity of distress. The therapist and the patient collaboratively develop a behavioural experiment to test out alternative thought. Once problems have been defined and clarified achievable goals can be set and solutions implemented.

Also at the Nurse Academy, Biogen Idec introduced the Avonex PEN[1] (interferon beta-1a). The PEN addresses some of the issues that patients face when considering injectable therapy for the treatment of their MS. Whilst treatment frequency may be the initial

> *"CBT is a talking therapy that asserts connection between the way we think (cognitions), feel (emotions), and behave (behaviours) and our physical bodily sensations."* Peter Phiri

[1]Avonex (interferon beta-1a) Prescribing Information may be found to the right.

> *"CBT aims to break cycles of negative thoughts by working with the patient and empowering them to make informed decisions."* Peter Phiri

concern, needle size can also act as a deterrent to some patients, with larger needles perceived to be more difficult to administer and more painful. Ease of injection is a primary concern. Self injection may give patients greater independence and empower them to feel more in control of their disease and should be facilitated where possible. In MS, autoinjectors may help to simplify the injection process and reduce injection-related anxiety. There was discussion and a demonstration of the new Avonex PEN which may provide such benefits to patients already using Avonex. The Avonex PEN uses a smaller needle than the Avonex pre-filled syringe and is designed to simplify the injection process, reduce injection anxiety and improve patient independence.

Caroline D'Arcy, an independent MS Specialist Nurse, who previously worked in the NHS, presented data on the annual audit of the natalizumab[2] service at Charing Cross Hospital. The audit was designed to help patients, medical and nursing staff and funders understand the effects of natalizumab and to provide a platform for any recommendations or suggestions about the service to be discussed and highlighted. Data on natalizumab and the natalizumab infusion service were collected, analysed and presented at a patient study day. The study day which had taken place in March last year, found 98% of attendees found the day valuable and 92% saying that they would come again. This year's audit found that natalizumab treatment is being started earlier than previously, is being used within the guidelines specified by NICE, and is being used in patients who are relapsing frequently. In terms of the natalizumab service itself, 98% of patients said they had seen the MS nurse and 98% found it valuable. Whilst 86% of patients had seen their neurologist, 56% of patients would like to see their neurologist more often. Since the audit in 2010, access to neurologists has increased and the infusion room has been changed to a new, more spacious area which patients prefer. In terms of clinical outcomes, the observations from this audit were consistent with those from previous clinical studies of natalizumab. Treatment with natalizumab was shown to reduce relapse rate over two years, lead to stability of progression of disability and reduce magnetic resonance imaging (MRI) activity. With 189 patients being treated with natalizumab, Charing Cross Hospital is the largest infusion centre of its kind in the UK. Annual audits will enable the natalizumab service to continue to improve and serve patients to maximum potential.

The Nurse Academy was a successful and engaging meeting which provided useful insight into a number of key areas of MS care. The meeting provided the attendees with the opportunity for lively and active debate with their peers as well as the opportunity to discuss current issues with leading clinicians.

The views expressed by the speakers are not necessarily those of Biogen Idec UK Ltd.
Job code: BI-PAN-0180
Date of preparation: July 2011

[2]Tysabri (natalizumab) Prescribing Information may be found to the right.

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Prescribing information: TYSABRI® (natalizumab)
Please refer to the Summary of Product Characteristics for full prescribing information.
Indications: Single disease modifying therapy in highly active relapsing remitting multiple sclerosis for the following patient groups: Patients with highly active relapsing remitting multiple sclerosis or patients with high disease activity despite treatment with interferon-beta. **Dosage and administration:** TYSABRI therapy is to be initiated and continuously supervised by specialised physicians experienced in the diagnosis and treatment of neurological conditions; centres should have resources for the management of hypersensitivity reactions and timely access to MRI. TYSABRI 300mg is administered by IV infusion once every 4 weeks. Infuse the diluted solution over approximately 1 hour at 2ml/min. Observe patients during infusion and for 1 hour afterwards for signs and symptoms of hypersensitivity reactions. **Contraindications:** Hypersensitivity to natalizumab or to any of the excipients; progressive multifocal leukoencephalopathy (PML); patients with increased risk of opportunistic infections, including immunocompromised patients (including those currently receiving immunosuppressive therapies or those immunocompromised by prior therapies, e.g. mitoxantrone or cyclophosphamide); combination with interferon-beta or glatiramer acetate; known active malignancies; children and adolescents under 18 years. TYSABRI is not recommended for use in patients aged over 65 years. **Warnings and precautions:** PML; use of TYSABRI has been associated with increased risk of PML. The risk increases with treatment duration, especially beyond 2 years; if the patient has received prior immunosuppressant treatment and/or if the patient is anti-JCV antibody positive. For risk stratification prior or during TYSABRI treatment, anti-JCV antibody testing may provide supportive information. Before initiation of treatment with TYSABRI, a recent (usually within 3 months) MRI should be available and should be repeated yearly. Patients must be monitored at regular intervals throughout. If PML is suspected, further dosing must be suspended until PML has been excluded. If the symptoms are suggestive of PML, or if any doubt exists, further evaluation, including MRI (compared with pre-treatment MRI) and repeat neurological assessments should be considered. Once PML has been excluded, dosing of TYSABRI may resume. If patients develop PML, the dosing of TYSABRI must be permanently discontinued. Educational guidance; all physicians who intend to prescribe TYSABRI must ensure they are familiar with the Physician Information and Management Guidelines. Physicians must discuss the benefits and risks of TYSABRI therapy with the patient, provide them with a Patient Alert Card and re-inform at 2 years. Patients and their caregiver should be instructed that if they develop any new or worsening symptoms they should inform their physician that they are being treated with TYSABRI. Physicians should counsel patients on the importance of uninterrupted dosing, particularly in the early months of treatment. Hypersensitivity; hypersensitivity reactions have been associated with TYSABRI, including serious systemic reactions. These reactions usually occur during the infusion or up to 1 hour after completion of infusion. If a hypersensitivity reaction occurs, TYSABRI must be permanently discontinued. Immunogenicity; in the case of disease exacerbations or infusion related events the presence of antibodies should be evaluated. Treatment should be discontinued if persistent antibodies develop. Hepatic events; Serious cases of liver injury have been reported. Patients should be monitored for liver impairment. TYSABRI should be discontinued if serious liver injury occurs. Stopping therapy; if therapy is discontinued the physician needs to be aware that TYSABRI has pharmacodynamic effects for up to 12 weeks. Pregnancy and lactation: If patients become pregnant while taking TYSABRI, discontinuation of TYSABRI should be considered. Patients receiving TYSABRI should not breastfeed their infants. Undesirable effects: The most commonly reported symptoms are: Infections and infestations; urinary tract infection, Nasopharyngitis. Immune system disorders; urticarial. Nervous system disorders; headache, dizziness. Gastrointestinal disorders; vomiting, nausea. Musculoskeletal and connective tissue disorders; arthralgia. General disorders and administration site conditions; rigors, pyrexia, fatigue. Other events: infusion reactions, hypersensitivity reactions, immunogenicity, PML, other opportunistic infections and serious liver injury. Legal classification: POM. Pack size: 1 vial/pack. Price: £1130/vial. Package quantities: 300mg/15ml. Marketing Authorisation Number: EU/1/06/346/001. Marketing Authorisation Holder: Elan Pharma International Ltd., Monksland, Athlone, County Westmeath, Ireland. Date of last revision of prescribing information: June 2011.

