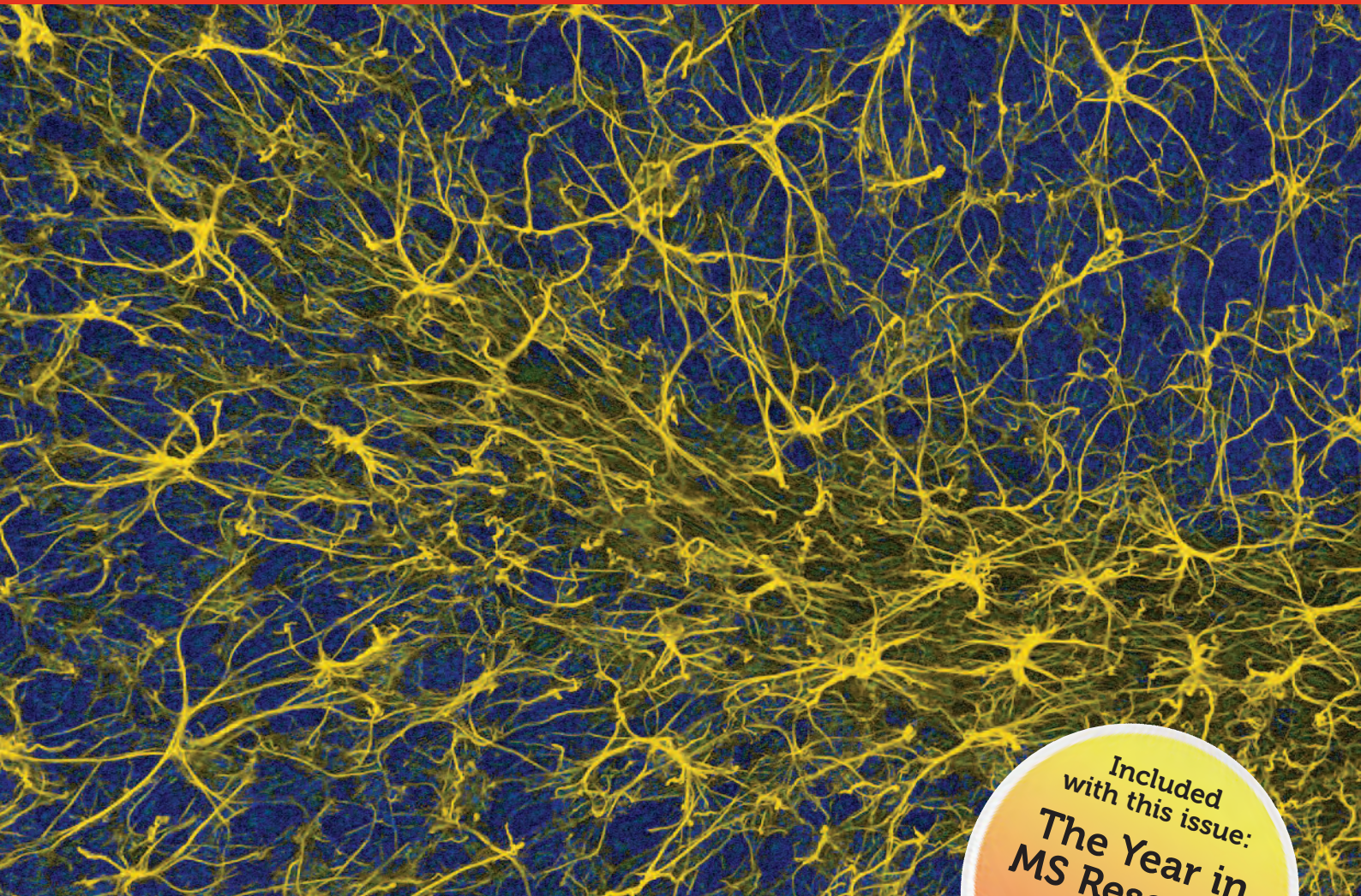


# ACNR

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ADVANCES IN CLINICAL NEUROSCIENCE & REHABILITATION



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**Motor Control – Paul Pope and Chris Miall**

– How Might the Cerebellum Participate in Motor Control, if Life Without One is Possible?

**Clinical Dilemmas in Neuropsychiatry – Simon Fleminger**

– Is Post Concussional Syndrome Due to Brain Damage?

**Neurosurgery – Pharrah Debono, Shawn Agius and Sohail Ansari**

– Paediatric Head Injuries

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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:**

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telephone number: 01296 719768.

#### References:

1. Olanow CW, Rascol O, Hauser R et al. A double-blind, delayed-start trial of rasagiline in Parkinson's disease. *N Engl J Med* 2009; 361: 1268-1278.
2. Stocchi F, Brooks DJ, Melamed E, et al. Effect 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.
3. Azilect Summary of Product Characteristics. October 2010.

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## Award for Professor Lees



Professor Andrew Lees (Director of the Reta Lila Weston Institute of Neurological Studies) has been elected as a foreign honorary member to the Academia Nacional de Medicina in Rio de Janeiro.

The Academia was founded in 1822 with the support of Emperor Dom Pedro segundo and is modelled on the Academie Francaise with only 100 titular members. The only two previous British neurologists to receive this honour were Lord Walton and Dr MacDonald Critchley. Professor Lees delivered a 15 minute presentation on Parkinsons disease in Portuguese at the Academia in Rio de Janeiro on October 22nd and was presented with a commemorative gold medal.

For more information contact: [www.ion.ucl.ac.uk](http://www.ion.ucl.ac.uk)

## University College of London neuroscientist named as 2010 Lennox Award recipient

The American Epilepsy Society (AES) has announced that Simon D Shorvon, MD, of University College of London (UCL), has been named recipient of The William G Lennox Award for 2010. Dr Shorvon is clinical subdean and professor of clinical neurology at the UCL Institute of Neurology and one of the foremost influential epileptologists in the world today. The award recognises his extraordinary body of work in elevating the level of epilepsy care and bringing the disorder into the mainstream of medical research in England, Europe and elsewhere around the globe.

The Lennox Award is conferred by the American

Epilepsy Society and the Lennox and Lombroso Trust for Epilepsy Research and Training.

Dr Shorvon was among the first to conduct studies documenting the treatment gap for people with epilepsy in the developing world. Among many contributions to the field are his creation of the world's first MRI unit dedicated solely to epilepsy research; extensive research on antiepileptic drugs; and, studies of prognosis, mortality and life expectancy in epilepsy.

For more information contact: Peter Van Haverbeke, AES Media Relations, T: +1 703 927 9639.

## Awards for Innovation in Acquired Brain Injury

The United Kingdom Acquired Brain Injury Forum announced the winners of their Awards Scheme at their annual conference on Thursday 11th November 2010. The winners were presented with their awards by eminent Neuroscientist Professor Colin Blakemore.

The winners were:

- Innovation by a law firm in the field of ABI – Bill Braithwaite QC
- Innovation by a clinician in the field of ABI – Sarah Haynes, Head of Speech and Language Therapy at the Royal Hospital for Neuro-disability, Putney.
- Innovation by a care provider in the field of ABI – The Technology Link Workers Project at Royal Hospital for Neuro-disability, Putney.
- Innovation by a social care worker in the field of ABI – Syd Summerfield, CCMS Ltd
- Innovation by a voluntary sector provider or registered charity in the field of ABI – Joint winners, Tom Balchin, ARNI, Trust-Ed

The aim of the awards is to acknowledge the good work which is being done in the sector and reward those who excel in their practice. It's also recognising the many people who go the extra mile or come up with a clever idea.

**UKABIF received a huge number of nominations and hopes to publicise the work which is being done to facilitate sharing of good practice and raise the profile of acquired brain injury and its repercussions. More details about the winners are available on the UKABIF website [www.ukabif.org.uk](http://www.ukabif.org.uk).**



Dr Tom Balchin of ARNI collects the Award for Innovation by a Voluntary Organisation from Professor Colin Blakemore.



Emma Gale from the Royal Hospital for Neuro-disability in Putney who picked up two awards; one for Innovation by a clinician in the field of ABI on behalf of Sarah Haynes and the other for Innovation by a care provider in the field of ABI for their The Technology Link Service.

## Travel bursaries available for the Anglo-Cuban meeting in Havana

The Guarantors of Brain have kindly agreed to provide travel bursaries for the Anglo-Cuban meeting in Havana on 4-6 April 2011. Those wishing to apply for a grant should apply direct to the Guarantors of Brain via <http://www.guarantorsofbrain.org/> where all the relevant information is listed.

You will need to allow a processing time of between two and six weeks, so you are advised to apply sooner than later in order that those who are successful can then go on to book flights/hotels etc.

Successful applicants will be required to submit an abstract of the work which they will be presenting, together with a brief head of department recommendation.

The Association of British Neurologists will also be providing ten travel bursaries, so once the quota has been reached with the Guarantors of Brain, the grant will come from the ABN. The closing date for abstracts is 23 January 2011.

For more information contact: Karen.Reeves@theabn.org

## World-Leading Scientist secures funding for Gene Research

A world leader in dementia research is embarking on a major study into Alzheimer's disease in London, UK funded by a grant from the Alzheimer's Research Trust, the UK's leading dementia research charity.

Professor John Hardy FRS and his team at the UCL Institute of Neurology (Department of Molecular Neuroscience), are beginning an ambitious new study that will see them attempt to identify genes that increase the risk of developing Alzheimer's.

Funded by a £346,000 grant from the Alzheimer's Research Trust, Professor Hardy plans to sequence every gene in 500 people with Alzheimer's, and will compare them with the genes of healthy people.

Their work will reveal the genetic changes responsible for Alzheimer's, giving doctors a better chance of predicting who is at risk of developing the disease.

Professor Hardy said, "Britain has played a leading role in research into the genetics of Alzheimer's disease, and already we are beginning to make real progress. This study should give us a much greater understanding of the causes of Alzheimer's, and should also tell us more about how we can intervene and stop the disease progressing."

For more information see [www.ion.ucl.ac.uk](http://www.ion.ucl.ac.uk)



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Immunomodulation in immune thrombocytopenic purpura (ITP), in children or adults at high risk of bleeding or prior to surgery to correct the platelet count; Guillain-Barré syndrome; Kawasaki Disease; allogeneic bone marrow transplantation. **Dosage:** The dose and dosage regimen is dependent on the indication. In replacement therapy the dosage may need to be individualised for each patient dependent on the pharmacokinetic and clinical response. **Replacement therapy in Primary Immunodeficiencies:** dose regimen should achieve trough IgG level at least 4-6g/l. Recommended starting dose is 0.4-0.8g/kg b.w. followed by at least 0.2g/kg b.w. every three weeks. **Replacement therapy in Secondary Immunodeficiencies (including children with AIDS) and recurrent infections:** recommended dose 0.2-0.4g/kg b.w. every three to four weeks. **Immune Thrombocytopenic Purpura:** acute episodes, 0.8-1g/kg b.w. on day one, which may be repeated once within 3 days, or 0.4 g/kg b.w. daily for 2 to 5 days. **Guillain-Barré syndrome:** 0.4g/kg b.w./day for 3 to 7 days. Experience in children is limited. **Kawasaki Disease:** 1.6-2.0g/kg b.w. in divided doses over 2 to 5 days or 2.0g/kg as a single dose. Patients should receive concomitant treatment with acetylsalicylic acid. **Allogeneic Bone Marrow Transplantation:** Starting dose is normally 0.5g/kg b.w./week, starting 7 days before transplantation and continued for up to 3 months after transplantation. **Method of administration:** For intravenous use only. The initial infusion rate is 0.3ml/kg b.w./hr. It may be gradually increased to 4.8ml/kg b.w./hr if well tolerated. Maximum recommended infusion rate in PID is 7.2ml/kg b.w./hr. Privigen may be diluted with 5% glucose solution to final concentration of 50mg/ml (5%). **Contraindications:** Hypersensitivity to the active substance or to any of the excipients. Hypersensitivity to homologous immunoglobulins, especially in the very rare cases of IgA deficiency when the patient has antibodies against IgA. Patients with hyperprolinaemia. **Special warnings, precautions for use:** Certain severe adverse drug reactions may be related to high infusion rate such as: hypo- or agammaglobulinaemia with or without IgA deficiency, patients who receive IVIg for the first time, switched therapy or have not received IVIg for a long period. Haemolytic anaemia can develop subsequent to IVIg therapy due to enhanced red blood cell sequestration. Monitor for symptoms of haemolysis. Caution should be exercised in obese patients and those with pre-existing risk factors for thrombotic events. Cases of acute renal failure have been reported in patients receiving IVIg therapy. IVIg administration requires adequate hydration prior to infusion, monitoring of urine output and serum creatinine levels and avoidance of concomitant use of loop diuretics. In case of adverse reaction, either the rate of administration must be reduced or the infusion stopped. Immunoglobulin administration may impair the efficacy of live attenuated virus vaccines and may result in transient misleading positive results in serological testing. Use with caution in pregnant women and breast-feeding mothers. **Safety with respect to transmissible agents:** Standard measures to prevent infections resulting from the use of medicinal products prepared from human blood or plasma are considered effective for enveloped viruses such as HIV, HBV, and HCV, and for the non-enveloped viruses HAV and B19V. Despite this, the possibility of transmitting infective agents cannot be totally excluded. This also applies to unknown or emerging viruses and other pathogens. There is reassuring clinical experience regarding the lack of hepatitis A or B19V transmission with immunoglobulins and it is also assumed that the antibody content makes an important contribution to the viral safety. For further information please refer to the Summary of Product Characteristics. **Side effects:** Chills, headache, fever, abdominal pain, vomiting, allergic reactions, nausea, arthralgia, fatigue, low blood pressure and moderate low back pain may occur. Rarely, a sudden fall in blood pressure and, in isolated cases, anaphylactic shock may be experienced. Cases of reversible aseptic meningitis, reversible haemolytic anaemia/haemolysis, transient cutaneous reactions, increase in serum creatinine level and/or acute renal failure have been observed with IVIg products. Very rarely, thromboembolic events have been reported. For further information please refer to the Summary of Product Characteristics. **Marketing Authorisation Numbers:** 25ml (2.5g): EU/1/08/446/004; 50ml (5g): EU/1/08/446/001; 100ml (10g): EU/1/08/446/002; 200ml (20g): EU/1/08/446/003. **Legal Category:** POM. **Date text last revised:** 16 September 2010. **Basic NHS price:** 25ml vial (2.5g): £135; 50ml vial (5g): £270.00; 100ml vial (10g): £540.00; 200ml vial (20g): £1080.00. **Further information is available from:** CSL Behring UK Limited, Hayworth House, Market Place, Haywards Heath, West Sussex, RH16 1DB.

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## International editorial liaison committee

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

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

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

Our review article by Professor Tim Griffiths and colleagues in this issue of ACNR takes as its theme the coding of timing in the auditory system. One of the amazing abilities of sensory systems is their ability to code for information over a wide range of stimulus intensities - so for example the normal human auditory system is able to hear sounds ranging in frequency from 20Hz to 20kHz. However, less is known about how we code for time intervals and in this wonderful succinct article we are told how this is done by the auditory system - and then how that information is used for a diversity of different perceptual functions.

Talking of timing, Bipin Bhakta and team in their article for our Rehabilitation series discuss the use of anti-epilepsy therapies in patients post stroke. Whilst it is unknown just how common this is, it has been reported that up to 20% of such patients will develop this, although how best to manage this common problem is not known and was studied in this paper. In this questionnaire based study, the numbers of respondents is disappointingly low which limits the significance of their conclusions, but nevertheless it does highlight a number of critical issues and reinforces the point that proper trials in this area are needed.

The articles in our Dilemmas in Neuropsychiatry series have been highly successful and the discussion of the Post-Concussional Syndrome by Simon Fleminger is no exception. Trying to understand how minor head injuries cause problems is an area of intense debate, from those who feel that deficits do exist but we are just not sympathetic enough to look for them, or that our tools for detecting them are too crude, to those who feel the whole area is nothing more than the expression of an affective state. In this article the arguments on all sides of the debate are expertly presented.

What does the cerebellum actually do? This topic has been the subject of debate for many years, as cases of "normal" motor function in the presence of cerebellar agenesis are often cited as being examples of the fact that this structure is not essential for normal motor control. This is despite the fact that all those involved in neurological practice often witness the disabling effects of cerebellar disease. Paul Pope and Chris Miall in their article for the Motor Control Series edited by Martyn Bracewell help us to better understand that patients with cerebellar agenesis are probably not motorically normal, before they go on to discuss how the cerebellum helps in the co-ordination and learning of movements.