Adverse events should be reported. Reporting forms and information can be found at www.yellowcard.gov.uk. Adverse events should also be reported to Biogen Idec on 0800 008 7401

ABN Annual Conference

Martin Rossor,
President, ABN.

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

For this year's ABN conference we have sole use of the Sage Gateshead, a stunning building overlooking the River Tyne. We start on the Tuesday afternoon October 4th with the Medical Students Roadshow and ABNT session and finish on the Friday afternoon October 7th with a joint session with the British Society of Neuroradiology. We have received a record number of abstracts and will be able to offer two or three parallel platform sessions which will alternate with the teaching/science update sessions and main lectures. This year's ABN medallist is David Neary and the Gordon Holmes lecturer Professor Eva Feldman from Michigan who will talk on stem cell therapy. The Gala Dinner will be at the Discovery Museum. All in all an exciting programme at a great venue and I look forward to welcoming delegates to the 2011 conference.

Martin Rossor,
President, ABN.

The meeting will start on the afternoon of Tuesday 4th October with sessions for medical students and SpRs. The Roadshow for Medical Students and Foundation Year Doctors aims to inform and inspire those considering a career in neurology. Our first Roadshow in Bournemouth last year was a great success (despite being timed just before finals) and we hope that this year's will be even bigger and better. The programme includes talks on careers in neurology and neurophysiology as well as updates on the latest advances in neurological treatments and an interactive panel discussion. Our first dedicated SpR session, sponsored by Merck Serono, aims to complement the main meeting with teaching specifically for trainees. Sessions will include oratory and presentation skills, a cognitive examination masterclass and interactive case-based teaching. The President's quiz will provide a challenge for both theSpRs and the speakers to make sure they perform as well as the students! Both sessions will be followed by this year's research forum, with talks on grant-writing and academic careers and an opportunity to explore research opportunities informally during the drinks reception.

Biba Stanton,
Chair, ABNT Committee.

Next year's annual ABN meeting will be in the Brighton Centre 28-31 May 2012. The plenary lectures will be given by neuro-ophthalmologist John Leigh, and psychiatrist Iain McGilchrist. The medallist lecture will be delivered by Mark Wiles. There will be teaching sessions on HIV, head injury, epilepsy, and neurological antibodies, with a neuroscience update which includes talks from Michel Goedert on neurodegeneration and proteinopathies, Martin Schwab on regeneration of the nervous system, and Dimitri Kullmann on channelopathies. There will also be a neuro-ophthalmology "meet the experts" case discussion session, a movement disorder video olympics, and a University Challenge, as well as the usual case presentation competition and CPC.

There is also a joint meeting with the American Neurological Association in Boston on 5-11 October 2012.

Correct at the time of going to press. For the most up to date programme, please see the ABN website at www.abn.org.uk/Meeting.aspx?type=1

Tuesday 4 October 2011

	Neurology Road-Show for Medical Students & Foundation Year Doctors [Newcastle Edinburgh Manchester Liverpool] Chairs: Ian Ormerod & Martin Rossor	**Specialist Registrar Session** ***Sponsored by Merck Serono*** Chairs: Ralph Gregory & Colin Mumford
1300		**Trainees Forum** Biba Stanton / ABNT Committee
1330		**Welcome & How I manage Parkinson's Disease** Ralph Gregory, ABN Honorary Assistant Secretary
1400	**Welcome & Introduction** Ian Ormerod & Martin Rossor	**Neurophysiology for Neurology SpRs** Roger Whittaker, Institute of Neuroscience, Newcastle
1410	**What do Neurologists do?** Geraint Fuller, ABN President Elect	
1430	**Training to be a Neurologist** Biba Stanton, Chair ABNT	**Cognitive Examination Masterclass** Martin Rossor, ABN President
1450	**Medical & Surgical Treatments for Parkinson's disease** Ralph Gregory, ABN Honorary Assistant Secretary	Tea Break
1500		Cases from the District General Hospital Geraint Fuller, ABN President Elect
1510	**New Treatments for Multiple Sclerosis** Colin Mumford, Western General Hospital, Edinburgh	
1520		**Cases from the District General Hospital** Geraint Fuller, ABN President Elect
1530	**What do Neurophysiologists do?** Roger Whittaker, Institute of Neuroscience, Newcastle	
1550	**Panel Discussion** Biba Stanton, Martin Rossor, Roger Whittaker & Geraint Fuller	**Oratory & Presentation Skills** Colin Mumford & Ed Fathers
1610	**Quiz with Prize** Martin Rossor, ABN President	
1640	**Research Forum Introduction** **Career Paths in Academic Neurology** [Rustam Al-Shahi Salman, Western General Hospital, Edinburgh] **How to get a Grant** [Wellcome Trust, tbc]	
1700-1800	**Drinks Reception & Research Forum Posters**	

Wednesday 5 October 2011

0730	Special Interest Group: Neuro-Ophthalmology		
0900	**Welcome & Opening Address** Martin Rossor & Lord Walton of Detchant		
	TEACHING/SCIENCE DGH Neurology Chair: Graham Lennox Dominic Heaney: Obstetric complications - A Neurologists Perspective Peter O'Callaghan: Transient Loss of Consciousness - A Cardiologist's Perspective Julia Newton: Managing Syncope & Falls- A Geriatricians Perspective		
1100	Coffee & Exhibition		
1130	Platforms	Platforms	**History of Neurology** Chair: Andrew Lees Michael Swash : Jackson and the Neurological Tradition at the London Gordon Plant: Hughlings Jackson at Moorfields and the National Hospital John Pearce: Yorkshire's influence in Neurology
1230	Lunch & Exhibition		
1300	**Sponsored Satellite Symposium: Biogen Idec** **Debate 1:** Welcome Chair Dr Eli Silber - King College NHS Foundation Trust, London **"We place too much emphasis on the risks of treatment rather than the risks of MS"** Dr Mike Boggild, Walton Centre for Neurology and Neurosurgery vs. TBC **Debate 2:** **"NHS reform provides an opportunity to improve services for people with neurological conditions"** Dr Chris Clough Kings College NHS Foundation Trust, London vs. Dr Heather Angus-Leppan Royal Free and Barnet Hospitals		
1400	***Presidential Address*** ***Professor Martin Rossor, ABN President 2011-2013***		

1445	**TEACHING/SCIENCE** **Neuropsychiatry** Klaas Enno Stephan: Computational neuroimaging for inference on mechanisms of brain disease Anthony David: Insight and awareness in neurology and psychiatry Ed Bullmore: Networks and Psychopathology
1615	Tea & Exhibition
1645	**Debate** This house believes that the ABN should be a college of clinical neuroscience Graham Venables v Gareth Llewelyn
1800	**Welcome reception** Sage Gateshead
2000	**ABNT trainee dinner**: Rasa (ticket must be prebooked in advance)

Thursday 6 October 2011

0730	**Sponsored Breakfast Session: Biogen Idec - MS – Emerging concepts for 2012** **Topic 1: Managing Mobility in MS** Mobility impairment is a significant issue for people with MS. In this session we will examine its impact on people with MS, evaluate clinical assessments of mobility and the latest ways of managing mobility problems for people with MS **Topic 2: Therapeutic expectations in 2012** In recent years the expectations of disease modifying therapy in MS have changed significantly. This session will look at what people with MS should expect from their therapy in terms of slowing, halting and even reversing disability progression		
0830	**TEACHING/SCIENCE** **Scientific frontiers** John Hardy: What has genetics done for us Hartmut Wekerle: Innate immunity and neurological disease Andrew Jackson: Neural prosthetics: Advances at the brain-machine interface		
1000	Coffee & Exhibition		
1030	Platforms	Platforms	Gareth Llewellyn, David Bateman & Stephen Pollock **Local Adult Neurology Services for the Next Decade**
1200	Lunch & Exhibition		
1200	**Sponsored Satellite Symposium: Teva Pharmaceuticals - First signs of wearing off in the elderly Parkinson's Disease patient** The symposium will be exploring all the options of treating /identifying first signs of wearing off in the elderly Parkinson disease patients. • What are the signs of wearing off in PD patients • Current management of wearing off in PD patients • Challenges of wearing off in PD patients • How is it managed? • Alternative approaches •		
1215	Training & Education Committee Meeting [closed]		
1330	**Poster session**		
1430	Medallist Lecture David Neary The Neurology of Dementia		
1530	Tea & Exhibition		
1600	Platform	Platform	
1715	Musical Performance by Spinndrift Spinndrift met in 2006 when four of the members all started the Folk and Traditional Music Degree in Newcastle. They went from playing in each other's living rooms, having tea and biscuits to gradually playing at bigger and bigger events. In fact, they liked each other's music and company so much that they moved in together two years later. In 2008 and 2009 they were finalists in the New Roots competition, and in the summers of 08 and 09 played at various festivals such as Sidmouth, Towersey, Warwick, Dartmoor and Bideford. After surviving their first few tours together they managed to raise the money to make their first Album: 'Far distant', which was released at the end of 2010. They recorded the album as they were graduating from their degree program, where they all excelled, achieving excellent marks and giving fantastic end-of-year performances. In 2011 Spinndrift became a partnership, and have been working on all aspects of their business and music.		
1830 for 2000	**Gala Dinner: Discovery Museum** (lounge suit)		

Friday 7 October 2011

0730	Breakfast Session: NMO Interest Group Meeting [open meeting, but numbers restricted]	
0830	**Platforms**	**Case Presentation Competition**
0945	Coffee & Exhibition	
1015	**17th Gordon Holmes Lecturer: Eva Feldman, Michigan, USA** Stem Cell Therapy: The New Frontier of Medicine [Supported by the Guarantors of Brain]	
1100	**TEACHING/SCIENCE** **Update on Muscle Disease** Kate Bushby: Filling in the Gaps Precise diagnosis for inherited muscle diseases Hanns Lochmuller: The diagnosis and treatment of protein aggregation myopathies Glenn Walter , University of Florida,Gainesville, USA : Imaging muscle disease	
1230	Lunch & Exhibition	
1400	**Clinico Pathological Conference** Patrick Chinnery & Dip Mitra Discussant: Kevin Talbot	
1430	**Joint Session with the British Society of Neuroradiology: Controversies in Neuroradiology** "Should we screen for familial aneurysms?"Andrew Clifton (For) Rustam Al-Shahi (Against) "Should GP direct access brain CT scanning be provided?" John Straiton (For) Richard Davenport (Against) "CT or MRI for acute stroke?" Peter Sandercock (CT) Robin Sellar (MRI)	
1600	Close of meeting	

2nd Oxford Neurology Course

Conference details: 29 June - 1 July 2011; Oxford, UK. ***Reviewed by:*** Alastair Webb, MRC Clinical Fellow / Neurology Trainee, Oxford.

An eclectic group of over 50 neurologists from first-year trainee to consultant gathered in the beautiful surroundings of St. Anne's College for the second Oxford Neurology Course, an excellent venue with superb hospitality for those all-important lunch and coffee breaks. The program was unusually well-balanced between practical neurology and academic insight delivered by local and visiting world-leading neurologists.

The course kicked off with a welcome from Christopher Kennard, Head of Neurosciences, before Michael Sharpe from Edinburgh gave us a tour through Medically Unexplained Symptoms, from theory to practice. He showed that these are not 'heart-sick' patients lacking intellectual challenge or therapeutic potential but are a critically important patient group with massive morbidity, occupying more than 40% of our clinics, a demand upon services far exceeding that of more 'organic' conditions. In addition, he demonstrated a simple approach with the potential for significant therapeutic benefits. The psychological theme continued with Simon Wessely giving a fascinating discourse on the psychological effects of war, focussing in particular on the earliest known footage of the effects on mental health, with a film of shell-shock victims from the First World War.

The afternoon concentrated on the diagnosis and classification of headache syndromes by Jes Olesen, Chairman of the International Headache Classification Committee. From classical migraine to hypnic headache, he demonstrated how the nuances of the new classification aid diagnosis and practical management, as well as discussing less common current treatment options and those yet to come. Manjit Matharu from Queen's Square then showed how SUNCT and SUNA fit into the spectrum from trigeminal autonomic cephalalgias to trigeminal neuralgia, with extensive elaboration of how current research helps to inform the classification and management of these diseases. After a brief history of Medicine at Oxford and its role in the development of our specialty by Alastair Buchan (Head of Medical Sciences, Oxford University), day 1 closed with Charles Warlow delivering a vigorous exhortation on how neurology has failed to resist pressures to limit medical training and increase over-specialisation and how our reticence to take on acute neurology and stroke harms our specialty, balanced by a positive view on the intrinsic wonder of neurology itself.

Day 2 started with a superb description of myotonic dystrophy 1 and 2 and their management, laced with practical tips based on David Hilton-Jones' copious experience in Oxford. The peripheral theme then continued with a run-through of peripheral neurophysiology by King's College's Kerry Mills, covering how clinical presentation should be matched with appropriate tests and their results. The flavour of the day was more academic after the next caffeinated hiatus. George Ebers from Oxford gave a fascinating, personal account of his seminal research into the epigenetic basis of multiple sclerosis, demonstrating how clinical insight plus genetic epidemiology of astonishing scope and imagination was brought into the lab, resulting in novel understanding with massive potential therapeutic benefit. The morning closed with Christopher Conlon, Reader in Infectious Diseases at Oxford, giving a national and global perspective on the neurological importance of tuberculosis, with practical tips such as the use of the T-spot test.

Three days of neurological updates were followed by a walking tour through the historic city centre to visit some of the sights showing the contribution of Oxford scholars to medicine through the centuries.

After another excellent lunch, the first session of the afternoon was anything but soporific: Paul Reading from Middlesborough explained clearly the physiological basis of sleep and how it is disturbed in neurological diseases such as narcolepsy-cataplexy, and Zenobia Zaiwalla from Oxford spoke on the differentiation of parasomnias from normal sleep behaviours and nocturnal epilepsy, both enlivened by videotelemetry footage. Following another caffeine-based wake-up call, the course proceeded with three unusual cases from Oxford Grand Rounds, ranging from coeliac encephalopathy and sneeze-induced stroke to semantic dementia, with willing victims expected to provide wisdom and insight. The educational part of the day finished with David Spence from Ontario delivering his view on cutting-edge aspects of secondary stroke prevention, from new antiplatelet agents to patent foramen ovale, before Colin Blakemore, Professor of Neuroscience at Oxford, finished the course with his perspective on the challenges facing neuroscience research, particularly our inappropriately small share of a declining funding pot due to limited political clout and the fragmented state of our third-sector organisations. We then happily retired to Wadham College for bubbly in the Cloisters and a sumptuous meal in their ancient, traditional hall.