Sohail Ansari, Pharrah Debono and Shawn Agius review best practice for the management of head injuries in the paediatric population. About a million patients in the UK are seen with head injuries, of which thankfully the majority are minor resulting in no sequelae. However, in children in cases where the injury is more severe, it is not clear how best they should be managed given most of the major trials exclude this age group. In this comprehensive review, current guidelines are explored and discussed with the conclusion that improvements to the process of assessment and management are needed along with new trials.

Have you ever found that you have managed to drive somewhere with no recollection of how you did this? Well it may be a little perplexing to know just how commonly this happens, but Andrew Larner in his new contribution on Neurological signs discusses just this and its significance.

We have our usual book reviews as well as an eclectic collection of journal reviews, some of which are from new reviewers and we welcome them on board.

Last but not least, we also enclose our new MS Supplement, edited by my Co-editor, Alasdair Coles, which summarises the major work in this area over the last year. A masterly piece of scholarship.

We hope you enjoy the journal as we enter a new year. ♦



*Roger Barker, Co-Editor.*

*Roger Barker, Co-Editor,  
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memory impairment, cognitive disorder, somnolence, tremor, nystagmus, blurred vision, vertigo, vomiting, constipation, flatulence, pruritus, gait disturbance, asthenia, fatigue, fall, skin laceration. Adverse reactions associated with PR prolongation may occur. 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 Bruxelles, 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:** 01/2010 (10VPE0010). Vimpat is a registered trademark. **References:** 1. Vimpat Summary of Product Characteristics, 2010. 2. Beyreuther BK et al. CNS Drug Rev 2007; **13**(1): 21-42. 3. UCB Data on file. **Date of preparation:** June 2010. 10VPE0137



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On the cover: An image of distinction from the Nikon Small World images competition showing 2-Photon fluorescence image of glial cells in the cerebellum (400X).

Thomas Deerinck, National Center for Microscopy and Imaging Research, University of California, San Diego, La Jolla, California, USA.

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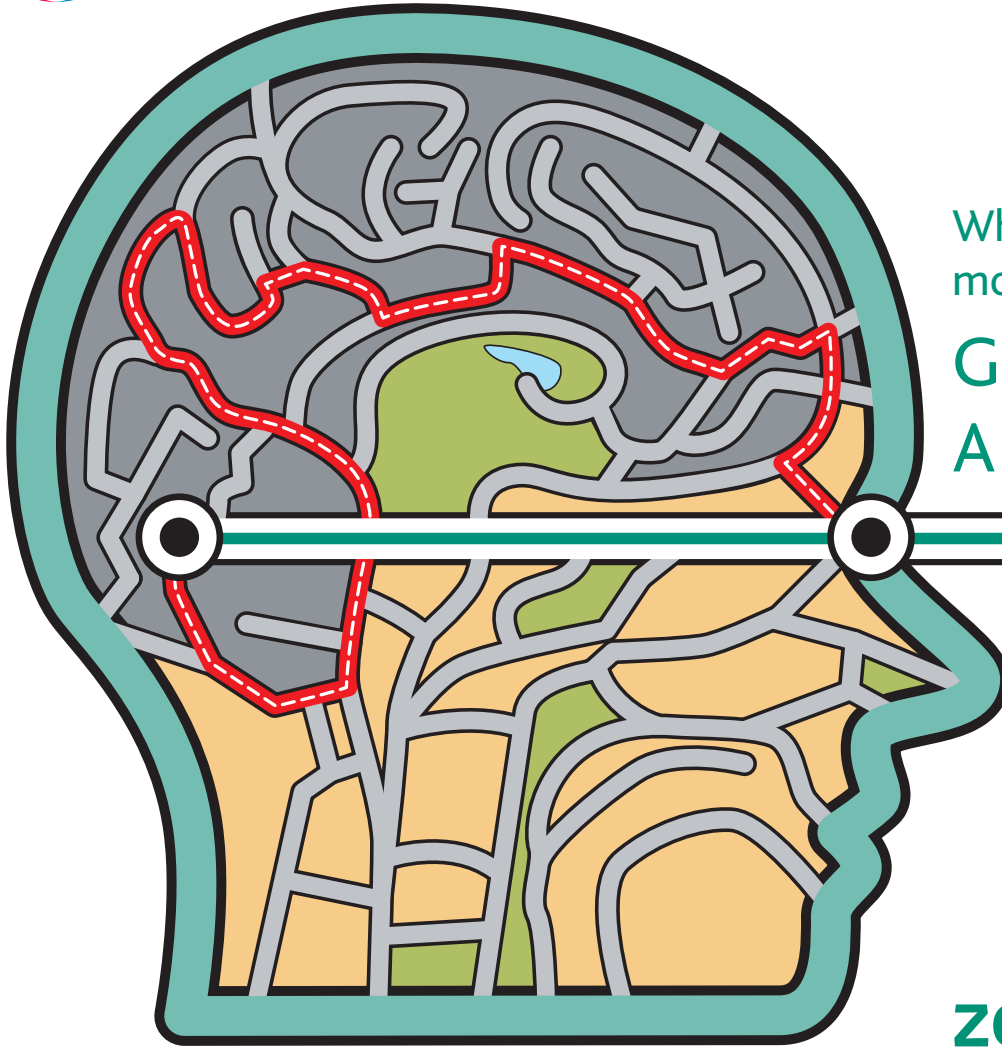


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# Timing and the Auditory Brain



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The human brain processes temporal information over an exceptionally wide range of scale, from microseconds relevant to sound localisation to hours in circadian rhythms.<sup>1</sup> In the auditory system alone, temporal features are encoded over six orders of magnitude; it is required to represent sound structure at the sub-millisecond and millisecond level of timing relevant to sound localisation and the processing of pitch, at the level of tens of milliseconds relevant to phoneme and environmental sound structure, and at the level of seconds and tens of seconds relevant to sentences and 'streams' of sounds.<sup>2</sup>

The auditory system has an hierarchical organisation, which is likely to have homologues in other sensory domains, in which increasing time windows are processed sequentially further from primary auditory cortex. The top levels of this hierarchy require analysis in widely distributed networks, involving structures that are affected by common neurological disorders such as the cerebellum and basal ganglia.

### Millisecond timing: pitch

Pitch describes the perceptual attribute of sound that forms the basis of melody in music or prosody in speech. Aspects of pitch can be related to physical attributes of sound, especially frequency structure (or spectrum) and regularity when considered in the time domain. Whilst early models emphasised the importance of frequency spectrum of a sound,<sup>3</sup> modern theories have required additional consideration of the time-domain properties of sound (See Griffiths 2010 for discussion<sup>4</sup>). Importantly, the perceptual property of pitch cannot be equated with a single sensory property; the brain's representation of pitch is not simply a reproduction of a sound's time or frequency structure. The situation has a parallel in the visual system in which the perception of colour, and the representation of that percept, does not equate to the analysis of the wavelength of light entering the eye, but requires high-level mechanisms beyond the primary visual cortex.<sup>5</sup> Pitch analysis requires both accurate analysis of stimulus timing information from the cochlea upwards and also high-level perceptual representation. We consider here how the critical time information at the millisecond level relevant to pitch is analysed in the brain.

We have conducted a series of experiments using synthetic stimuli in which the regularity at the millisecond level and rate of repetition can be systematically manipulated to examine how these critical timing properties are represented in the brain. The sounds are based on a synthetic noise, manipulated to contain regularity in the time domain, called Regular Interval Noise (RIN).<sup>2</sup> Functional imaging using indirect measures of neural activity (the BOLD response related to blood flow measured using fMRI) demonstrates increased

activity as a function of stimulus regularity in auditory centres from the cochlear nuclei in the brainstem to the auditory cortices, emphasising the representation of regularity at all of those levels.<sup>6,7</sup> The direct measurement of neural activity relevant to pitch has previously only been possible in non-human primates<sup>8</sup> but has recently been examined in experiments on volunteers with epilepsy who have depth electrodes placed in their auditory cortices as in Figure 1.<sup>4</sup> These studies demonstrate regularity of the neural responses in both primary and non-primary auditory cortex that is 'tuned' to the regularity of the pitch stimulus. This tuning must also occur in the centres of the ascending pathway, and the work is consistent with the mapping of sound regularity in the time domain being as important an organisational principle for sensory information in the auditory system as the mapping of frequency (tonotopy). Ongoing experiments by our group using primate fMRI examine the way in which mappings of these sensory properties might relate to each other; current work is examining a theory that orthogonal maps of frequency and time structure<sup>9</sup> exist in brainstem auditory centres.

In addition to the demonstration of timing responses in auditory cortex in the depth electrode experiments, we also sought responses that might be related specifically to the perception of pitch. This was done by presenting RIN with different repetition rates, below and above the lower limit of pitch (about 30Hz in humans). Below the lower limit of pitch the noise stimuli sound like a 'shuddering noise' that does not have pitch. Figure 1 shows brain oscillatory responses that occur above, but not below, the lower limit of pitch in the high gamma range (80-120Hz), consistent with a specific response to the presence of the pitch percept. Unlike the responses to sound regularity mentioned above these responses are not 'tuned' to the pitch heard (the gamma response is always in the same frequency range) and the responses are not precisely time locked to the stimulus. These responses are candidate neural correlates of the pitch percept. Such local oscillations have been implicated in a number of other types of perceptual phenomena in other types of cortex. Ongoing work is examining the way in which the sensory mapping of regularity and perceptual mapping of pitch might interrelate and the emerging picture from these studies is of a complex interconnected system for pitch representation in the auditory cortex that is not adequately characterised by early proposals of a simple 'pitch centre'.

### Tens-of-milliseconds timing and beyond: spectral flux

Spectral flux refers to the change of the frequency structure of sounds over time and is an important feature of speech. When we make the utterance /ba/, for example, there are changes in the

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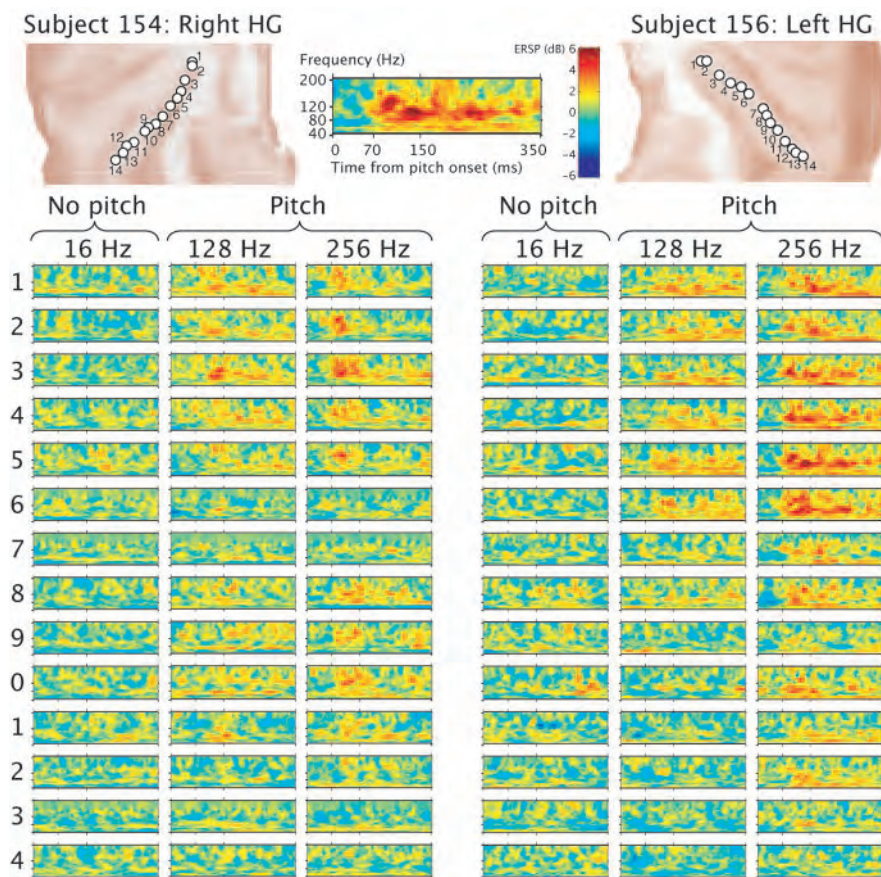


Figure 1: Time-frequency analyses of transition period from random noise to regular-interval noise (RIN) with frequencies of 16 Hz (which does not elicit a pitch), 128 Hz and 256 Hz (which elicit a pitch). Reproduced with permission from Griffiths et al. 2010.<sup>4</sup> Vertical axes represent frequency, horizontal axes time, and colour denotes strength of oscillatory activity at that frequency/time point. Rows 1-14 represent electrode locations from medial to lateral Heschl's gyrus, as illustrated in anatomical maps. Strong, sustained responses in the high gamma range (80-120 Hz) are present, throughout most of Heschl's gyrus, from around 70ms, but only to RIN stimuli that elicit a pitch.

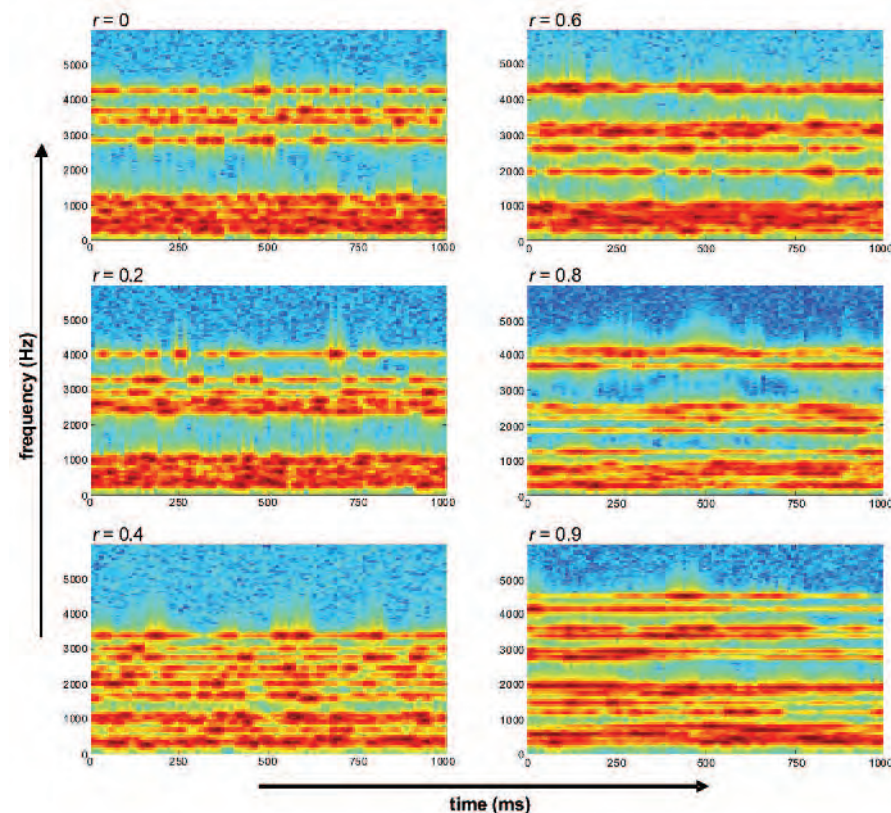


Figure 2: Spectrograms of synthetic sounds with decreasing spectral flux, reproduced with permission from Overath et al., 2008.<sup>8</sup> *r* values represent correlation coefficients. Sounds with a high degree of spectral flux vary over short time windows and have low moment to moment spectral correlation (top left), while more correlated sounds (bottom right) are integrated over a longer period.

frequency composition of the sound that occur over tens of milliseconds. Figure 2 shows a synthetic stimulus we have used in which the spectrum is changed at different rates. The use of an artificial stimulus like this without a semantic label (like /ba/) allows the examination of fundamental time structure in different windows from tens of milliseconds to hundreds of milliseconds. fMRI work using such stimuli implicates non-primary auditory cortex in the superior temporal plane in processing time windows in the tens-of-milliseconds range, whilst very long time windows appear to be analysed by right sided mechanisms in the superior temporal sulcus.<sup>10</sup> Overall the data support, firstly, the idea that increasingly long temporal windows are processed sequentially further from primary auditory cortex. The principle is reminiscent of demonstrations in the visual system of increasing receptive field size in 'higher' cortical areas.<sup>11</sup> Secondly, the data support the suggestion that the hemispheres might differ in their involvement in the processing of different time windows, where left sided auditory areas preferentially sample short time windows, relevant to speech semantics, while right sided areas integrate over a longer period, relevant to prosody.<sup>12,13</sup> The use of synthetic stimuli in these experiments allows the lateralisation of timing to be investigated without the problems associated with considering speech stimuli.

**Hundreds-of-milliseconds timing: interval timing**

Interval timing involves the measurement and comparison of time periods with clearly defined start and end points. Behavioural studies support the existence of a central mechanism that operates on intervals with length ranging from a few hundred milliseconds to one second.<sup>14</sup> At this level of timing organisation there is clear evidence for the interaction of timing mechanisms involving different modalities, in contrast to the specific auditory timing mechanisms considered above. Practice effects are shown at this level of timing analysis where training in one domain improves performance in others, provided that interval length remains constant.<sup>15-16</sup>

The cerebellum has been proposed to be a critical structure for interval timing, and lesions here have long been known to impair performance on sensory and motor timing tasks.<sup>17</sup> Recent work, however, distinguishes absolute, duration-based timing of single intervals from relative analysis of time intervals based on a regular beat. Patients with spinocerebellar ataxia type 6 (SCA-6), causing a 'pure' and stereotyped cerebellar degeneration, performed five separate tasks that tested either absolute or beat-based timing<sup>18</sup> (Figure 3). SCA-6 patients were impaired compared to controls on two tasks that tested absolute timing, in which subjects were required to judge changes in the interval between two tones. They were not impaired in relative or

beat-based tasks, which required judgements of time change in complex sequences where a regular beat provided context for the judgement. In a separate experiment, in which the cerebellum was a temporarily 'de-activated' by repeated transcranial magnetic stimulation, a similar impairment was demonstrated.<sup>19,20</sup> These results support a view of the cerebellum as a stopwatch-like mechanism for interval timing,<sup>21</sup> for which it possesses the appropriate neural machinery.<sup>22</sup> The work suggests mechanisms beyond the cerebellum for accurate beat-based timing.

### Timing over seconds: beats

The analysis of relative time intervals based on a regular beat requires the comparison of intervals of hundreds of milliseconds embedded within sequences of a few seconds' duration. PET,<sup>23</sup> fMRI<sup>24,25</sup> and MEG<sup>26</sup> functional imaging has demonstrated an extensive network of cortical and sub-cortical areas (including the cerebellum) involved in timing tasks, but increased activation of only the basal ganglia, specifically the putamen and pallidum, when beat perception or internal beat generation is required.<sup>24,27,28</sup> Further evidence for a role of the basal ganglia in beat generation comes from studies of patients with idiopathic Parkinson's disease whose timing judgements benefit less from the presence of a beat than controls.<sup>27</sup>

During beat-based tasks, the basal ganglia display greater functional connectivity with supplementary motor areas, pre-motor cortex, and primary auditory cortex.<sup>28</sup> Activation in these areas correlates with individual ability to perceive beats,<sup>25</sup> whereas the basal ganglia are strongly activated in all individuals. Therefore, while it is clear that the basal ganglia are involved in beat analysis, their precise role in beat-based timing remains to be explored. The contribution of dopamine levels to beat-based timing is also an area of ongoing interest, as dopaminergic modulation has been shown to directly influence timing processes in humans<sup>29</sup> and most patient studies in this area to date have used idiopathic Parkinson's disease as their model.

### Conclusion

The human brain can precisely analyse time intervals at a remarkable range of different lengths and use this information to form percepts as diverse as location, pitch, duration, beat and the time of day. The neural machinery to perform these diverse tasks is complex, and varies according to task requirements, but converging evidence suggests an arrangement in which longer time windows are dealt with hierarchically further from primary sensory cortex.

Investigation of basal ganglia contributions to these processes is ongoing, and is an example of a high level of the hierarchy

affected by common neurological disorders that might be manipulated therapeutically. More complete understanding of brain timing mechanisms could lead to the improvement of existing timing based rehabilitative therapies, such as rhythmic auditory stimulation. This technique, in which there is external replacement of lost internal beat generation, has already shown potential in the rehabilitation of gait in sufferers of Parkinson's disease.<sup>30</sup> It has been demonstrated to be effective even when cognitive impairment is present,<sup>31</sup> and is thought to reduce falls risk by reducing the high stride-to-stride variability that is characteristic of Parkinsonian gait.<sup>32</sup> ♦

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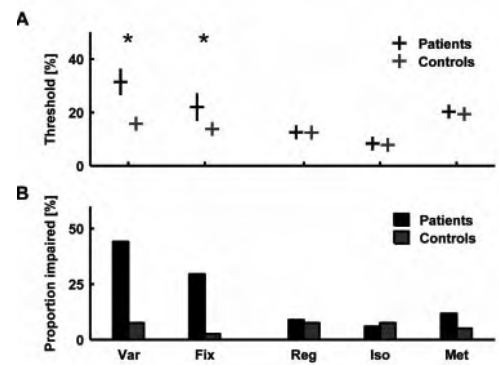


Figure 3: Performance of SCA-6 patients (n=34; black) compared to controls (n=40; grey) on timing tasks, reproduced from Grube et al., 2010.<sup>19</sup> Var and Fix involved simple discrimination of the length of variable and fixed intervals respectively. SCA-6 patients were impaired on these tasks. Reg, Iso and Met were all beat-based or regularity-based timing tasks. SCA-6 patients performed as well as controls on these tasks.

# BOTOX® (Botulinum toxin type A, BoNTA, Allergan) in the management of chronic migraine

Dr Manjit S. Matharu

Migraine is a neurovascular disorder characterised by headaches that are usually unilateral, throbbing, and accompanied by nausea and sensitivity to light, sound or movement.<sup>1</sup> Migraine can be classified based on the frequency of headache attacks.<sup>2,3</sup> Episodic migraine is diagnosed when patients have up to 14 headache days per month,<sup>2</sup> while more frequent, chronic migraine is characterised by at least 15 headache days per month for at least 3 months, where at least 8 of those days are with migraine.<sup>3</sup>

Patients with chronic migraine form a significant part of general neurology and subspecialty headache practice, and often pose an ongoing therapeutic challenge. The first step towards effective management of chronic migraine is identification of factors which can contribute to headache chronicity, including medication overuse, co-administration of medications (such as nitrates) which may exacerbate migraine, and consideration of other medical factors (obstructive sleep apnoea, intracranial hyper- or hypotension or other causes of secondary headache) that may coexist.<sup>4,5</sup>

Treatment of chronic migraine involves a combination of effective, abortive strategies in addition to a prophylactic agent.<sup>6</sup> Options for abortive therapy include simple analgesics, non-steroidal anti-inflammatory drugs (NSAIDs), triptans and ergots while opioids should be avoided.<sup>6</sup> However, overuse of abortive treatments exists in a significant proportion of chronic migraine patients, and therefore the focus of management is often on limiting their intake.<sup>7</sup>

The issue of how to optimally treat medication overuse in chronic migraine is one where received wisdom prevails without a strong evidence base. The traditional approach has been firstly to discontinue the overused medication where possible, or at least limit it to the recommended maximum frequencies outlined by the ICHD-II criteria.<sup>3</sup> This approach has been justified on the basis that medication overuse can in itself cause headache, as well as making the features of the underlying pain harder to characterise, and may interfere with the efficacy of prophylactic treatment.<sup>6</sup> This final point in particular is open to dispute, as it lacks well-controlled supportive data. Strategies for efficient management of medication overuse must centre on patient education: it is vital to discuss the treatment plan, explain what symptoms can be expected, that an increase in headache severity may occur initially and should be transient, and that a 'wash-out' period will enable subsequent treatment to be directed at the patient's true underlying headache rather than a secondary, drug-induced one.<sup>6</sup>

The use of prophylaxis in the management of chronic migraine has been recommended to reduce headache frequency, severity and duration in addition to improving the disability associated with the disease.<sup>8</sup> However, whilst many currently available prophylactic migraine treatments have been shown to be beneficial in the treatment of episodic migraine, few studies have been conducted in the chronic migraine population. The current evidence base of preventive drugs in chronic migraine is limited to randomised controlled trials (RCT) of topiramate<sup>9,10</sup> besides a small RCT and a comparator trial of valproate.<sup>11,12</sup>

## Introduction to BOTOX® (botulinum toxin type A, BoNTA, Allergan)

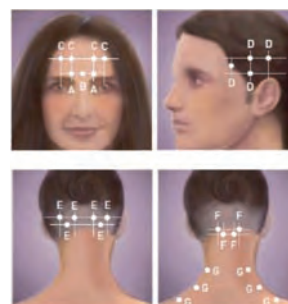
Botulinum toxin is produced by *Clostridium botulinum*, a Gram-positive anaerobic bacterium.<sup>13</sup> *Clostridium botulinum* toxin type A, the active constituent of BOTOX® (Allergan), has recently been specifically licensed for headache prophylaxis in adults with chronic migraine (headaches on ≥15 days per month of which at least 8 days are with migraine).<sup>13</sup> In addition to chronic migraine, BOTOX® is licensed in the UK for blepharospasm, hemifacial spasm, idiopathic cervical dystonia including spasmodic torticollis, severe hyperhidrosis of the axillae and focal spasticity.<sup>13</sup>

## Examining the evidence for BOTOX® in chronic migraine

The safety and efficacy of BOTOX® as a prophylactic treatment option for patients with chronic migraine have been assessed in the Phase III Research Evaluating Migraine Prophylaxis Therapy (PREEMPT) programme, the largest comprehensive clinical trial programme in chronic migraine to date.<sup>14</sup> The PREEMPT clinical trial programme consisted of two Phase III studies of chronic migraine patients, involving a total of 1384 adults from sites across Europe and North America.<sup>14</sup> The studies comprised a 24-week randomised, double-blind, placebo-controlled phase followed by a 32-week open-label phase.<sup>14</sup> The individual PREEMPT studies were conducted simultaneously with essentially identical designs, allowing the results to be pooled to determine the precision of and variability around the results for the primary and all secondary endpoints.<sup>14</sup>

In the PREEMPT studies, eligible patients were randomised to receive BOTOX® (155–195 units\*) or placebo administered at 31–39 sites across seven specific muscle groups of the head, neck and shoulders every 12 weeks (Figure 1).<sup>14</sup> Patients recorded headache symptoms and medications via a daily telephone diary.<sup>14</sup> Two-thirds of patients overused acute pain medications during the 28-day baseline period.<sup>14</sup>

Figure 1. Injection protocol for BOTOX® in chronic migraine.<sup>13</sup>



Site	Muscle	Number of units*	Additional units*, if necessary
A	Corrugator	10 (5 each side)	–
B	Procerus	5	–
C	Frontalis	20 (10 each side)	–
D	Temporalis	40 (20 each side)	10 (up to 2 sites)
E	Occipitalis	30 (15 each side)	10 (up to 2 sites)
F	Cervical paraspinal	20 (10 each side)	–
G	Trapezius	30 (15 each side)	20 (up to 4 sites)

\*The 'unit' by which the potency of preparations of BOTOX® is measured should be used to calculate dosages of BOTOX® only and is not transferable to other preparations of botulinum toxin.<sup>13</sup>

## Efficacy of BOTOX® in chronic migraine

Results from the PREEMPT study demonstrated statistically significant reductions across multiple headache symptom measures. Patients treated with BOTOX® had an average of 8.4 fewer headache days at week 24 compared with baseline, versus 6.6 for placebo ( $p < 0.001$ ). In addition, a greater percentage of BOTOX®-treated than placebo-treated patients had a decrease of at least 50% from baseline in the frequency of headache days at all time points from week 4 to 24 (47% vs 35% at week 24;  $p < 0.001$ ).<sup>14</sup> Patients in the BOTOX® group also experienced a significantly greater reduction in the frequency of migraine days, moderate/severe headache days and cumulative total headache hours on headache days (all  $p < 0.001$ ), as well as in the frequency of headache episodes ( $p = 0.009$ ) and migraine episodes ( $p = 0.004$ ).<sup>14</sup>

The reduction from baseline in headache days achieved in the 24-week double-blind phase was maintained in the open-label phase, with a continued fall in the frequency of headache days up to

56 weeks.<sup>15</sup> In the open-label phase, patients receiving BOTOX® throughout achieved significantly greater reductions from baseline in headache days compared with patients initially treated with placebo ( $p < 0.05$ ).<sup>15</sup>

Patients treated with BOTOX® experienced an improvement in health-related quality of life.<sup>14,15</sup>

### Safety of BOTOX® in chronic migraine

In the PREEMPT studies, treatment-related adverse events were consistent with the known tolerability profile of botulinum toxin type A when injected into the head and neck muscles, and no newly emerged safety findings were observed.<sup>14</sup> Additionally, during the 24-week double-blind phase, the nature and frequency of adverse events were similar in the two arms.<sup>14</sup>

In the double-blind phase of the PREEMPT study, the only adverse events reported with an incidence of more than 5% were neck pain (8.7%) and muscular weakness (5.5%) in the BOTOX® group, and upper respiratory tract infection (5.3%) in the placebo group.<sup>14</sup> Most events were mild or moderate in severity and resolved without sequelae.<sup>14</sup> Serious adverse events occurred in 4.8% of BOTOX® patients and 2.3% of placebo patients.<sup>14</sup> In the open-label phase, during which all patients were exposed to BOTOX®, the adverse events occurring at a rate more than 5% were neck pain (5.8%) and sinusitis (5.1%), while serious adverse events occurred in 3.8% of patients.<sup>15</sup> There was one treatment-related serious adverse event in the group receiving BOTOX® that resulted in hospitalization due to migraine.<sup>14,15</sup>

### Summary

BOTOX® is currently the only pharmacotherapy specifically licensed for the prophylactic treatment of headache in adults with chronic migraine (headaches on  $\geq 15$  days per month of which at least 8 days are with migraine) in the UK.<sup>13</sup> Results from the PREEMPT clinical trial programme have demonstrated that BOTOX® is effective and generally well tolerated in the prophylactic treatment of chronic migraine when it is administered as described in the PREEMPT injection protocol.<sup>14</sup>