The final morning began with a light-hearted view of the relationship between neurology and neurosurgery over the past thirty years, and how it really should function, by Richard Kerr, Neurosurgeon in Oxford and a lead investigator on the ISAT trial. Keith Muir from Glasgow followed with an excellent lecture on hemicraniectomy for malignant MCA infarction, from early research into clinical trials and how these studies inform practical decision-making. The final session focussed on brainstem reflexes with a tremendously practical talk on the assessment and management of dizzy patients by Adolfo Bronstein, Neuro-otologist at Queen's Square, followed by Christopher Kennard giving a detailed physiological description of the control of extraocular movements and how these mechanisms fail, resulting in a plethora of clinical manifestations. The course finished with another delicious lunch, and the option of a walking tour in the sunshine around the 'dreaming spires,' illustrating the contribution of Oxford's more notable sons to medicine, putting everything learnt into historical context.

Overall, the course offered a rarely-found, well-balanced programme of clinical practice and academic insight and demonstrated how the latter informs the former. However, there were still plentiful practical neurological tips to satisfy any neurologist, whether a green trainee or an experienced consultant seeking a refresher or further development of their skills. As an added bonus, all of this took place in the stunning setting of Oxford in summer, heightening the atmosphere of the course through its historical location and fabulous hospitality. ◆

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

2011

September

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.europeglia2011prague.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

Carmarthen Cardiac Update Course
15th September, 2011; Carmarthen, Wales
www.stars.org.uk/news-events/events-healthcare%20professionals)

17th Joint Annual Meeting of the German-Austrianswiss 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
T. 01276 472 369
E. enquiries@braintreetraining.co.uk
www.braintreetraining.co.uk

Czech Conference on multidisciplinary care for patients with spinal atrophy
16-18 September, 2011; České Budějovice, Czech Republic
T. 0191 241 8605
www.treat-nmd.eu/events/240/

Duchenne Family Support Group Annual Conference
17 September, 2011; Stratford-upon-Avon, UK
T. 0191 241 8605
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 ACPIN MS Study Day
20 September, 2011; Maidstone, UK
T. 0800 032 3839
E: education@mstrust.org.uk
www.mstrust.org.uk/studydays

Dementia
21 September, 2011; London, UK
T. 020 7647 3577
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

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
T. +39 06 330531
E. esnr2011@aimgroup.eu
www.esnr2011.org

Sinapsa Neuroscience Conference, 11
22-25 September, 2011; Ljubljana, Slovenia
T. + 386 1 241 7133
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.regonline.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
T. 952 545 6284
www.aneuroa.org

11th International Conference on Cognitive Neuroscience
25-29 September, 2011; Palma, Mallorca, Spain
T. +34 971 172750
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
T. 0191 241 8605
www.treat-nmd.eu/events/200/

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

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

Gene-environment interplay: shaping behaviour and CNS dysfunction
29th September, 2011; Liverpool, UK
T. 01223 766450
www.bna.org.uk/events/

Cognition Disorders in MS
30 September – 1 October, 2011; Florence, Italy
T. +39 06 420 413
W: 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@1CNS.org
www.neurosurgeon.org

STARS Patients Day
2 October, 2011; Birmingham, UK
www.stars.org.uk/news-events/patient-events

HRC 2011
2-5 October, 2011; Birmingham, UK
T. 01789 451822
www.heartrhythmcongress.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
T. 0191 241 8605
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
T. 020 7405 4060
www.theabn.org

One day workshop: jitter analysis in children
6 October, 2011, London, UK
T. 0191 241 8605
www.treat-nmd.eu/events/284/

21st Alzheimer Europe Conference
6-8 October, 2011; Warsaw, Poland
T. +352-29 79 70
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
T. +41 22 908 0488 ext: 531
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

5th World Congress on Controversies in Neurology: Life Course Related Conditions (CONy) - Asia Pacific
13-16 October, 2011; Bejing, China
T. +972-3-5666166
www.comtecmed.com/cony/2011/Default.aspx

Fatigue/Managing Sleep
14 October, 2011; Cambridge, UK
T. 01353 652173
E. Rachel.everett@ozc.nhs.uk

Neurology Update Meeting 2011
14 October, 2011; Galway, Ireland
T. +353 (0)61 622652
E. info@iicn.ie

MDC National Conference
15 October, 2011; Nottingham, UK
T. 020 7803 4804
E. 2011conference@muscular-dystrophy.org

Ninth WMS Satellite Teaching Course
17-18 October, 2011; Algarve, Portugal
T. 351 214048772
E. wms2011@parceiro-base.pt

WMS Congress 2011
18-22 October, 2011; Algarve, Portugal
T. 351 214048772
E. wms2011@parceiro-base.pt

ECTRIMS 2011: 27th Congress of the European Committee for Treatment and Research in MS
19–22 October, 2011; Amsterdam, The Netherlands
(with ACTRIMS & LACTRIMS)
E. secretariat@ectrims.eu

ENRC 1st European Neuro-rehabilitation Congress
20-22 October, 2011; Merano, Italy
T. +43-512-575600
E. enrc2011@come-innsbruck.at
www.enrc2011.eu

7th International Congress on Vascular Dementia
20-23 October, 2011; Riga, Latvia
T. + 41 22 908 0488
E. vascular@kenes.com
www.kenes.com/Vascular

How to do Cognitive Rehabilitation Therapy
22 October, 2011; London, UK
T. 01276 472 369
E. enquiries@braintreetraining.co.uk
www.braintreetraining.co.uk

November

Stroke services: Controversies in management and service delivery
3 November, 2011; London, UK
T. 020 7290 3940
www.rsm.ac.uk/academ/cnc02.php

Action Duchenne 9th Annual International Conference
4-5 November, 2011; London, UK
T. 020 8556 9955
www.treat-nmd.eu/events/289/

TREAT-NMD curator and oversight committee meeting
11-12 November, 2011; Geneva, Switzerland
T. 0191 241 8605
E. info@treat-nmd.eu

187th ENMC workshop on Dystroglycan and Dystroglycanopathies
11-13 November, 2011; Naarden, Netherlands
T. 0191 241 8605
E. info@treat-nmd.eu

7th Essential Neuro MRI Course
12 November, 2011: Liverpool, UK
T. 07799 723 925
essentialneuromri@hotmail.co.uk

Neuroscience 2011
12-16th November; 2011, Washington, DC, USA
T. (202) 962-4000
www.sfn.org/AM2011

20th World Congress of Neurology
12–18 November, 2011; Marrakesh, Morocco
T. +41 22 908 0488
E. wcn@kenes.com
www.wcn-neurology.org

MS Trust Annual Conference 2011
13th-15th November, 2011; Kenilworth UK
T. 0800 032 3839
E. conference@mstrust.org.uk
www.mstrust.org.uk/conference

Neurology Symposium
16 November, 2011; RCP Edinburgh, Scotland
E. c.gray@rcpe.ac.uk
http://events.rcpe.ac.uk/events/142/neurology

SNO 2011
17-20 November, 2011; California, USA
T. (281) 554 6589
F. (713) 583 1345
E. Linda@soc-neuro-onc.org
www.soc-neuro-onc.org/index.cfm

The West of England Seminars in Advanced Neurology (WESAN)
24-25 November, 2011; Exeter, UK
E. cgardnerthorpe@doctors.org.uk

Mood Assessment and Compassionate Mind
25 November, 2011; Cambridge, UK
T. 01353 652173
E. Rachel.everett@ozc.nhs.uk

BIO-NMD steering committee Meeting
28-30 November, 2011, Ferrara, Italy
T. 0191 241 8605
E. info@treat-nmd.eu