### BOTOX® (botulinum toxin type A) Abbreviated Prescribing Information

**Presentation:** Botulinum toxin type A (from clostridium botulinum), 50 or 100 or 200 Allergan Units/vial. **Indications:** Symptomatic relief of blepharospasm, hemifacial spasm, idiopathic cervical dystonia (spasmodic torticollis) and severe axillary hyperhidrosis in adults. Focal spasticity – dynamic equinus foot deformity due to spasticity in ambulant paediatric cerebral palsy patients (two years or older), wrist and hand disability due to upper limb spasticity associated with stroke in adults. Prophylaxis of headaches in adults with chronic migraine ( $\geq 15$  headache days,  $\geq 8$  days with migraine per month). **Dosage and Administration:** See Summary of Product Characteristics for full information. Reconstitute with sterile unpreserved normal saline (0.9% sodium chloride for injection). BOTOX® doses are not interchangeable with other preparations of botulinum toxin. **Blepharospasm:** Inject using a 27–30 gauge needle. Initially, 1.25–2.5 U injected into the medial/lateral orbicularis oculi of the upper lid and the lateral orbicularis oculi of the lower lid. Subsequently, dose may be increased up to two-fold. Initial dose should not exceed 25 U per eye. Total dose 100 U. **Hemifacial spasm:** Treat as for unilateral blepharospasm (as above). Inject other affected facial muscles as needed. **Cervical dystonia:** Inject using a 25, 27 or 30 gauge needle (for superficial muscles) or 22 gauge (deeper musculature). Tailor dosing to individual patient based on the head and neck position, location of pain, muscle hypertrophy, body weight and response. Do not inject sternocleidomastoid muscle bilaterally. Total dose 200U. **Hyperhidrosis of the axillae:** Inject using a 30 gauge needle. Inject 50U intradermally to each axilla, evenly distributed in multiple sites 1–2 cm apart. **Paediatric cerebral palsy:** Inject using a 23–26 gauge needle into the medial and lateral heads of the affected gastrocnemius muscle. Recommended total dose is 4 U/kg body weight, divided between two limbs if injected on same occasion. **Focal spasticity associated with stroke:** Inject using a 25, 27 or 30 gauge needle (superficial muscles) or longer needle for deeper musculature. Tailor dose and number of sites based on size, number and location of muscles involved, severity of spasticity, and the presence of local muscle weakness. Total dose 360U, divided among selected muscles. **Chronic Migraine:** Inject using 30 gauge, 0.5 inch needle, or 1 inch needle for thicker muscles in neck region if required. Inject 0.1ml (5U) intramuscularly to 31 (up to 39) injection sites, divided across seven specific head/neck muscle areas including frontalis, corrugator, procerus, temporalis, trapezius and cervical paraspinal muscles. Inject bilaterally, with the exception of procerus. Total dose 155U–195U. **Contra-indications:** Known hypersensitivity to any constituent. Pregnancy or lactation. Presence of infection at proposed injection site(s). **Warnings/Precautions:** Relevant anatomy and changes due to prior surgical procedures must be understood prior to administration. Adrenaline and other anti-anaphylactic measures should be available. Reports of side effects related to spread of toxin distant from injection site, sometimes resulting in death. Caution in patients with underlying neurological disorder and history of dysphagia and aspiration. Patients should seek medical help if swallowing, speech or respiratory disorders arise. Clinical fluctuations may occur during repeated use. Too frequent or excessive dosing can lead to antibody formation and treatment resistance. The previously sedentary patient should resume activities gradually. Caution in the presence of inflammation at injection site(s) or when excessive weakness/atrophy is present in target muscle. Caution when used for treatment of patients with peripheral motor neuropathic disease. Use with extreme caution and close supervision in patients with defective neuromuscular transmission (myasthenia gravis, Eaton Lambert Syndrome). Contains human serum albumin. Procedure related injury could occur. May cause asthenia, muscle weakness, somnolence, dizziness and visual disturbance which could affect driving and operation of machinery. **Blepharospasm:** Reduced blinking following injection of the orbicularis muscle can lead to corneal pathology. Careful testing of corneal sensation in eyes previously operated upon, avoidance of injection into the lower lid areas to avoid ectropion, and vigorous treatment of any epithelial defect should be employed. Ecchymosis and facial swelling can occur. Caution when treating patients at risk for angle closure glaucoma. **Cervical Dystonia:** Possibility of dysphagia which may be mild but could

While introducing BOTOX® into clinical practice may pose a challenge for service provision, with the requirement for three-monthly injections by a trained injector, the required investment in the infrastructure of headache services is likely to be rewarding as this novel therapeutic approach in the management of chronic migraine holds the potential to significantly improve the quality of life of this patient group.

### Disclosure

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be severe. Limiting dose into the sternocleidomastoid muscle to less than 100 U may decrease the risk of dysphagia. *Focal Spasticity associated with paediatric cerebral palsy and stroke:* Not intended as a replacement for the usual standard of care regimens. Not likely to be effective in improving range of motion at a joint affected by a fixed contracture. *Hyperhidrosis of the axillae:* Consider secondary causes of hyperhidrosis to avoid symptomatic treatment without the diagnosis and/or treatment of underlying disease. *Chronic Migraine:* Efficacy has not been shown in prophylaxis of episodic migraine (headaches  $< 15$  days per month). **Interactions:** Theoretically, effect may be potentiated by aminoglycoside antibiotics or other drugs that interfere with neuromuscular transmission e.g. tubocurarine-type muscle relaxants. **Adverse Effects:** See Summary of Product Characteristics for full information on side effects, including details of uncommon, rare and very rare events. **General:** Usually occur within the first few days following injection and are transient, but rarely persist for several months or longer. Local muscle weakness represents the expected pharmacological action. Localised pain, tenderness and/or bruising may be associated with the injection. Fever and flu syndrome have been reported. **Frequency By Indication:** Defined as follows: Very Common ( $> 1/10$ ); Common ( $> 1/100, < 1/10$ ); Uncommon ( $> 1/1,000, < 1/100$ ); Rare ( $> 1/10,000, < 1/1,000$ ); Very Rare ( $< 1/10,000$ ). **Blepharospasm:** Very common: Eyelid ptosis. Common: Punctate keratitis, lagophthalmos, dry eye, photophobia, lacrimation increase, irritation, face oedema. **Cervical dystonia:** Very common: Dysphagia, muscular weakness, pain. Common: Rhinitis, upper respiratory infection, dizziness, hypertonia, hypoesthesia, somnolence, headache, dry mouth, nausea, musculoskeletal stiffness and soreness, asthenia, influenza like illness, malaise. **Cerebral palsy:** Very common: Viral infection, ear infection. Common: Somnolence, paraesthesia, rash, myalgia, muscular weakness, urinary incontinence, gait disturbance, malaise. **Focal upper limb spasticity:** Common: Hypertonia, ecchymosis, purpura, pain in extremity, muscle weakness, injection site hemorrhage and irritation. **Axillary hyperhidrosis:** Common: headache, hot flushes, non-axillary sweating, injection site reactions and pain. **Chronic Migraine:** Common: Headache, migraine, facial paresis, eyelid ptosis, pruritis, rash, neck pain, myalgia, musculoskeletal pain, musculoskeletal stiffness, muscle spasms, muscle tightness, muscular weakness, injection site pain. **Additional Information:** Side effects related to spread of toxin distant from site of administration reported very rarely (including exaggerated muscle weakness, dysphagia, aspiration/aspiration pneumonia, with fatal outcome in some cases). Rare reports of adverse events involving the cardiovascular system, including arrhythmia and myocardial infarction, some with fatal outcomes. Rare reports of serious and/or immediate hypersensitivity (including anaphylaxis, serum sickness, urticaria, soft tissue oedema and dyspnoea) associated with BOTOX® use alone or in conjunction with other agents known to cause similar reaction. Very rare reports of angle closure glaucoma following treatment for blepharospasm. New onset or recurrent seizure occurred rarely in predisposed patients, however relationship to botulinum toxin has not been established. Needle related pain and/or anxiety may result in vasovagal response. **Basic NHS Price:** 50 Units: £77.50, 100 Units: £138.20, 200 Units £276.40 **Marketing Authorisation Number:** 50 Units: 426/0118, 100 Units: 426/0074, 200 Units 426/0119. **Marketing Authorisation Holder:** Allergan Ltd, Marlow International, The Parkway, Marlow, Bucks, SL7 1YL, UK. **Legal Category:** POM.

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# How Might the Cerebellum Participate in Motor Control, if Life Without One is Possible?



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## Chris Miall

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In the third article in our series on motor control, Paul Pope and Chris Miall provide an elegant overview of current concepts of cerebellar function, drawing on modelling, electrophysiology, imaging, and behavioural studies in healthy participants and patients. They highlight three key areas: motor coordination, motor learning and motor timing. They explain how some clinical phenomena can be understood in the light of the findings of preclinical research.

*Martyn Bracewell, series editor*

The cerebellum has long been considered an important motor control structure, but there are reports in the literature of people who have led a relatively normal life without a cerebellum. Such cases of cerebellar agenesis are rare, but it is clear that patients (e.g. HC,<sup>1</sup> & HK<sup>2</sup>) with only a rudimentary cerebellum can lead an independent life and possess the motor skills required to maintain employment (a manual labourer in the case of HC and work within an electronics workshop in the case of HK). These details of adequate motor performance, however, are incompatible with the 'myth' that suggests one can possess normal motor functions without a cerebellum. His early development is uncertain, but in later life HC is said to have exhibited slow/slurred speech, a squint and problems with gait, although, as Lemon and Edgley<sup>3</sup> point out, it is difficult to conclude whether these problems were due to cerebellum agenesis or just old age. Like HC, HK is also reported to have problems with speech and gait, together with deficits in motor coordination and learning, and possibly intellect. Nonetheless, cerebellar agenesis appears compatible with leading a relatively 'simple' life.<sup>3</sup> Given these details, what might be the irreplaceable functions that the cerebellum normally contributes to motor control? Over the years, theories of cerebellar function have largely involved its role in motor coordination, motor learning or motor timing.

### The cerebellum participates in motor co-ordination

Damage to the adult cerebellum provides strong clues as to its function, unconfounded by the quite dramatic compensation that appears possible if the damage is in early development. For over 200 years it has been known that lesions of the cerebellum impair movement and coordination. In 1891, Luciani published his monograph

on the cerebellum and formulated his triad of cerebellar symptoms, which include: atonia (loss of muscle tone), asthenia (loss of muscle strength) and ataxia (loss of movement continuity). To account for additional observations he added ataxia, or poor movement coordination.<sup>4</sup> In healthy people, normal movements require the coordination in both time and in strength of contraction of agonist and antagonist muscles at different joints in order for movement to have a smooth trajectory and to smoothly brake at the desired endpoint. In patients with cerebellar lesions, movements have an irregular course, consisting of continuous overshooting, over-correcting and then overshooting again around the intended trajectory (as evident in the finger-to-nose test). The cerebellum is therefore thought to be an important structure in coordinating the joints of different limbs, and coordinating between the eye and hand in various manual tasks and during gait. Miall and co-workers<sup>5</sup> provided direct evidence from functional imaging of the brain that the cerebellum supports motor coordination in an eye-hand tracking task when subjects were instructed to follow a moving target with their eyes while simultaneously moving a joystick to control a cursor. Areas in the lateral hemispheres and in the vermis that are concerned with the independent control of hand and eye, respectively, were modulated by the degree of timed coordination between the hand and eye. Additional studies showed learning related changes in these same regions of the cerebellum as participants became familiar with this difficult motor task over a week of practice.<sup>6</sup>

While a person with cerebellar pathology will produce movements slowly and erratically, and with many mid-course corrections, they are still able to initiate movements and decide which movements to execute. Thus, the cerebellum would appear not to initiate movements, or to



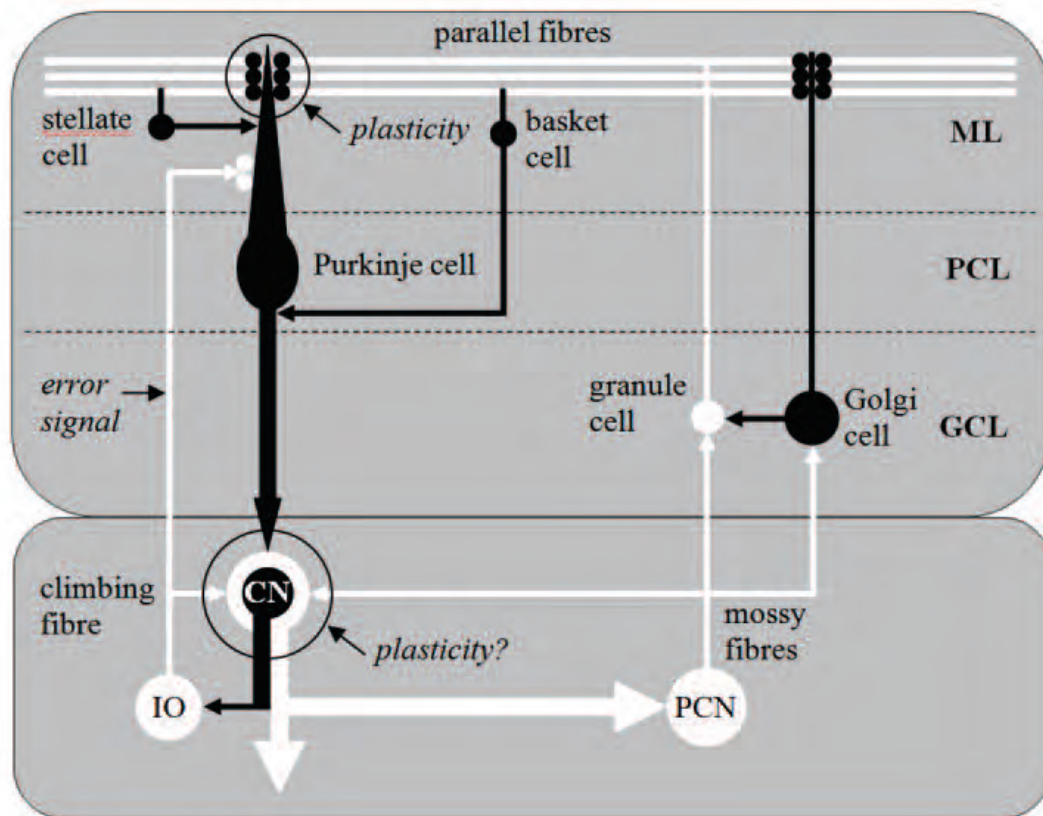


Figure 1: A schematic diagram of the main circuits and interneurons in the cerebellar cortex (after Voogd and Glickstein [1998]. Redrawn by authors). Black cells and arrows make inhibitory connections, white cells and arrows make excitatory connections. ML, molecular layer; PCL, Purkinje cell layer; GCL, granule cell layer; CN, cerebellar nuclei; IO, inferior olive; PCN, precerebellar neurones.

compute which movements to execute, but rather to make on-line adjustments to the form of a movement. Supporting this view is the finding that cerebellar patients exhibit problems making adjustments of eye-hand coordination in throwing while adapting to seeing the world through laterally displacing prisms.<sup>7,8</sup> Studies of cerebellar function that suggest it helps to re-calibrate movement commands are based on the idea of the cerebellum as an 'error-detecting' mechanism. This view is assumed by models of the cerebellum by Marr<sup>9</sup> and Albus,<sup>10</sup> which proposed that the cerebellum is a structure important for motor skill learning, adapting motor commands over repeated experience of an action in order to reduce the performance errors. The details of Marr's theory have been shown to be wrong, but the principles of both models are still thought to be largely correct, and the Marr-Albus-Ito view of the cerebellum dominates all others.<sup>11</sup>

### The cerebellum participates in motor learning

The organised structure of the cerebellar cortex has made it a fertile ground for developing theories of cerebellar function. Marr<sup>9</sup> first proposed that the cerebellum is a device for learning to associate information encoded by the two main excitatory inputs to the cerebellar

cortex: the mossy fibres and the climbing fibres, which together encode the sensory context of the movement (See Figure 1).

The climbing fibres appear to act as an error-detecting device during the learning of a motor task. This idea was demonstrated in a classic paper by Gilbert and Thach,<sup>12</sup> who recorded activity directly from Purkinje cells in monkeys as they learned an arm movement task, and showed increased complex spike activity during the learning phase. The complex spikes in Purkinje cells are known to reliably indicate activity of climbing fibre inputs which originate in the inferior olive of the brainstem. There are now many studies broadly in agreement with Gilbert and Thach's findings, but it has been difficult to nail down exactly what the climbing fibre activity encodes. The inferior olivary cells that are the source of the climbing fibres fire infrequently, and this infrequent but powerful input to the cerebellar cortex can only record the occurrence of an error, or of an unexpected sensory event,<sup>13</sup> rather than the magnitude of the error. It is also evident that the Marr-Albus-Ito theory that proposed that the site of plasticity was at the synapse between the parallel fibres and Purkinje cells is only part of the story, and plasticity is likely at several other points, especially at the synapse between Purkinje cells and the cerebellar nuclei (See Figure 1). The functional impact of this complexity is still unclear.

Models of motor control also capture the idea that the cerebellum is a learning machine which supports the adaptive plasticity needed for the emergence of automatised motor skills. These models typically contain three basic elements (a) internal models that either predict the sensory consequences of our actions (forward models), or predict the movements necessary to achieve a goal (inverse models), (b) a comparator that detects mismatches between predicted and actual output by comparing internal and external feedback signals, and (c) a learning process that uses error information to modify internal models so that movements become fast and accurate. Evidence that the cerebellum can predictively update a representation of the current status of the peripheral motor system (i.e. central state estimate) is provided by work with transcranial magnetic stimulation (TMS): a non-invasive method that depolarises neurons in the brain. For example, Miall and colleagues<sup>15</sup> disrupted the cerebellum during a task in which subjects were required to point to a previously observed target. Errors in the initial direction and in the final position were consistent with the reaching movements being planned from an estimated position of the hand, which was about 140 msec out of date. In short, internal models can help to explain the clumsiness observed in cerebellar

patients, and the problems they have in coordinating actions.

### The cerebellum participates in motor timing

The hypothesis that the cerebellum computes timing requirements for motor performance has been advocated by Keele and Ivry<sup>16</sup>: a view that is supported by numerous findings. In one particular study,<sup>17</sup> the authors asked cerebellar patients to maintain a simple rhythm in one task, and to discriminate between two different interval durations in another. Compared to normal controls, patients were found to be impaired in both tasks; producing temporal intervals that were more variable, and making temporal judgments that were less accurate. Relating the patients' lesion data with their performance data also revealed that medial cerebellar damage impairs motor execution, while lateral cerebellar damage impairs the internal timing of responses.<sup>18</sup> Interestingly, it is damage to a localised region within lateral portions of the cerebellum (lobule HVI) that disrupt the timing of a conditioned eye-blink response in rabbits<sup>19</sup>, and also in humans<sup>20</sup>, including patient HK<sup>2</sup>. The eye-blink conditioning paradigm, which is an associative learning task in which the challenge is to learn the predictive cue, and the moment at which to blink, demonstrates that the cerebellum is capable of motor learning, but it also demonstrates the role of this structure in motor timing.

Further support for the hypothesis that the cerebellum is critical for motor timing is revealed by studies of fast single-joint movements with simultaneous electromyographic (EMG) recordings in cerebellar patients. Normally, these movements are characterised

by a triphasic pattern of muscle activity, firstly in the agonist muscle providing a launching force, followed by a second burst in the antagonist muscle providing a braking force, followed by a second burst in the agonist muscle providing a clamping force.<sup>21</sup> Manto and others have identified deficits in the timing, duration and amplitude of sequential bursts of EMG activity during rapid movements in cerebellar patients when inertial loading is artificially increased.<sup>22,23</sup>

Despite those patient studies that support a pure timing function for the cerebellum, there is little evidence that it behaves like a time-keeper or 'clock', as suggested by the work of Lamarre and Mercier<sup>24</sup> and Llinas and Yarom<sup>25</sup> on the basis of clock-like periodic cell discharges in the inferior olive. Indeed, Keating and Thach<sup>26,27</sup> failed to observe a clock-like timing signal in the discharge patterns of cells in the deep cerebellar nuclei or Purkinje cells, which were found to fire aperiodically. Instead, the inferior olive may help to organise movement in time via the synchronized firing of cell ensembles that allow the use of individual muscles.<sup>28</sup>

### Conclusion

The cerebellum integrates sensory information from many different parts of the brain to help correct mismatches between predicted and actual movements, and can change its output at the correct time to ensure that movements are smooth and error-free. To ensure these operations are optimised, the cerebellum would have to correctly predict the relationship between sensory stimuli during motor learning performance. There is increasing evidence that predictive control is a major function of the cerebellum. Prediction

is critically important in motor control because actions are often required to be performed rapidly, despite relatively slow transmission of sensory and motor signals throughout the CNS. As an example, while typing this manuscript my finger moves to each key on the keyboard within perhaps 400 ms – and much faster than that for a skilled typist who would perform perhaps 8 keystrokes per second (120 ms). And yet, the visual signals reach primary visual cortex with a delay of at least this size, and delays in further visual processing, in conduction delays in the corticospinal tracts and motor nerves, and in neuromuscular coupling means that the fingers cannot be guided by sensory signals but must be predictively controlled. Short term predictions about the current state of the peripheral motor system can help overcome this difficulty, as corrections and updating of the motor commands can be based on these internal state estimates, rather than on sensory feedback. Failure of these predictions would lead to errors in performance similar to the motor symptoms of cerebellar patients, including hypermetria, intention tremor and loss of coordinated action across the joints. Predictions must be learnt based on past experience, and must be time-sensitive. Hence prediction might be the overall function of the cerebellum. It is perhaps this ability that is dysfunctional in patients with cerebellar damage. It is possible, but not yet proven, that the cerebellum might also contribute predictive information to other non-motor processes. For example, there is evidence of disrupted executive function and planning, of linguistic processing, and even of sympathetic functions that might be normally assisted by the cerebellum.<sup>29</sup> ♦

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Series Editor

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Welcome to the fourth 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.

Author



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# Is Post Concussional Syndrome Due to Brain Damage?

## Case

A 43-year-old woman presents with a six month history of persistent headache, substantive memory and concentration impairments, fatigue, irritability, and insomnia. Her partner reports the problem as dating from a fall that knocked her unconscious for a very brief period. She also broke her wrist. She is a policewoman and has been off work since. Her A & E notes (one hour later) record her Glasgow Coma Scale as 15/15. She has no memory of the accident but is described as now having an Abbreviated Mental test Score of 10/10. An MRI brain is normal. Her wrist has healed normally. She has been told that she has post concussional syndrome but has become increasingly worried that she has permanent brain damage from which she will not recover. Can a head injury of this severity cause brain damage and, in particular, substantive cognitive impairment?

When considering this patient it is worth remembering that if symptoms attributed to a mild to moderate TBI persist then the longer the time post injury and the milder the injury the more likely it is that psychological factors, rather than brain damage, are responsible.<sup>1</sup>

### What is brain damage?

This policewoman meets ICD 10 criteria for post concussional syndrome; she has had a head injury and has at least three common post concussion symptoms. But she may not be interested in the diagnosis because it does not tell her whether or not she has brain damage. It is not surprising that a diagnosis that does not tell you what is wrong with the patient is "the bugbear of the clear-minded doctor and lawyer."<sup>2</sup>

But perhaps that is its virtue. The diagnosis post concussional syndrome does not pretend to know whether or not there has been brain damage. When we are dealing with a condition that often occurs at the very margins of what constitutes "brain damage", this is probably a wise move. As our ability to identify more and more subtle evidence of brain damage / injury increases, so it

becomes increasingly difficult to be sure if any abnormality we are detecting actually explains the problems the patient has. So, for example, in a study of fractional anisotropy (FA) after mild traumatic brain injury (mTBI), the evidence that there had been some degree of brain damage, presumably resulting from the mTBI, was based on analysis of the number of regions of interest (ROI) on MRI with FA scores that were greater than one standard deviation from the norm.<sup>3</sup> Unsurprisingly, many of the normal control subjects had several ROIs that met this criteria. Patients after an mTBI had more ROIs with abnormal fractional anisotropy, but there was a large overlap with controls. Perhaps any changes in the mTBI group were present before their head injury, and it was the problems they had associated with an apparently less healthy brain that explained why they had a head injury in the first place.

### Its OK to have some brain damage

We hear a lot about patients with lots of symptoms yet normal routine neuroimaging after a head injury. We tend not to hear so much about those with good evidence of brain damage on

neuroimaging, for example mild contusional change, but who make a full recovery in a few months. These patients tell us that permanent disability is not a necessary consequence of brain injury. So in this policewoman's case it is perfectly possible that even if she does have some degree of brain injury she can make a full recovery. Indeed perhaps we should be telling her that frank brain injury in the early months post injury may be a good prognostic marker. It has been shown that in those selected for persistent symptoms after a not very severe head injury a normal EEG is associated with a worse prognosis.<sup>4</sup> This is probably because those with frank brain injury to explain their symptoms will improve as they recover from their brain injury, whereas in those in whom psychological factors explain their persistent symptoms, the psychological factors are unlikely to change much, and their symptoms are likely to persist.

### What about substantive cognitive impairment?

Is it possible that she has suffered substantive cognitive impairment due to brain damage? Two observations need to be acknowledged when attempting to answer this.

1. After an mTBI in unselected cases it is difficult to identify cognitive impairment beyond 3 months;<sup>5</sup> but in selected cases, eg. those presenting for compensation, poor performance on cognitive tests can be found many months post injury.
2. Evidence of brain dysfunction undertaking a cognitive task may be observed at least one to two months after an mTBI, in the absence of poor performance on the task.<sup>6</sup> Compared with control subjects, patients undertaking a working memory task show increased cerebral blood flow across more widespread areas of cortical tissue. But they perform the task just as well as controls. The patients seem to have to work harder to maintain their performance.

So the chances are that by six months she no longer has substantive cognitive impairment despite complaints of poor concentration and memory. In the early days and weeks post injury it is likely that some degree of brain dysfunction was present, particularly if her injury had resulted in loss of consciousness of many minutes rather than just a few seconds.

But a score on the Abbreviated Mental Test Score of 10/10 does not rule out significant cognitive impairment and she may well ask for more detailed neuropsychological testing to see whether there is evidence of brain damage. The problem here is that it is often difficult to be sure that mild to moderate degrees of poor performance on formal neuropsychological tests is due to brain damage.<sup>7</sup> So even if she does not do very well on neuropsychometric testing, is it really going to help answer her question?

Despite these uncertainties I would recommend neuropsychometric testing; the results often show good levels of performance, which can be encouraging for the patient. And

neuropsychometry may show an unexpected pattern of impairment which is useful for the patient to be aware of, and may help focus rehabilitation strategies.

### What is her prognosis?

She has suffered a mild TBI; loss of consciousness less than 30 minutes, GCS 13, 14 or 15, and probably has post traumatic amnesia duration of less than 24 hours.<sup>8</sup> When followed up at 3, 6 and 12 months respectively approximately a half, a quarter and an eighth of mTBI patients have significant post concussion symptoms. So she has about a 50% chance of recovering over the next six months.<sup>1</sup> Perhaps being optimistic will improve her chances of recovery; those who believe they have suffered a serious injury may do worse.<sup>9</sup>

### If its not brain damage what is causing her persistent symptoms?

My best guess is that persistent post concussional disorder, in the absence of evidence of brain damage, is best understood as akin to a somatisation disorder. So, for example, the symptoms of post concussional disorder are not very specific to those with a head injury, and share a lot in common with symptoms seen in patients who have never had a head injury but have been injured to the body<sup>10</sup> or have chronic pain<sup>11</sup> or chronic fatigue. Just as irritable bowel syndrome may be triggered by an episode of infectious gastroenteritis, or chronic fatigue by a viral illness, so persistent post concussional syndrome is triggered by a blow to the head. Symptoms that initially are largely driven by pathophysiology later come to depend on psychopathology.

Anxiety is probably a key factor in many of these syndromes. In the case of post concussional syndrome Lishman has proposed a model in which anxiety disrupts the healthy recovery from the physical trauma to the brain.<sup>12</sup>

### How should we manage this patient?

A good history is essential. This will enable us to confirm that this seems to have been an uncomplicated mTBI, rather than, for example, due to a systemic illness or seizure. The psychological implications of the injury can be explored; was there hidden meaning in the situation that caused the fall that is psychologically traumatic, an example of Pilowsky's cryptotrauma;<sup>13</sup> was the fall the last straw in a string of incidents that have been stressful for her; does she now find herself in unbearable tension between demands to return to work and her fear of further injury at work? A good history will reassure her that you have taken her case seriously and not perhaps jumped to conclusions on the basis of somebody else's assessment that it is all psychological.

In her case the normal MRI has excluded the possibility that she suffered a significant contusion; the occasional patient with an mTBI does in fact suffer significant contusions which are responsible for mental sequelae. But it must be accepted that a normal MRI does not rule out

significant brain damage, particularly mild diffuse axonal injury.

Our approach is agnostic; to accept that there is uncertainty as to whether or not there has been brain damage and that no sophisticated investigation is going to resolve this. We suggest to the patient that regardless of cause, physiogenesis or psychogenesis, the treatment is the same. ♦

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# Specialty Certificate Examination in Neurology



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Just when you thought you'd sat enough exams, another one comes along! This aim of this article is to provide a brief overview of the Specialty Certificate Examination (SCE) in Neurology. Much of the information below and further handy hints for success can be found on the ABNT website and MRCP (UK) website.

## Background

The SCE in Neurology was formally introduced in May 2009. Attainment of this examination is now compulsory for trainees who began their specialist training in or after August 2007 in order to obtain their Certificate of Completion of Training (CCT). On successful completion of the exam, trainees are awarded a specialty certificate and are eligible for the title MRCP (UK) (Neurology) when recommended for CCT.

A standard-setting procedure is used to determine the passmark for the exam. This is based on the perception of a group of neurology specialists on how difficult the exam material is and further adjustments are made after the examination to take into account variability in performance. In 2010, 75 candidates undertook the exam. The passmark was 53%. 47 of the 55 UK candidates (i.e. 85.5%) and 8 of the 20 non-UK candidates passed.

## Eligibility and timing

The MRCP (UK) website states that to be eligible to take the exam, UK candidates must have: successful completion of all parts of the MRCP (UK) and/or been appointed to a substantive STR programme and awarded a National Training Number (NTN). This means that trainees who possess an NTN but are currently on out of programme experience (e.g. doing research), or trainees who don't yet have an NTN but do have MRCP (UK) are eligible to sit the exam. However this situation may well change and we would advise those without an NTN to contact the college prior to applying for the exam (see end of article for email address). Trainees who began their specialist training before 2007 are not required to undertake this exam.

It is recommended the exam is undertaken before your final year of registrar training, ideally in your penultimate year although, as noted above, it can be done earlier.

## Format

This is a computerised exam with a best-of-5 format. Most questions take the form of a clinical scenario. It is divided into two papers, each comprising 100 questions. Each paper lasts three hours and both are done on the same day. There is no negative marking.

## Practicalities

The exam is held once a year. The date and deadline for application can be found on the MRCP UK website. At present the cost is £825 for 2011, which is an increase from the cost in 2010 (£800). The high cost results from the rigorous process for question-setting combined with the small number of candidates: even at this price the College anticipate making a loss. Some departments may provide you with money towards the exam so it is worth checking beforehand. If you fail the exam in 2011 you are eligible for a free second attempt in 2012. However from 2012, you will need to pay the full cost of the exam again to resit.

You can apply for the exam online on the MRCP (UK) website. To do this, you will need your RCP code number. You need to register for an online My MRCP (UK) account and pay the fee. You will then be sent a confirmatory email. Then you can book a place at an allocated Pearson Vue test centre.

## Revision

In theory, knowledge for the exam is meant to be acquired during your clinical training through your inpatient and outpatient work, grand rounds and training days. For this reason, you may feel more comfortable sitting the exam during the later stages of your training. Most people who have sat the exam successfully would agree you do need to revise for it. In particular, it is worth remembering the exam includes interpretation of neuroimaging (CT, MRI) and neurophysiology (EEG, NCS/EMG). Good luck! ♦

## Further information:

### Relevant links:

- Official MRCP website: <http://www.mrcpuk.org/SCE/Specialties/Pages/Neurology.aspx>
- Exam application link: <http://www.mrcpuk.org/SCE/Pages/Application.aspx>
- Sample questions: <http://www.mrcpuk.org/SiteCollectionDocuments/SCENeurologySampleQs.pdf>
- Email enquiries to: [SCE.queries@rcplondon.ac.uk](mailto:SCE.queries@rcplondon.ac.uk)
- ABNT website: <http://www.theabn.org/Members/ABNT.aspx>
- ABNT SCE advice: <http://theabn.org/Publications/AdviceforSCE.aspx>

### Further reading:

- *Practical Neurology journal*, especially the 'Bare Essentials' series
- *Clinical Neurology*, 3rd Edition edited by Fowler and Scadding
- *Aids to the Examination of the Peripheral Nervous System*
- *Neurology: A Queen Square Textbook*. Clarke, Howard, Rossor, Shorvon.



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**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.



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# Neurological Signs: Unconscious Driving Phenomenon



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It is possible that some readers will have had the experience of driving a familiar route, perhaps the morning commute to the neurology clinic, and then having no very clear, or indeed any, recollection of the journey they have made, apparently without mishap. This "unconscious driving phenomenon" has been adduced as an example of the variable distribution of attentional resources.<sup>1</sup>

As such, the unconscious driving phenomenon may be physiological, but other examples may perhaps reflect neurological disease.

### Case Report

A 27-year-old lady was referred to the clinic following a strange driving experience. During daylight hours she set off on the familiar route to her boyfriend's house, part of which involved driving along a motorway. She recollected joining the motorway, but then had no recollection until she found herself six junctions further on, when she should have turned off after only three. At this point she stopped to telephone her boyfriend to explain what had happened and that she would be late. On arrival, he noted that she looked shaken, complained of a headache, and took some analgesics, but on direct questioning there was no history of repetitive questioning or loss of personal identity. The patient had a prior history of migraine as a teenager, and headaches had recurred some five months earlier. Neurological examination and structural brain imaging were normal. The provisional diagnosis of her unconscious driving phenomenon was migraine.