6th UK Stroke Forum Conference
29 November-1 December, 2011;
Glasgow, Scotland
T. 0845 521 2505
E. sally.atkinson@stroke.org.uk
www.ukstrokeforum.org

International Myotonic Dystrophy Consortium IDMC-8
30 November – 3 December, 2011;
Florida, USA
T. (352) 294-0846
E. cgentilman@dce.ufl.edu

University Classes in Multiple Sclerosis VIII, focused on Symptomatic Treatments
30 November, 2011; Marbella, Spain
E. m.friedrichs@charcot-ms.eu
www.charcot-ms.eu

December

CARE-NMD midterm meeting
1-2 December, 2011; Czech Republic
T. +49 761 27043440
E. info@care-nmd.eu

International Symposium on Learning, Memory and Cognitive Function
1-3 December, 2011; Valencia, Spain
T. 0034 96 197 4670
E. catedrasg@cac.es
www.fundacioncac.es/catedrasg

Towards Personalized Treatment in Multiple Sclerosis
1-3 December, 2011; Marbella, Spain
E. m.friedrichs@charcot-ms.eu
www.charcot-ms.eu.

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

Advanced Cognitive Rehabilitation Workshop (Attention & Information Processing)
2–3 December, 2011; London, UK
T. 01276 472 369
E. enquiries@braintreetraining.co.uk
www.braintreetraining.co.uk

XIX WFN World Congress on Parkinson's Disease and other Movement Disorders
11-14 December, 2011; Shanghai, China
T. + 41 22 908 0488
E. parkinson2011@kenes.com
www.kenes.com/parkinson

2012

January

Cognitive Rehabilitation Workshop
13–14 January, 2012; London, UK
T. 01276 472 369
E. enquiries@braintreetraining.co.uk
www.braintreetraining.co.uk

How to do Cognitive Rehabilitation Therapy
28 January, 2012; London, UK
T. 01276 472 369
E. enquiries@braintreetraining.co.uk
www.braintreetraining.co.uk

March

1st International Conference on Heart and Brain - ICHB 2012
1-3 March, 2012; Paris, France
E. heart-brain@kenes.com

Insight Workshop
2–3 March, 2012; London, UK
T. 01276 472 369
E. enquiries@braintreetraining.co.uk
www.braintreetraining.co.uk

XIII Pan American Congress of Neurology
4-8 March, 2012; La Paz, Bolivia
T. +56-2-946 2633
www2.kenes.com/pcn2012/pages/home.aspx

The 6th World Congress on Controversies in Neurology (CONy)
8-11 March, 2012; Vienna, Austria
T. 972-3-566-6166
noam@comtecmed.com
www.comtecmed.com/

Cell culture technology: recent advances, future prospects
9 March, 2012; Welwyn Garden City, UK
E. enquiries@euroscicon.com
www.regonline.co.uk/workihc2010

10th Austrian Society of Neurology (ÖGN) Annual Congress
14-17 March, 2012; Graz, Austria
T. +43 1 512 80 91-19
E. weinhart@oegn.at
www.oegn.at/kongress2012

9th World Congress on Brain Injury
21-25 March, 2012; Edinburgh, Scotland, UK
T. 01512 80 9119
E. mjroberts@internationalbrain.org
www.internationalbrain.org

9th International Brain Injury Association World Congress
22-25 March, 2012; Edinburgh, Scotland
T. + 703 960 0027
www.internationalbrain.org

International Congress on Neurology and Epidemiology
22-25 March, 2012; Seville, Spain
T. +33 4 78 176 176
www.neuro-conference.com/2012/

2nd International Congress on Epilepsy, Brain and Mind
28-31 March, 2012; Prague, Czech Republic
www.epilepsy-brain-mind2012.eu

April

ASNR 2012
21-26 April, 2012; New York, USA
T. (630) 574 0020
www.asnr.org/

May

8th International Congress On Mental Dysfunction & Other Non-Motor Features In Parkinson's Disease and Related Disorders
3-6 May, 2012; Berlin, Germany
T. + 41 22 9080488 ext. 524
E. Dnuriel@kenes.com
www.kenes.com+4

7th World Congress for NeuroRehabilitation
16-19 May, 2012; Melbourne, Australia
T. +612 9954 4400
W: www.dcconferences.com.au/wcnr2012

A bit more about the devils you know

Much awaited and longer in coming than even the most precious baby are these results from a pan-European register of epilepsy in pregnancy, with a smattering of cases from America (1%), South East Asia (3%) and somewhat more from the Western Pacific (10%). Even after many exclusions, there were still a massive 4540 monotherapy pregnancies which could be analysed: 1402 on carbamazepine; 1280 on lamotrigine, 1010 on valproic acid and 217 on phenobarbital. The cases were defined according to treatment at the time of conception on an "intention to treat" basis and subsequent drug changes during the pregnancy were not considered. Seizure freedom rates during pregnancy were similar for all the drugs at about 70%. The headline figures of this study are that the risk of major malformation from carbamazepine at doses less than 400mg per day was 3%, with doses of 400-1000mg per day, it was 5% and above 1000mg per day it was 9%. For lamotrigine doses less than 300mg per day malformation rate was 2% and over 300mg per day it was 4%. For valproic acid doses less than 700mg per day, the rate was 6%, 700-1500mg per day it was 10% and over 1500mg per day (n=99) 24%. Phenobarbital in doses less than 150mg per day was associated with a risk of 5% but with a risk of 14% in higher doses. The commonest malformations were cardiac but hypospadias was also common and neural tube defects with valproic acid and carbamazepine especially. Although of the commonly used drugs, valproic acid clearly carried the highest risk, in high doses, it is noteworthy that in doses less than 700mg, the risks were comparable (overlapping confidence intervals) to more than 300mg of lamotrigine per day or 400-1000mg of carbamazepine. Although far from ideal, it lends some reassurance to those of us who find ourselves in the situation where it is the only drug that seems to control a woman's epilepsy. It also gives us more information on which to base our choices in treating these women. It will be interesting to see how new drugs (the devils we don't know) compare, as the number of monotherapy pregnancies with them increases. Already, there are starting to be moderate numbers with levetiracetam and promising but inconclusive results.

– Dr Mark Manford, Consultant Neurologist, Addenbrooke's Hospital and Bedford Hospitals NHS Trust.

Tornson T, et al. Dose-dependent risk of malformations with antiepileptic drugs: an analysis of data from the EURAP epilepsy and pregnancy register.
LANCET NEUROLOGY 2011;10:609-17.

Glucocerebrosidase administration corrects memory deficits in a mouse model of Gaucher's/Parkinson's disease

The link between Gaucher's disease/mutant glucocerebrosidase (GBA1) and Parkinson's disease (PD) is now well established. This paper shows that GBA1 mutant mice display progressive synucleinopathy (previously known), increased glucosylsphingosine (GlcSph) (its neurotoxicity having been previously demonstrated *in vitro*) although not glucosylceramide (GlcCer), and cognitive deficits likely via both gain- and loss- of function (using a variety of mutant, knock-in and knock-out mice), which can be reversed by exogenous intra-hippocampal administration of GCA. Gba1D409V/ D409V mice exhibit alpha-synuclein and ubiquitin aggregates in hippocampal neurites (and to a lesser extent the cortex and cerebellum; no mention was made of the basal ganglia), from six months of age (but not at two months), increasing at 12 months. Beclin was reduced, suggesting that initiation of autophagy may be impaired (another potential story in the pathophysiology of PD). In contrast to humans and some other mouse models, Gba1D409V/ D409V mice exhibited no markers of inflammation or cell death. Perhaps the 25% residual GCA activity may be enough to cause cellular toxicity and cognitive deficits without inflammation and cell death. It is possible that this model represents an 'early stage' of PD and thus may negate the theory that inflammation initiates the disease cascade.

Mutant mice displayed deficits in tests of hippocampal function, although the earliest mice were tested was four months. It would have been interesting to test two-month-old mice (that have increased GlcSph but not synucleinopathy). Having said that, Gba1D409V/+ mice did not display memory deficits (at six months), suggesting that it is indeed GlcSph accumulation rather than synucleinopathy that produces the memory deficits – this clearly has interesting implications for the pathophysiology of PD. It may also have been useful to perform motor tests on these mice.

The authors suggested that both loss- and gain-of function of GCA cause pathology. Mice carrying one normal Gba1 allele (Gba+/- and Gba1D409V/+) did not accumulate GlcSph but Gba1D409V/+ mice had synucleinopathy (at 50% of Gba1D409V/ D409V mice). Thus, one mutant allele causes synucleinopathy (not present in mice lacking one allele), implying a toxic gain of function. That the deficits can be largely rescued by administration of normal GCA implies an additional loss of function (and knock-outs accumulate GlcCer and GlcSph and die aged 14 days).

Human GCA1 (carried by a viral vector) was administered directly into the hippocampus of mutant mice at two months of age. At four months of age, the memory deficits were reversed, and synuclein, ubiquitin and GlcSph were significantly reduced in those mice. The effect of administering GCA to older mice (once synucleinopathy is established) would also have been of interest.

This study then takes the field forward in suggesting that GCA causes disease by both a gain and loss of function; that GlySph accumulation can cause hippocampal deficits; and that these effects can be substantially ameliorated using direct exogenous administration of GCA. It therefore has implications for the pathophysiology of not only Gaucher's related PD but also idiopathic PD, and raises intriguing therapeutic possibilities.

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

Sardi SP, et al. CNS expression of glucocerebrosidase corrects α-synuclein pathology and memory in a mouse model of Gaucher-related synucleinopathy. Proceedings of the National Academy of Sciences 2011. On-line 5 July 2011.

Expression by skipping

Twenty-five years have passed since the identification of the gene mutated in Duchenne Muscular Dystrophy. The X-linked gene, DMD, was found to encode a large cytosolic protein named dystrophin, which was later shown to link the underlying cytoskeleton in muscle to the sarcolemma by binding to actin via its N-terminus and to β-dystroglycan via its C-terminus. Spanning 2.4 megabases, DMD is the largest known gene in the human genome and contains 79 exons encoding a protein of molecular weight 427 kDa. Duchenne Muscular Dystrophy is associated with deletions, duplications and point mutations in the DMD gene, many resulting in loss of protein expression. Since the identification of DMD, a host of suggested therapeutic strategies have been promised to patients and their families but most developments have been disappointing. However, the recent publication by Cirak et al. has the potential to revolutionise not only the field of Muscular Dystrophy, but also other diseases whose underlying molecular defect is genetic.

Cirak et al.'s work is based on previous knowledge that the milder form of muscular dystrophy, Becker Muscular Dystrophy, is also associated with mutations in DMD. However, unlike Duchenne Muscular Dystrophy, DMD mutations associated with Becker Muscular Dystrophy do not disrupt the open reading frame and therefore lead to truncated but partially-functional dystrophin protein. Therefore, if it were possible to 'skip' across a deleted area of the gene during transcription of messenger RNA and maintain an open reading frame, then a functional, albeit smaller version of dystrophin will be expressed. Indeed, this technique has become reality over the past decade in vitro, known as exon skipping, and has been applied with some success in animal models of the disease and also when administered locally to specific muscles.

In an exciting development, Cirak et al. now report in *The Lancet* that systemic intravenous administration of the splice-switching phosphorodiamidate morpholino oligomer (PMO), AVI-4658, results in increased expression of dystrophin in biopsied muscles. Moreover, the newly expressed dystrophin appears functionally active by also increasing the expression of α-sarcoglycan and neuronal nitric oxide synthase (nNOS) at the sarcolemma. Nineteen boys in total were included in this open

labelled dose-escalation study with seven patients responding to treatment, all receiving the higher dose of AVI-4658. Importantly, no serious drug-related adverse events were reported and no evidence of an immune-response to the drug or to the newly expressed dystrophin protein was seen.

Despite these promising results, a few questions remain. The expression level of dystrophin in responders was variable between patients and it is unclear how this can be explained. Furthermore, the restoration of dystrophin expression was variable within the muscle itself suggesting that complex factors may be relevant with respect to uptake and function of the drug within individual muscle fibres. One must also remember that the selection criteria for this study included a genetically-confirmed diagnosis of Duchenne Muscular Dystrophy with an out-of-frame deletion in DMD eligible for correction by skipping exon 51 and therefore AVI-4658 will not be applicable to all patients. Most importantly, the current study did not set out to determine the clinical effectiveness of this drug in preventing muscle degeneration or reversing the currently inevitable disabilities that we see as the boys grow older. It is likely that AVI-4658 would need to be taken lifelong and therefore many questions can only be answered by a study lasting significantly longer than 12 weeks. However, on the basis of Cirak et al.'s work, a clinical trial is now urgently needed to determine the effectiveness of AVI-4658 in the clinical setting.

With the long history of false hopes for patients and families living with Duchenne Muscular Dystrophy since the beginning of the genetic age, the time may have finally come when real advances made in manipulating gene expression in vitro can at last be applied to offer hope not only to patients harbouring mutations in DMD, but also to patients with other genetic diseases amenable to exon skipping.

– Dr Rhys Roberts, Honorary Consultant in Neurology, Addenbrooke's Hospital, Cambridge.

Cirak, S et al. Exon skipping and dystrophin restoration in patients with Duchenne muscular dystrophy after systemic phosphorodiamidate morpholino oligomer treatment: an open-label, phase 2, dose-escalation study. (2011) LANCET. DOI:10.1016/S0140-6736(11)60756-3.

What's in a name?

Acronyms are only really effective in communicating information when they become an accepted part of common medical terminology. Who decides when and how this happens? Clearly there is a memetic spread of widely used terms. This process is far from flawless – "FSH" may mean something very different to a gynaecologist (follicle-stimulating hormone) and a neurologist (facioscapulohumeral muscular dystrophy). The process is more opaque when naming well defined but unlabelled clinical entities. The eponymous route has fallen from favour, somewhat, and it may be more helpful to try to name things according to what they actually are. Although this may seem to be intuitively simpler and less confusing, consider the emotional baggage and meaning of "chronic fatigue syndrome" compared with "myalgic encephalomyelitis".

A small number of patients who have sustained a severe brain injury (from a range of different causes) are seen to develop a stereotyped set of autonomic changes with tachycardia, pyrexia, muscle rigidity and sweating. The treatment is really symptomatic and supportive, but it is important to recognise this constellation of features as secondary to brain injury rather than representative of ongoing untreated infection or another pathological entity. This review paper looks at attempts to classify and demarcate these features over the years into a clinically discrete syndrome. Of course, an important part of this process is attributing a specific name and hence identity. The current favourite is "paroxysmal sympathetic hyperactivity" (PSH) although in their attempts to characterise and label this, previous authors have gone for "dysautonomia", "central autonomic dysfunction", "paroxysmal autonomic instability with dystonia", "autonomic storming" and "dysautonomic crisis". There are nine different sets of criteria that have been used to describe the salient features. Although they share many common parameters (tachycardia, pyrexia), the duration, time of onset and aetiology are different for each set. The authors clearly demonstrate how the criteria employed by different groups have evolved over time, with the majority evolving from two separate studies. What is concerning in trying to use this literature in a broader sense is the fact that only a third of published papers attempted to use any criteria above and beyond a simple description of the condition.