### Discussion

Unconscious driving phenomenon may be seen in transient global amnesia (TGA): instrumental activities, some of them quite complex (e.g. conducting an orchestra<sup>2</sup>) are usually preserved in TGA despite the profound anterograde amnesia. As an occasional cause of transient amnesia, it would seem possible that migraine might also produce unconscious driving, as one of the many transient perceptual phenomena which may be encountered in migraine attacks (Table). Psychogenic amnesia or psychogenic fugue may also furnish an explanation for unrecalled long drives.

A study of two experienced drivers who suffered bilateral hippocampal lesions causing severe amnesia showed that most aspects of their driving performance, as assessed in a simu-

### Table: Some transient perceptual phenomena in migraine<sup>4</sup>

Alice in Wonderland syndrome (micro- and macrosomatognosia)
Angor animi
Autoscopy
Cinematic vision
Entomopia, polyopia
Fortification spectra/Teichopsia
Metamorphopsias: micropsia, macropsia
Oscillucius
Osmophobia
Phonophobia
Photophobia
Physical duality
Zoom effect
Zeitraffer phenomenon

lator, were not impaired, such as vehicle control by means of steering, speed control, and driving with distraction. They also remained familiar with driving rules, road sign meaning, and safety procedures, but did show impairments in following route directions.<sup>3</sup> Such findings support the notion that, as in the patient described, memory impairment does not necessarily impair most aspects of driving performance. ♦

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# Use of Anti-epileptic Drugs in Post-stroke Seizures: A Cross-sectional Survey Among British Stroke Physicians

## Introduction

The incidence of seizures after stroke has been estimated at 4-20%.<sup>1,2</sup> It is also estimated that epilepsy affects 1% of patients aged over 65 and that the majority of these cases (20-40%) are secondary to cerebrovascular disease.<sup>3,4</sup> The risk factors for developing seizures have been identified as cerebral haemorrhage, cortical location of lesion and the severity of stroke, for example those involving multiple lobes.<sup>5,6,7</sup> The incidence of seizures has a bimodal distribution with a peak two weeks post-stroke and a second peak 6-12 months post-stroke.<sup>8</sup> Early, or "acute symptomatic" seizures, are seizures occurring in the first two weeks following an acute stroke. Late or "remote symptomatic" seizures, are those occurring after the first two weeks following an acute stroke.<sup>2</sup>

Most of the seizures are either simple partial seizures or complex partial seizures and, less commonly, generalised tonic clonic seizures.<sup>8</sup> One study showed 35% of the patients with early seizures went on to develop epilepsy, a pre-disposition to unprovoked seizures, compared to 90% of those with late seizures.<sup>8</sup> A large prospective hospital-based study by Bladin et al. found that 8.9% of patients with stroke experienced seizures, although epilepsy only occurred in 2.5%.

There are currently no clear guidelines on use of anti-epileptic drugs (AED) in the management of seizures after a stroke. There is no clear consensus on when to start an AED, which is the best AED to use and for how long to treat patients with an AED. Current practice is often based on the existing guidelines for adult onset epilepsy, both idiopathic and localisation related, and individual physicians experience and preferences.<sup>9,10,11</sup> This study aims to look at consultant stroke physicians' preferences in the use of AEDs with particular emphasis on the choice of AED, initiation of drug therapy, the duration of treatment, and the withdrawal of treatment in the adult and elderly population.

## Methods

A questionnaire comprising four clinical vignettes and a series of clinical questions was designed to capture the required information. Figure 1 contains the four vignettes.

Each of the four vignettes was followed by a similar series of clinical questions. The questions

### Figure 1: Clinical vignettes of the questionnaire

#### 1. Younger adult – Acute post-stroke seizure

A 50-yr-old man has suffered a lobar intracerebral haemorrhage. Twenty-four hours after the event, he suffers an otherwise unprovoked complex partial seizure. He has no history of any previous seizures. If the patient is willing and there are no contraindications to start any anti epileptic medication, which medication would you prefer to start?

#### 2. Younger adult – Late onset / remote post-stroke seizure

A 55-yr-old female with previous MCA territory ischaemic stroke suffers an unprovoked complex partial seizure six months after her stroke. She has no history of any previous seizures. If the patient is willing and there are no contraindications to start any anti epileptic medication, which medication would you commence?

#### 3. Elderly – Acute post-stroke seizure

An 80-yr-old male suffers an otherwise unprovoked complex partial seizure 24 hours after a MCA territory ischaemic stroke. He has no history of any previous seizures. If the patient is willing and there are no contraindications to start any anti epileptic medication, which medication would you commence?

#### 4. Elderly – Late onset / Remote post-stroke seizure

An 82-yr-old female suffers an unprovoked complex partial seizure eight months after a MCA territory ischaemic stroke. She has no history of any previous seizures. If the patient is willing and there are no contraindications to start any anti epileptic medication, which medication would you prefer to start?

for the first vignette are shown in Figure 2.

The questionnaire was sent by e-mail to all members of the British Association of Stroke Physicians (BASP), as it was not practical to selectively email the consultants alone. The association has 408 consultant physician members, 203 trainee members and 11 nurse specialists. Two reminder emails were sent over a period of two months to maximise the response rate. The questionnaire was also set up as an online survey and the website link was sent to all members via the BASP membership email service.

The questionnaire also collected basic demographic data, including the year of qualification, parent specialty and epilepsy training details. The responses did not gather any identifiable data allowing responses to be anonymous.

**Results**

Eighty-two fully completed questionnaires were received. Ten trainee responses were excluded from final analysis. The parent speciality of the 72 consultant physicians who responded was: Geriatrics 77%, Neurology 14%, General Medicine 6% and Rehabilitation Medicine 3%. Figure 3 and Tables 1-4 summarise the results.

We found that 83% of consultant physicians would initiate the same AED in both partial and generalised seizures, and therefore only 17% of physicians would select an AED based upon the presenting seizure type. All respondents would choose to titrate up the first line AED to an optimal dose if it did not initially control seizure activity. If the first line AED failed to control seizures at an optimal dose, 87% physicians said they would add in a second AED, 9% would switch to another AED as a monotherapy and 5% would seek advice from an expert colleague in this situation.

**Discussion**

The survey has a few limitations. Firstly, the small number of fully completed questionnaires returned limits any generalisation of results. Secondly, the clinical scenarios could be understood differently by individual physicians, particularly when responding to postal or online questionnaires where the information provided is limited. The accuracy of responses is also affected by the artificial situation created by using a theoretical model to capture a real-life scenario. The group of physicians chosen for the survey and the responses is not representative of the wider international community of physicians involved in this area.

In the United Kingdom guidelines produced by the National Institute for Health and Clinical Excellence (NICE) and the Scottish Intercollegiate Guidelines Network (SIGN) on the diagnosis and management of epilepsy are widely used.<sup>9,10</sup> However, neither of these guidelines provides specific advice on the use of AEDs in patients with post-stroke epilepsy. SIGN guidelines do make a distinction between idiopathic generalised epilepsies and focal (localisation-related) epilepsies of

**Figure 2. Questions in vignette 1**

No medication

What time frame would you consider treatment (answer one only)

First seizure after first week

Second seizure

Which treatment would you use?

Lamotrigine (Lamictal)

Phenytoin

Sodium Valproate (Epilim / Epilim Chrono)

Carbamazepine (Tegretol / Tegretol Retard)

Levetiracetam (Keppra)

Other – please mention medication

Assuming the patient remains seizure free, how long would you continue the medication

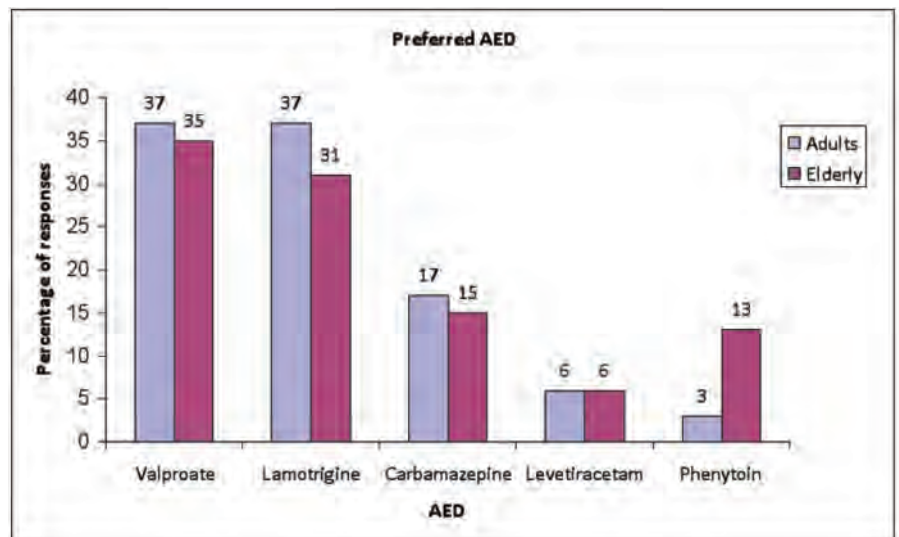
Would your management change if the above patient suffered an unprovoked generalised tonic-clonic seizure?

Yes  (if so which medication below would you start) No

Please mention medication

Any other comments

**Figure 3: First line AED choice in adult and elderly patients**



which post-stroke epilepsy is an example.<sup>9</sup> There are also guidelines from the International League Against Epilepsy (ILAE), specifically analysing the evidence for AED use in elderly patients, defined as age over 60 years, but again it does not provide specific recommendations in post-stroke seizures.<sup>9</sup>

NICE guidelines suggest considering AED for a patient after a first unprovoked seizure if the patient has a neurological deficit or abnormality on brain imaging, which could be said to apply to stroke patients.<sup>10</sup> The decision to

start AED therapy also depends on the perceived risk of recurrent seizures, whose associated risks outweigh the potential side effects of the medications. The risk of recurrence of post-stroke seizures is 50-90% in those with late-onset seizures.<sup>2,8</sup>

Both NICE and SIGN guidelines recommend carbamazepine, sodium valproate, lamotrigine or oxcarbazepine as first line treatments for partial seizures and secondary generalised seizures.<sup>9,10</sup> The International League Against Epilepsy (ILAE) suggest that

**Table 1. Early onset seizures – indication to start AED**

	After 1st seizure	After 1st seizure (> 7 days post-event)	After second seizure
Adult patients	47%	34%	18%
Elderly patients	63%	14%	23%

**Table 2. Early onset seizures – duration of treatment if seizure free**

	6 months	1-2 years	Long term
Adult patients	19%	53%	14%
Elderly patients	13%	38%	38%

**Table 3. Late onset seizures – indication to commence AED**

	After 1st seizure	After 2nd seizure
Adult patients	70%	30%
Elderly patients	71%	29%

**Table 4. Late onset seizures – duration of treatment if seizure free**

	6 months	1-2 years	Long term
Adult patients	1%	37%	62%
Elderly patients	1%	23%	76%

lamotrigine and gabapentin are as effective as carbamazepine in partial-onset seizures and that lamotrigine is better tolerated than carbamazepine in older people.<sup>11</sup> In our survey, valproate and lamotrigine were the preferred agents. Six percent of respondents preferred levetiracetam which is not one of the first line agents as recommended by the guidelines.

Both guidelines suggest discontinuing AED after two years seizure free, although this is a generalised statement and not specific to post-stroke seizures. In our survey, the majority of respondents preferred to withdraw medications after one to two years for early onset seizures (53% in younger patient vignette and 38% in the elderly patient vignette) and continue medications life-long for late onset seizures (62% in the younger patient vignette and 76% in the elderly patient vignette).

Both SIGN and NICE guidelines recommend initial AED monotherapy, with trial of a second first-line agent as monotherapy if the first-line drug fails after it has been titrated to a maximum dose.<sup>9,10</sup> This is in contrast with the results of our survey where the majority of stroke physicians stated they would first titrate up the dose of a first-line AED, then add in a second agent if this treatment fails, using a combination approach rather than switching to another AED as monotherapy.

Choosing to treat with an AED may also be influenced by other factors such as the patients wish to continue driving in the future, occupation, and impact of further seizures on acute or long term care needs. The Driver and Vehicle Licensing Agency (DVLA) in the UK has explicit guidelines regarding driving after seizures.<sup>12</sup> Following a first seizure, a standard

group 1 driving license is revoked for six months and a group 2 licence (heavy goods vehicle or public service vehicle) is revoked for 5 years from the date of seizure. In case of recurrent seizures or epilepsy the revoked period is one year (group 1 license) and 10 years (group 2 license) since the last seizure. In cases where the AED is being withdrawn, the agency advises no driving for six months after commencement of withdrawal of medication.<sup>12</sup>

### Conclusion

Current management is based on national guidelines which do not specifically cover seizures in stroke patients and expert opinion which, as shown by the results of our study, does not reach consensus either. This is an area demanding further research to allow development of evidence based guidelines to improve management of this common problem.

Based on best available evidence, we would recommend treating the initial seizure post-stroke if it occurs more than seven days after the event. We would suggest, after careful discussion with the patient or relatives about the risks and intended benefits of AED therapy, treating with an appropriate first-line AED, such as lamotrigine or sodium valproate, for at least 1 year before considering tapering the dose. For late-onset seizures, we would recommend long term treatment as the recurrent rate is higher. We would consider newer AEDs, such as lamotrigine, in older patients given the preferable side effects profile in this patient cohort. If the first-line AED fails to control seizures after being titrated up to an optimal

dose as a monotherapy, then switching to another first line agent is recommended with titration up to a maximal dose. Combination therapy with two or more AEDs is only indicated once two first line agents have been used as monotherapy at optimal doses and should be managed under expert supervision.

The poor response rate in the survey may relate to a lack of interest in this area amongst physicians, despite post-stroke epilepsy being an important syndrome which is likely to increase with increasing survival after stroke due to improved stroke management. Our small sample of BASP physicians demonstrated variation in AED prescribing depending on patient age and whether the seizures were early or late in onset. Our survey demonstrated the need for further exploration of the best treatments in localisation related epilepsy and research is needed in a clinical trial setting to allow more focussed guidance to be developed. ♦

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# Paediatric Head Injuries – a Review

Severe traumatic brain injury (TBI) in children is a significant cause of morbidity and mortality worldwide.<sup>1</sup> It involves a specialised area of care, in specialised centres, led by a dedicated multidisciplinary team with adequate clinical expertise. The application of protocol-based guidelines designed primarily for adults to the field of paediatrics, remains challenging. In fact, children have been largely excluded from the ongoing, international, randomised control trials, including the RESCUEicp trial, the DECRA trial and the Eurotherm3235 trial, with the lower age limits for inclusion being 10, 15 and 16 years respectively.<sup>2,3,4</sup> The NICE guidelines for the triage, assessment, investigation and early management of head injury include infants (<1 year) and children (1-15 years).<sup>5</sup> This paper describes the surgical and non-surgical treatment options applied to the paediatric population in the management of traumatic brain injury.