The lack of unified and universally agreed criteria potentially hamper attempts at research into the causes and management of PSH. A consensus on clinical features and nomenclature would allow a greater recognition and awareness of the condition, particularly in non-specialist settings.

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

Perkes IE, Menon DK, Nott MT, Baguley IJ. Paroxysmal sympathetic hyperactivity after acquired brain injury: A review of diagnostic criteria. BRAIN INJURY 2011;25(10):925–32.

An SMA motor neuron: I will survive!

Despite being associated with the commonest genetic cause of death in young children, we know very little about the physiological function of the ubiquitously expressed protein, survival of motor neuron (SMN). SMN is found in large multi-protein complexes within cells both within the nucleus (in the form of 'gems') and in the cytoplasm. What roles SMN plays at these sites remains unclear. However, we know that mutations in SMN that lead to reduced expression of the SMN protein, resulting in cellular levels of <80% of control, cause the childhood-onset motor neuron disease, spinal muscular atrophy (SMA).

Function aside, Makhortova et al. set out to look at compounds that may increase the levels of SMN in cells as previous work had suggested that this may prevent motor neuron cell death. To do this, they developed an image-based screen using fibroblasts taken from parental SMA carriers and patients and incubated these cells with compounds known to act on membrane receptors, channels and kinases. The levels of SMN were determined by immunofluorescence using automated confocal microscopy. 188 compounds were shown to increase SMN levels in this assay, and, interestingly, the site of increased SMN (nucleus or cytoplasm) varied from compound to compound. By careful dissection of intracellular signalling pathways, the authors proposed that compounds that inhibit the specific signalling kinase, GSK-3 (glycogen synthase kinase 3) lead to elevated SMN levels by blocking SMN degredation mediated by phosphorylation. To support this hypothesis, Makhortova et al. show that SMN levels can be stabilised in fibroblasts by depleting GSK-3 using inhibitory RNA techniques. Finally, using cultured mouse motor neurons depleted of SMN (analogous to the situation seen in SMA patients), the authors show that alsterpaullone, a GSK-3 inhibitor, rescues these cells from cell death leading to similar survival as seen in controls.

There are many interesting aspects of SMA at the molecular level that remain unexplained. Intriguingly, primates appear to have gained an extra copy of the gene (SMN2), albeit containing a nucleotide substitution rendering the expressed protein unstable and prone to truncation and degradation. Moreover, as is the case in many genetic disorders seen in our neurology clinics, why does a defect in a ubiquitously expressed protein cause the death of a specific specialised cell such as the motor neuron? While it may take some time to unravel the precise function of SMN, this report illustrates the importance of developing specific cell-based assays to test hypotheses in parallel with functional studies, and that this approach appears to have identified a promising intracellular drug target in this case.

Currently, we have very little to offer these patients and their families in terms of modifying motor neuron cell death, but Makhortova et al.'s work may precipitate real therapeutic breakthroughs as we tackle hitherto incurable genetic neurological diseases.

– Dr Rhys Roberts, Honorary Consultant in Neurology, Addenbrooke's Hospital, Cambridge.

Makhortova NR, Hayhurst M, Cerqueira A, Sinor-Anderson AD, Zhao WN, Heiser PW, Arvanites AC, Davidow LS, Waldon ZO, Steen JA et al. A screen for regulators of survival of motor neuron protein levels. NAT CHEM BIOL 2011;7:544-52.

Predicting Parkinson's disease dementia using EEG microstructure

There is an urgent need for reliable biomarkers capable of predicting Parkinson's disease (PD) complications, particularly dementia. Whilst most attention is given to genetics, brain imaging and biological fluid markers (mainly in CSF), Klassen et al from the Mayo Clinic set out to determine whether quantitative EEG could fulfil this role.

They longitudinally studied 106 PD patients (mean age = 76 years) following a baseline resting EEG. They excluded those taking anticonvulsants and benzodiazepines. By collecting 100 seconds of EEG data when the patient was in a state of "relaxed wakefulness" (sat in reclining chair with eyes shut) and transforming this into its component waveforms, they calculated the global EEG bandpower for each of the four frequency bands (δ = 1.5-3.9 Hz, θ = 4-7.9 Hz, α = 8-12.9 Hz, β = 13-30 Hz). They also calculated the background rhythm frequency (BRF) which was defined as the dominant waveform present in the posterior electrodes. The mean follow-up duration was 3.3 years (range 0.31 - 8.8 years), during which time patients underwent annual neuropsychological testing to detect emerging PD dementia. Clinicians were blinded to the baseline EEG.

Using a Kaplan Meier curve, the incidence of dementia within 5 years of baseline EEG for the entire sample was 34%. Patients with mild cognitive impairment (MCI) at baseline had a hazard ratio (HR) of 4.3 compared to those who did not. Surprisingly, age or PD duration at baseline did not significantly alter dementia risk.

After dichotomising at the median, patients with 'low' BRF (less than cut-off of 8.5 Hz) had a significantly greater dementia risk (HR 13) compared to those with 'high' BRF. This translates into a dementia incidence within 5 years of EEG of 66% compared to 8.1%. Those with 'high' θ bandpower had a smaller but still significant increased incidence of PD dementia (HR 3.0) compared to those with 'low' θ bandpower. Other bandpowers did not significantly alter dementia risk. The BRF hazard was not reduced in the multivariate modelling by more than 15% by either PD-MCI or any of the other neuropsychological tests. The authors believe that this supports the argument that BRF truly predicts dementia risk rather than simply acting as a surrogate marker of current cognitive deficits. θ bandpower, on the other hand, was confounded by both PD duration and MMSE.

The authors hypothesise that structural pathology in PD may interfere with the normal background alpha rhythm generated by subcortical and corticocortical circuits, thereby resulting in a downward spectral shift (i.e. slowing) of the BRF frequency. However, they acknowledge that further work is needed to understand the neural substrates of cognitive deterioration in PD.

The findings are interesting but do they help our PD patients? In the shorter term, it and other biomarkers may allow enrichment of neuroprotective drug trials with cognitively 'at-risk' patients. The usefulness of quantitative EEG in detecting cognitive decline and predicting future risk on an individual basis still needs to be proven in larger studies with longer follow-up, and the need for specialist training and equipment should be borne in mind. Nonetheless, the concept of using EEG microstructure to predict disease progression is an exciting one.

– Dr David P Breen, Clinical Research Fellow in Neurology, Cambridge Centre for Brain Repair.

Klassen BT, et al. Quantitative EEG as a predictor biomarker for Parkinson's disease dementia. NEUROLOGY 2011;77:118-24.

Graft and block

Diaphragmatic paralysis is a major complication of high cervical cord injury. Unfortunately, many patients sustaining such injuries require long-term mechanical ventilation with its myriad of associated complications and obvious negative impact on quality of life. A bleak outlook, most would agree. Alilain et al, however, writing in *Nature*, provide hope for those left in this desperate state. Using rats receiving C2 hemisection as their model of injury, the authors describe their experiments that eventually lead to apparent recovery of diaphragmatic innervation on the lesioned side.

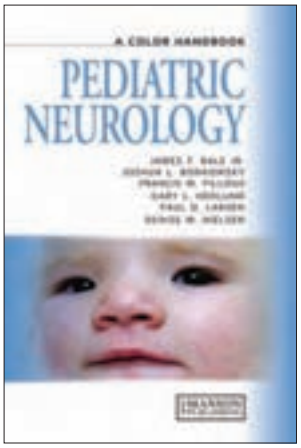
It is known that the extracellular space within the mature spinal cord contains chondroitin sulphate proteoglycans (CSPGs), creating a potent inhibitory environment for neuronal regeneration. Moreover, it is known that this inhibitory extracellular matrix is upregulated at sites of injury. Firstly, Alilain et al. show that enzymatic breakdown of this inhibitory extracellular matrix at the level of the phrenic nerve nuclei leads to increased number of serotonergic neurons, known to be involved in respiratory plasticity. Although functional recovery was disappointing, the authors then investigated the effects of implanting autologous nerve grafts in addition to enzymatic treatment, hypothesising that the Schwann cells contained in the grafted nerve would provide the necessary factors and support to guide lesioned axons to the denervated phrenic nerve nuclei ipsilateral and caudal to the C2 hemisection. Remarkably, by 12 weeks, the hemisectioned rats receiving both enzymatic breakdown of CSPGs and peripheral nerve grafts showed recovery of ipsilateral diaphragmatic function, often surpassing measures of activity compared to the contralateral side and the diaphragms of uninjured animals. Importantly, the authors show that recovery is dependent on the implanted nerve graft as transection leads to complete loss of ipsilateral diaphragmatic activity.

Time will tell whether these findings can be translated in order to help patients who have sustained high cervical cord injuries. Furthermore, Alilain et al.'s work points again to the remarkable potential ability of the nervous system to regenerate, given the appropriate environment, and gives hope that such approaches may be applied to a wide range of neurological injuries in the context of neurorehabilitation in years to come.

– Dr Rhys Roberts, Honorary Consultant in Neurology, Addenbrooke's Hospital, Cambridge.

Alilain WJ, Horn KP, Hu H, Dick TE and Silver J. Functional regeneration of respiratory pathways after spinal cord injury. NATURE 2011;475:196-200.

Pediatric Neurology – A Color Handbook



This new book is written by specialist authors who recognise the needs of nonspecialists and trainees.

Recognising patterns of disease can be the first step to successful management of the child with a neurological problem; this is emphasised by the authors throughout the book. Their concise, precise account reflects the remarkable recent advances in paediatric neurology and related disciplines, while stressing the fundamentals of clinical examination and history taking in reaching an accurate diagnosis. The book begins with a detailed discussion of neurological examination techniques and the basic formulation of differential diagnoses and management, using neuroradiology, electrophysiology, cerebrospinal fluids, genetic and metabolic testing. The second section of the book follows a problem-based approach, just as diseases present in the real world. It employs practical, symptom- and sign-based strategies for virtually all conditions encountered by the practitioner. The final section on neurological emergencies recognises that such conditions present first to someone other than a paediatric neurologist.

Authors: James F Bale, Joshua L Bonkowsky, Francis M Filloux, Gary L Hedlund, Denise M Nielsen, University of Utah School of Medicine, Salt Lake City, Utah, USA, Paul D Larsen, University of Nebraska College of Medicine, USA. ISBN 9781840761344.

For more information
Email. matt@mansonpublishing.com

Increase in sales of Ambu's Inoject needle

Ambu are a Danish headquartered company with an impressive portfolio of products. One product that is now making its way into many hospital departments and has seen a recent increase in demand is the Inoject needle used for EMG procedures. When asked why use of this needle seemed to be more frequent Chris Smith, UK sales manager for the range, replied " The Inoject needle provides superior performance with reduced friction for ease of skin penetration and a high quality signal for consistent reliable results, helping in the accurate use of Botulinum for many conditions. Inoject needles are currently being used for the relaxation of muscles that are spasmodic in the face, particularly around the eyes, head and neck. The needles also help bring relief to sufferers of cerebral palsy and other genetic nerve diseases, as well as general nerve spasms that cannot be relaxed by manipulation, including laryngeal spasms. These high quality products are available in a full range of sizes and I believe this is reflected in their popularity."

For more information Email. skg@ambu.com

Merck Serono submits application for extension of indication for Rebif® in Europe

Merck Serono, a division of Merck KGaA, Darmstadt, Germany has submitted an application to the European Medicines Agency (EMA) to extend the indication of Rebif®, its leading treatment for multiple sclerosis (MS). The requested label extension is for the use of Rebif® in patients who have experienced a single demyelinating event, an early sign of the disease, and who are at high risk of converting to MS.

"Our application to extend the indication of Rebif® is based on the REFLEX study, which focused on patients with early signs of multiple sclerosis," said Dr. Bernhard Kirschbaum, Executive Vice President for Global Research and Development at Merck Serono. "We remain strongly committed to addressing the medical needs of patients with multiple sclerosis at the various stages of this devastating disease."

Merck Serono's submission of a type II variation to extend the indication of Rebif® is supported by results of the REFLEX study, which were presented at the American Academy of Neurology (AAN) in April 2011. The REFLEX study was designed to evaluate the effect of two different doses of Rebif – the currently approved 44mcg three times a week and 44mcg once a week – versus placebo, on the "Time to conversion to McDonald MS (2005)" in patients with a first clinical demyelinating event and having magnetic resonance imaging (MRI) brain scans consistent with early signs of MS. The study met its primary endpoint for both doses by demonstrating that Rebif® significantly delayed conversion to McDonald MS (2005) in those patients.

The REFLEX study was conducted with the human serum albumin (HSA) – free formulation of Rebif®, which is now available in all European Union countries, Australia, Canada and Switzerland, as well as a number of countries in Asia, Latin America, Africa and the Middle East. The HSA-free formulation of Rebif® is currently not available in the United States.

Tremendous achievement of climbers with MS or PD

In July, 7 men and women with Multiple Sclerosis (MS) and 4 with Parkinson's disease (PD), along with nine climbing companions, reached the highest peak in Africa. This is the first time that a group of people with both of these neurodegenerative diseases have united to reach a summit this high. The climb clearly demonstrated that neurodegenerative diseases do not represent the end of 'normal' life. Mount Kilimanjaro in Tanzania stands at 19,340 feet, not only making it the highest peak in Africa, but also the highest free-standing mountain in the world.

"This 'Kilimanjaro Leap of Faith Adventure' was meant to challenge the body, expand the mind and foster courage in dealing with the diagnosis of a neurodegenerative disease. There have been some really tough parts of the trek, especially altitude sickness, for which there is nothing you can do. Imagine that on top of our neurodegenerative diseases. But, we've made it and that's a credit to all of us who believe that we can go beyond the limitations of our disease and still achieve incredible results, both physically and mentally," said trip organiser Lori Schneider, founder of Empowerment Through Adventure.

"Most of the group dedicated themselves to training to prepare themselves for this challenge. A key attribute of the group is their outstandingly positive outlook, regardless of the hurdles they face, and their unwavering commitment to supporting one another throughout the trip".

Communication activities for the Kilimanjaro Leap of Faith Adventure 2011 are kindly supported by Sanofi.

For further information on Empowerment Through Adventure see www.EmpowermentThroughAdventure.com

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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.

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Standing up to RRMS everyday