## Epidemiology

Around 1 million patients or 0.3% of the population are seen in emergency departments in the UK with head injuries per year. Almost half are children under 16 years of age, who account for 30% of head injury admissions, with the majority (80%) being treated on a general paediatric ward. The mortality rate is 25 per 100,000 in North America and 9 per 100,000 in the UK, accounting for 1% of all deaths, but up to 15-20% of deaths between the ages of 5 and 35 years.<sup>6</sup> Incidence and mortality rates vary with age and gender with peaks occurring in children at the age of school entry.<sup>7</sup> The two age groups at highest risk for TBI are the 0 to 4 year olds and 15 to 19 year olds.<sup>8</sup>

Falls are the most commonly observed cause of minor head injuries in children and adolescents, followed by motor vehicle accidents, pedestrian and bicycle accidents, sports related trauma and child abuse.<sup>9</sup>

## Types of head injury

A force applied to the skull may be distributed evenly throughout the skull without causing a skull fracture (closed head injury) but damaging the less rigid brain tissue. When the skull vault is fractured it is described as an open head injury. Open head injuries are much less common in children.<sup>10</sup> Focal injury refers to localised contusions or haematomas as opposed to diffuse axonal injury and hypoxic-ischaemic injury. Pathology following paediatric traumatic brain injury is age-dependent with subdural haematomas and diffuse axonal injury being more common than focal injuries in infants and young children.<sup>10,11</sup> Hypoxic-ischaemic injury is observed more commonly in non-accidental injury.<sup>12</sup>

Primary brain injury is inflicted at the time of trauma. Contusions may occur at (coup) or opposite (contre coupe) the site of impact, the latter typically involving the frontal or temporal lobes. Contusions may bleed, giving rise to an intracerebral space-occupying haematomas. Sudden minor blows (classically antero-posterior) may tear the superior cerebral veins as they enter the superior sagittal sinus resulting in a subdural haematoma. In infants, subdural haemorrhage is usually widespread, bilateral and thin unlike the more localised subdural in adults.<sup>13</sup> Those with an acute subdural who are not treated are at an increased risk of developing a chronic subdural haematoma which can result in significant morbidity and mortality.<sup>14</sup> An extradural haematoma typically results from a skull fracture (classically on the pterion) with a tear of the middle meningeal artery or occasionally from damage to the sagittal or transverse sinus. Shearing forces and acceleration/deceleration injuries cause mechanical stretching of the axons' cytoskeletal proteins. The damage is diffuse and not immediately localised on CT. Diffuse brain injury tends to involve the corpus callosum, basal ganglia and brain stem.<sup>15,16</sup>

Primary brain injury is followed by evolution of the injury when the decreased cerebral blood flow is insufficient to sustain normal neurological functioning. Secondary insults such as elevated intracranial pressure, hypovolaemia, hypoxia and hyperthermia may lead to secondary brain injury. The management of traumatic brain injury is aimed primarily at preventing these potential secondary insults.

## Pathophysiology

The Monro-Kellie doctrine describes the skull as a rigid structure with a fixed capacity. A rise in intracranial pressure (ICP) is initially compensated for by cerebral autoregulatory mechanisms. When this mechanism is overwhelmed, cerebral hypoperfusion triggers a cascade of mechanisms leading to aggravation of the initial injury with worsening oedema and culminating in cerebral herniation<sup>15</sup> (Figure 1). Oedema may be vasogenic due to leaking from damaged vessels, cytotoxic due to osmolar changes and disruption of the cell membrane or interstitial due to increased CSF pressure.<sup>16</sup> Myelination is absent at birth and in infants the skull is more compliant in view of the open anterior and posterior fontanelles. The posterior fontanelle cannot be palpated after six weeks. The anterior fontanelle is often small by six months with complete closure between 10 and 20 months. Such differences may affect the threshold for treatment and prognosis.<sup>17</sup>

Following the primary brain injury, axons and glial cells, in particular those of the corpus callosum, basal ganglia and periventricular gray

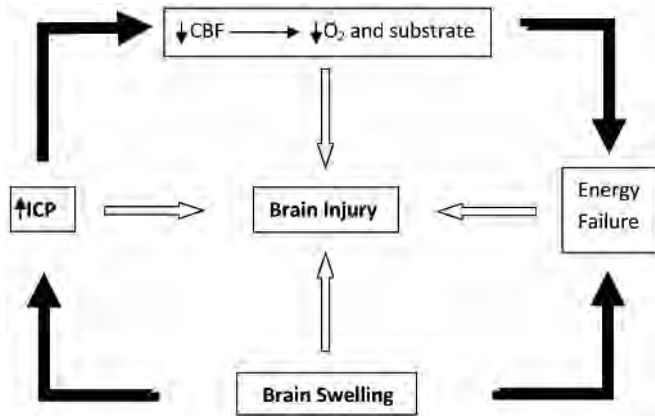


Figure 1: Pathophysiology of brain swelling

matter, sustain a disruption of their cytoskeletal proteins resulting in failure of axonal transport. Surrounding this area of primary injury is a labile area – a penumbra, where brain tissue is potentially salvageable but prone to secondary insults.<sup>18</sup> A large amount of cytokines, including interleukin-6, IL-10 and soluble adhesion molecules, is released following the primary injury. Higher concentrations of IL-10 were observed in children younger than four years following traumatic brain injury.<sup>19</sup> The initial high concentrations are probably detrimental to the penumbra zone, but might have a neuroregenerative effect in the long term and at lower concentrations.<sup>19,20,21</sup>

High concentrations of glutamate are found in synapses following brain injury. Sodium and calcium channels are activated leading to an accumulation of sodium and water intracellularly. Hypoxia leads to energy depletion thus disabling the sodium - potassium ATPase pump and reducing calcium exchange. This results in sodium dependent neuronal swelling followed by calcium mediated activation of intracellular protease and lipase which would result in neuronal degeneration and necrotic cell death.<sup>22</sup> This process is accelerated by leakage of calcium from the endoplasmic reticulum and mitochondria following disruption of the cell membrane after injury. This excitotoxic effect culminates in necrosis or apoptosis, depending on which receptors are activated – NMDAR in necrosis and non-NMDAR in apoptosis. Animal studies have shown that immature neurons are more vulnerable to these effects suggesting that the response to excitotoxicity and apoptosis appears to be age-dependent.<sup>23</sup>

**Management of paediatric head trauma:**

**Initial management**

Stabilisation of the airway, breathing and circulation together with three-point cervical spine immobilisation should be instituted in any child following traumatic brain injury (TBI). The risk of a clinically significant brain or cervical spine injury should then be assessed, using a modified paediatric Glasgow Coma Scale (GCS) in the non-verbal child (Table 1) Assessment should establish the need for CT scanning of the brain and/or cervical spine in a child <16 years of age<sup>5</sup> (Table 2). Children ≤10 years of age with a GCS of ≤8 or a strong suspicion of injury despite normal plain films (A/P and lateral views for children <10 years of age, without an A/P peg view) or if plain films are inadequate, should have CT scanning of the cervical spine within an hour of presentation or when sufficiently stable.<sup>5</sup>

Fluid resuscitation and maintenance of blood pressure is essential to ensure cerebral perfusion and resolve shock. Fluid resuscitation should be initiated in all cases of TBI using 10mls/kg boluses of 0.9% saline followed by re-assessment.<sup>24</sup> Mechanical ventilation with endotracheal intubation should be instituted in any patient with a GCS ≤8 or when severe brain injury is suspected, followed by transfer to a specialised unit<sup>5</sup> (Table 3 overleaf). Nasotracheal intubation should be avoided in all head injuries particularly in patients with facial trauma or basilar skull fractures. More invasive monitoring including central venous pressure (CVP), arterial pressure and intracranial pressure are indicated to guide protocol-driven therapies<sup>25</sup> (Figure 2 overleaf).

**Table 1: The Paediatric Glasgow Coma Scale<sup>26</sup>**

Category	Best Response	
<b>Eye opening</b>		
Spontaneous	4	
To speech	3	
To pain	2	
None	1	
<b>Verbal (Modified for infants)</b>		
Oriented	Babbles	5
Confused	Irritable	4
Inappropriate words	Cries to pain	3
Moans	Moans	2
None	None	1
<b>Motor</b>		
Follows commands		6
Localises pain		5
Withdraws to pain		4
Flexes to pain		3
Extends to pain		2
None		1
<b>Glasgow Coma Scale</b>		
Best possible score		15
Worse possible score		3
<b>If tracheal intubation then verbal designated with 'T'</b>		
Best possible score while intubated		10T
Worse possible score while intubated		2T

**Table 2: Indications for CT scanning of the head in children (1-16 years of age) NICE guidelines<sup>5</sup>**

Witnessed loss of consciousness lasting >5 minutes
Amnesia (antegrade or retrograde) lasting >5 minutes
Abnormal drowsiness
Three or more discrete episodes of vomiting
Clinical suspicion of non-accidental injury
Post-traumatic seizure but no history of epilepsy
Age >1 year: GCS <14 on assessment in the emergency department
Age <1 year: GCS (paediatric) <15 on assessment in the emergency department
Suspicion of open or depressed skull injury or tense fontanelle
Any sign of basal skull fracture (haemotympanum, 'panda' eyes, cerebrospinal leakage from ears or nose, Battle's sign)
Focal neurological deficit
Age <1 year: presence of bruise, swelling or laceration >5cm on the head
Dangerous mechanism of injury (high-speed road traffic accident either as a pedestrian, cyclist or vehicle occupant, fall from >3m, high-speed injury from a projectile or an object)

Elevating the head to 30° in midline position decreases venous obstruction and may help to control ICP.<sup>26</sup> Sedation and analgesia are also important adjuncts to minimize increases in ICP. Pain and stress increase metabolic demands and increase blood pressure and ICP. Analgesics and sedatives such as fentanyl and midazolam are also commonly used.<sup>26</sup> Neuro-muscular blockade is useful to avoid shivering with cooling and allows better control of ventilation by preventing patient-ventilator asynchrony.

**Cerebral perfusion pressure (CPP)**

Compared to children without TBI, children with TBI have lower cerebral blood flow (CBF) and cerebral hypoperfusion (CBF < 20-25ml/100g/min) is the dominant derangement.<sup>27</sup> In addition, there is impairment of cerebral

**Table 3: Guidelines for intubation and ventilation NICE guidelines<sup>5</sup>**

<p>Coma- GCS <math>\leq</math>8 (use paediatric scale for children)</p> <p>Loss of protective laryngeal reflexes</p> <p>Ventilatory insufficiency:</p> <ul style="list-style-type: none"> <li>-hypoxaemia (PaO<sub>2</sub> <math>&lt;</math>13 kPa on oxygen)</li> <li>-hypercarbia (PaCO<sub>2</sub> <math>&gt;</math>6kPa)</li> </ul> <p>Spontaneous hyperventilation causing PaCO<sub>2</sub> <math>&lt;</math>4kPa</p> <p>Irregular respirations</p>	<p>Intubate and ventilate immediately</p>
<p>Significantly deteriorating conscious level (1 or more points on motor score) even if not coma</p> <p>Unstable fractures of the facial skeleton</p> <p>Copious bleeding into mouth</p> <p>Seizures</p>	<p>Intubate and ventilate prior to transfer</p>
<p>Ventilate an intubated patient with muscle relaxation and appropriate short-acting sedation and analgesia</p> <p>Aim for:</p> <ul style="list-style-type: none"> <li>-PaO<sub>2</sub> <math>&gt;</math>13kPa; PaCO<sub>2</sub> 4.5-5.0 kPa</li> </ul> <p>If clinical or radiological evidence of raised intracranial pressure, more aggressive hyperventilation is justified</p> <p>Increase the inspired oxygen concentration if hyperventilation is used</p> <p>Child: Maintain blood pressure at level appropriate for age</p>	

autoregulation following traumatic brain injury in children.<sup>28</sup> Maintaining optimal, age-based cerebral perfusion pressure (CPP) has been demonstrated to improve outcome.<sup>29</sup> [CPP = MAP (mean arterial pressure) – ICP]. In infants and children lower levels of CPP are accepted (40-70mmHg) with CPP values outside this range associated with an unfavourable outcome.<sup>30</sup> Aggressive management of CPP can lead to good neurological outcomes despite extremely high ICP.<sup>31</sup> Normovolaemia with augmentation of the CVP to 8 to 10cm should be ensured prior to commencing inotropes. Dopamine has been associated with an increase in cerebral oedema and suppression of most anterior pituitary-dependant hormones and norepinephrine may be the most suitable catecholamine to maintain or restore adequate cerebral perfusion.<sup>32</sup>

Intracranial pressure (ICP) control and cerebral perfusion pressure (CPP) manipulation have significantly reduced the mortality but not the morbidity rate<sup>33</sup>. The prevention and aggressive treatment of cerebral hypo-oxygenation and control of ICP with a PbtO<sub>2</sub>-directed protocol ( $>$ 25mmHg) has been shown to reduced the mortality rate after TBI in major trauma but, more importantly, resulted in improved 6-month clinical outcomes over the standard ICP/CPP-directed therapy.<sup>33</sup>

**Hypoxia and hyperventilation**

The association between observed early hypoxia [SpO<sub>2</sub>  $<$  90% or  $<$ 7.9 kPa (60mmHg)] and poor outcome is well documented.<sup>34</sup> This association is not as strong as hypotension, with mortality only slightly increased in children with both hypoxia and hypotension over those with hypotension alone.<sup>35,36</sup> Hypoxia should be avoided by maintaining PaO<sub>2</sub>  $>$  12KPa mmHg and SaO<sub>2</sub>  $\geq$ 98%. PEEP should be limited since increases in intrathoracic pressure may impede jugular venous drainage and diminish compensatory mechanisms based on the Munro–Kellie doctrine.<sup>29</sup>

Hyperventilation leads to decreased cerebral blood flow with a 1mmHg change in the [PaCO<sub>2</sub>] decreasing CBF by 3% in regions of intact autoregulation. The decreased cerebral blood volume lowers the ICP. Profound hyperventilation with PaCO<sub>2</sub>  $<$ 35mmHg may be instituted as second tier therapy in the case of refractory intracranial hypertension after a cerebral CT scan.<sup>14,37</sup> However, routine, severe hyperventilation presents a significant risk for brain hypoxia. Targeting brain tissue oxygen tension (PbtO<sub>2</sub>) to  $>$ 25mmHg has shown to improve both the mortality and morbidity after TBI<sup>33</sup>. Similarly, if jugular venous oxygen tension (sJvO<sub>2</sub>) is reduced below 60%, a state of relative ischaemia exists,

Figure 2

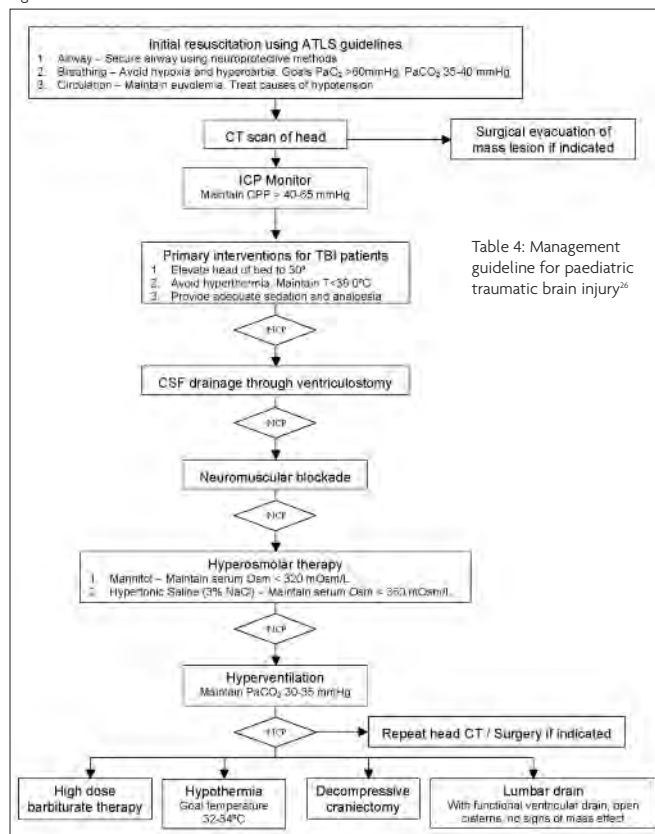


Table 4: Management guideline for paediatric traumatic brain injury<sup>36</sup>

cautioning against any further reduction of PaCO<sub>2</sub>.<sup>38</sup> There may also be an association between mortality and a lower mean PbtO<sub>2</sub>, and hence compromised cerebral oxygenation, in patients following subarachnoid haemorrhage (SAH).<sup>39</sup>

**Hyperosmolar therapies**

Hyperosmolar therapies include intravenous mannitol (2.5-5mls/kg of 20% mannitol over 20mins) and hypertonic saline (3-5mls/kg of 3% saline). Both induce a shift of fluid from the intracellular to the extracellular space across an osmotic gradient leading to decreased cerebral oedema, relative brain dehydration and decreased ICP.

Hypertonic saline (HS) is as effective as mannitol for the treatment of raised intracranial pressure in traumatic brain injury in children. However, HS may produce less “rebound” intracranial hypertension when compared to mannitol as it cannot be easily removed from intracellular space. HS does not cause obligatory osmotic diuresis and hence is likely to preserve or augment plasma volume rather than deplete it.<sup>40</sup> Mannitol may precipitate acute renal failure at extremes of serum osmolality (limiting multiple doses) and may not be excreted in oligo-anuria whereas HS is renoprotective.

HS directly increases plasma Na<sup>+</sup>, measurable changes in blood osmolality can be easily monitored by measuring plasma Na<sup>+</sup>. Plasma sodium levels of  $>$ 150mmol/L up to 170 mmol/L have been targeted to control ICP ( $<$ 20-25mmHg) although levels  $>$ 160mmol/L (with serum osmolalities  $>$ 320mOsm/L) have been associated with reversible renal insufficiency.<sup>41,42</sup> 3mls/kg of 3% saline may increase plasma Na<sup>+</sup> by approximately 2-3 mmol/L. A greater increase may occur if a large diuresis occurs. Conversely, the effect of mannitol on plasma osmolality can only be estimated using an osmole gap.

When evaluating the potential side effects of continuous hypertonic 3% saline (CHS) as maintenance fluid in patients with brain injury, the incidence of moderate hypernatraemia (Na<sup>+</sup>  $>$ 155 mmol/L) and severe hypernatraemia (Na<sup>+</sup>  $>$ 160 mmol/L) was found to be significantly higher in the CHS therapy group than in the normal saline group and moderate and severe hypernatraemia was associated with a higher risk of elevated blood urea nitrogen and creatinine levels.<sup>43</sup> However, CHS therapy was not associated with an increased rate of infection, deep vein thrombosis, or renal failure. Therefore CHS administration in patients with severe injuries was considered to be safe as long as sodium levels are carefully monitored.<sup>43</sup>



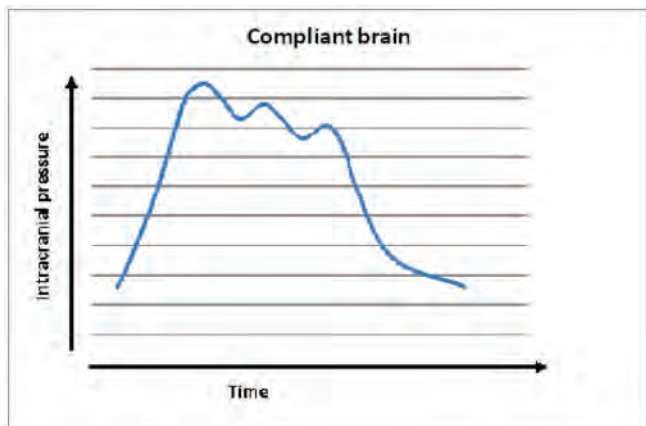


Figure 3: ICP waveforms in compliant brain.

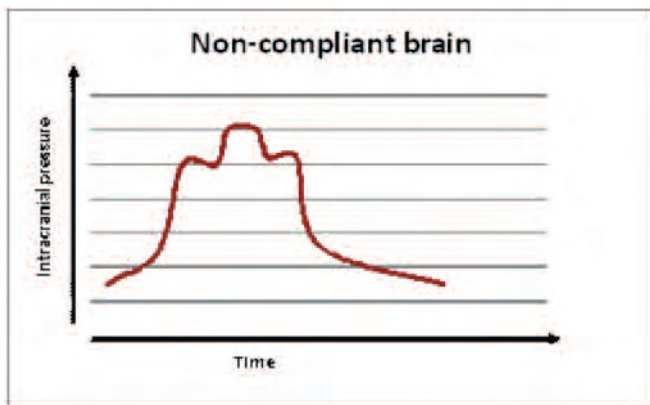


Figure 4: ICP waveform in noncompliant brain.

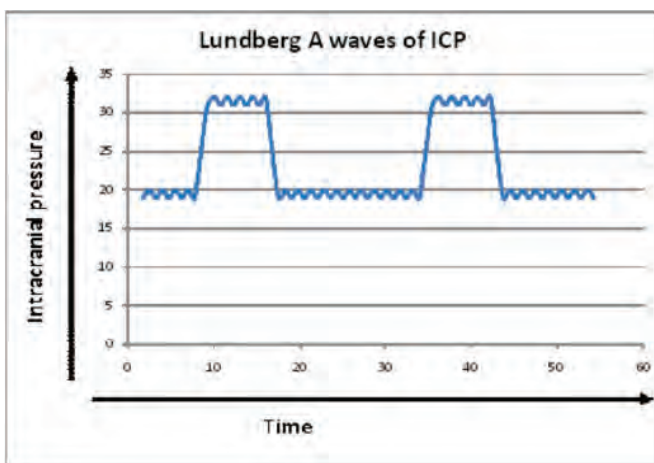


Figure 5: Intracranial pressure waveforms (P1,P2,P3 waves and Lundberg A waves).

Various concentrations of hypertonic saline have been reported, but most studies in children involve administration of 3% saline. In studies on adult TBI patients, HTS (7.5%) was associated with lower ICP and higher CPP and cardiac output when compared with 25% mannitol.<sup>44</sup> 23.4% HTS was found to be more efficacious than mannitol in reducing ICP.<sup>45</sup>

### Barbiturate coma

Barbiturates should only be considered as second line therapy in cases of refractory elevated ICP. Thiopentone produces a dose dependent reduction in CBF and cerebral metabolic rate until the EEG becomes isoelectric (flat) or shows burst suppression, at which point no further reduction occurs despite an increase in barbiturate dose. When comparing pentobarbital versus thiopental in the treatment of refractory intracranial hypertension in patients with traumatic brain injury, ICP was controlled in 18% and 50% of patients, respectively, without any statistically significant difference between groups in the rate of infectious complications or hemodynamic compromise.<sup>46</sup> High-dose barbiturate therapy may be considered in haemodynamically stable patients with salvageable severe head injury

and refractory intracranial hypertension. Thiopental appears to be more effective than pentobarbital in controlling intracranial hypertension refractory to first-line measures.<sup>46</sup>

### Induced hypothermia

Oxidative stress contributes to secondary damage after traumatic brain injury.<sup>47</sup> With normothermia (36.5-37.5°C), the mechanisms of secondary injury are lessened with decreased cerebral metabolism, inflammation, lipid peroxidation, axonal injury, excitotoxicity, cell death, and acute seizures.<sup>48,49</sup> Hyperthermia should be avoided in the acute period following paediatric severe TBI.

Hypothermia attenuates oxidative stress after severe TBI in infants and children.<sup>47</sup> Moderate hypothermia (32-33°C) initiated within the first 24 hours after severe TBI and maintained for 48 hours will have a protective effect on the paediatric brain and can be done safely although arrhythmias and rebound elevated ICP with rewarming have been observed.<sup>50,51,52</sup> In a separate larger randomised control trial in children following severe traumatic brain injury, hypothermia therapy initiated within eight hours after injury and continued for 24 hours did not improve outcome<sup>53</sup> and may even cause harm.<sup>54,55</sup> The value of early induced hypothermia (32-35°C) started early after traumatic brain injury ( $\leq 72$  hours) is currently being assessed in the Eurotherm3235 trial.<sup>2</sup> Although the minimum recruitment age for this trial is 16 years, the same protocol could be applied to children if modified. Current recommendations are to induce hypothermia in the delayed phase as a rescue therapy for refractory intracranial hypertension rather than early after TBI as a neuroprotectant.<sup>29</sup>

### Surgical management

The aim of surgery is to reduce the intracranial pressure either by reducing the volume of the skull contents or by modifying the skull itself in order to prevent further damage and promote healing of the penumbra. Indications for surgery are both clinical and radiological. A subdural haematoma thicker than 10mm on CT scan, or midline shift greater than 5mm, should be considered for surgery. Asymmetrical or fixed, dilated pupils, a fall in GCS in a comatose (GCS<9) patient by more than two points between injury and admission, or an ICP >20mmHg despite a smaller subdural as well as a midline shift should also be considered for surgical intervention.<sup>56</sup> Contusions alert the surgeon to the possibility of mass expansion. The site of the contusion is also significant as temporal lobe lesions are more likely to cause uncal herniation with compression of the midbrain.<sup>57</sup>

### ICP monitoring and CSF drainage

ICP monitoring is an essential tool in the paediatric intensive care unit. With ICP monitoring, timely intervention can be applied to maintain an adequate CPP based on MAP and ICP values. ICP can be measured directly via a ventriculostomy drain but may be difficult to insert in view of slit-like ventricles seen in diffuse cerebral swelling and can be a source of infection despite giving precise readings. An external ventricular drain (EVD) allows removal of CSF as a means of reducing ICP in patients with intracranial hypertension. Intraparenchymal monitors are similar but more expensive. Richmond screws and Becker bolts are inserted in the extradural space. Pressure in the subdural space can be measured via a fluid filled catheter. A Ladd device is a fibre-optic monitor with a transducer at the tip which can be applied to the subdural or extradural space or extracranially.<sup>58</sup>

Controlled external lumbar subarachnoid drainage may be a treatment option following paediatric traumatic brain injury and elevated ICP that has not responded to medical therapy in the presence of a functional ventricular drainage. After lumbar drainage was instituted in patients with discernible basal cisterns on CT scan, an abrupt and lasting decrease in ICP was observed.<sup>59,60</sup> Transtentorial or cerebellar herniation did not occur in any patient as a result of lumbar drainage<sup>59</sup> if performed in patients with discernible basal cisterns only.<sup>60,61</sup> However, external lumbar drains may be associated with a higher risk of infection when compared to EVD.<sup>62,63</sup>

Electronic devices (Camino and Codman design) allow analysis of the ICP waveform in addition to ICP monitoring, which provides a useful adjunct to treatment. The ICP waveform is a modified arterial pressure trace and shows a characteristic waveform composed of three peaks P1, P2 and P3 (Figure 3). An increase in the amplitude of P2 is suggestive of decreased brain compliance<sup>64</sup> (Figure 4). Analysis of the ICP waveform in

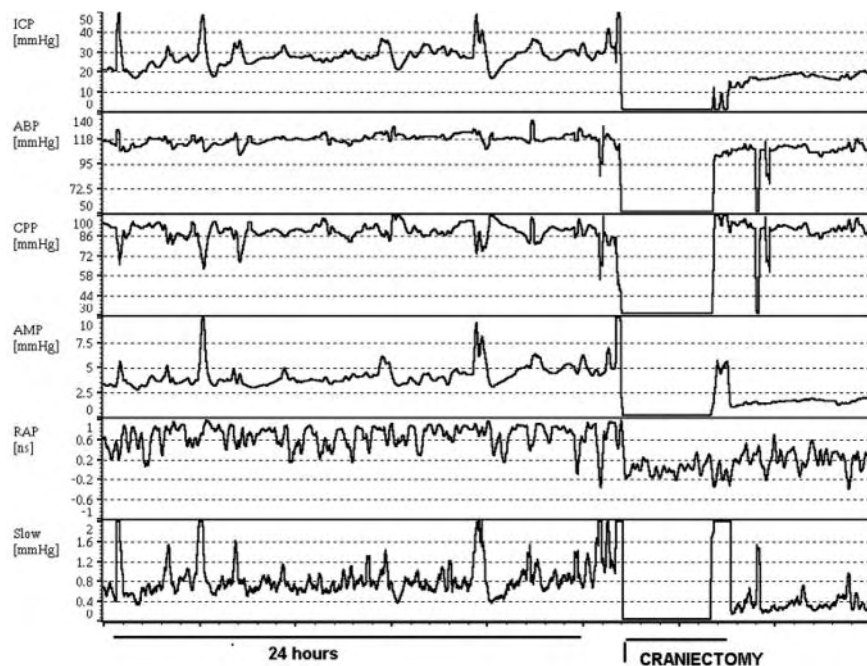


Figure 6: Effect of decompressive craniectomy on ICP and related parameters<sup>78</sup>

the time domain may reveal 3 wave patterns (Lundberg waves A, B, and C). A waves and 'plateau' waves are always pathological and indicative of early brain herniation. There is a rapid rise in ICP up to 50-100mmHg followed by a variable period during which the ICP remains elevated followed by a rapid fall to the baseline (Figure 5). B and C waves are related to respiration and are of little clinical significance.<sup>64</sup>

#### Evacuation of haematomas

Acute intracranial haematoma is best evacuated via a craniotomy with or without a bone flap removal and duraplasty, especially when the patient is comatose.<sup>65</sup> This provides access to potential bleeders and the traumatised brain which when severe might require a lobectomy.<sup>66</sup>

Organised haematomas can be evacuated either via twist drill craniostomy or via burr hole trepanation. This can be done in conjunction with a craniectomy. Craniotomy may have a higher rate of recurrence than burr hole trepanation and a craniectomy might be a good therapeutic option for recurrence.<sup>67</sup> Twist drill craniostomy is a quicker procedure with faster regression of the residual subdural effusion but there is no difference in outcome when compared to burr hole trepanation.<sup>68,69</sup> Double burr hole drainage did not offer any further advantage, unless specifically indicated.<sup>70</sup> In the paediatric population chronic subdural haematomas typically present in patients less than four months of old with a history suggestive of non-accidental injury.<sup>71</sup> External drainage as a treatment option for chronic subdurals was found to have a low complication rate and a good clinical outcome in children.<sup>72</sup>

An extended surgical approach with a partial membranectomy is sometimes undertaken but this offers no advantage. Burr hole

drainage with irrigation of the haematoma cavity and closed-system drainage is currently recommended. Extensive craniotomy with membranectomy should be reserved for those with acute rebleeding with solid haematoma.<sup>73</sup>

#### Decompressive craniectomy

The standard decompressive craniectomy procedure described in the RESCUEicp trial suggests excising a bone flap of at least 12cm diameter (avoiding herniation) and opening the dura and leaving it open (possibly with a duroplasty). When the swelling is predominantly unilateral and there is midline shift, the craniectomy should be on the side of the swelling and should decompress the temporal lobe. Bifrontal decompressive craniectomy with bilateral U-shaped opening of the dura is recommended for diffuse brain swelling. Maximum decompression is achieved by ligating and dividing the superior sagittal sinus and the falx (anteriorly). If the frontal sinus is inadvertently opened it should be cranialised by excising the posterior wall, stripping the mucosa and plugging it with pericranium, free muscle and/or tissue glue.

The ICP should be monitored even post-craniectomy (Figure 6) using a burr hole or bolt at least 3cm away from the bony edge of the craniectomy. Tight bandaging or positioning the patient's head on the craniotomy side after decompression should be avoided. Cranioplasty is recommended within six months following decompressive craniectomy.

Craniectomy can be used alone or in combination with a barbiturate coma.<sup>74,75</sup> Outcome is improved when decompressive craniectomy is used to treat raised intracranial pressure in children.<sup>76,77</sup> Conversely, according to a nine-year retrospective study from Utah there was a high rate of mortality in those paediatric patients where the craniectomy was done for raised ICP only (compared to raised ICP and

evacuation of a mass lesion).<sup>78</sup> The value of a decompressive craniectomy for the management of traumatic brain injury is currently being assessed in the RESCUEicp trial in children  $\geq 10$  years of age.<sup>4</sup>

#### Conclusion

Current management of paediatric traumatic brain injury needs to be streamlined and new trials instituted to include the paediatric population, in order to provide standardised guidelines, which achieve the best possible outcome in terms of morbidity and mortality. Equally important is the environment in which paediatric traumatic brain injury occurs. When dealing with trauma in children, a clinician must be alert to the possibility of non-accidental injury and investigate appropriately with the involvement of a multidisciplinary team. Safeguarding children by preventing accidental and identifying non-accidental injury remains a key factor in management. ♦

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To list your event in this diary, email brief details to Anna Phelps at [anna@acnr.co.uk](mailto:anna@acnr.co.uk) by 6th February, 2011

# 2011

## January

**Cognitive Rehabilitation Workshop**  
14-15 January, 2011; Gatwick Airport, London, UK  
E. [enquiries@braintreetraining.co.uk](mailto:enquiries@braintreetraining.co.uk)  
[www.braintreetraining.co.uk](http://www.braintreetraining.co.uk)

**Education**  
18 January, 2011; Guildford, UK  
E. [louisewilkinson@cbituk.org](mailto:louisewilkinson@cbituk.org)  
[www.cbituk.org](http://www.cbituk.org)

**Health & Social Care**  
20 January, 2011; Northampton, UK  
E. [louisewilkinson@cbituk.org](mailto:louisewilkinson@cbituk.org)  
[www.cbituk.org](http://www.cbituk.org)

**Education**  
25 January, 2011; Nottingham, UK  
E. [louisewilkinson@cbituk.org](mailto:louisewilkinson@cbituk.org)  
[www.cbituk.org](http://www.cbituk.org)

**Youth Offending**  
26 January, 2011; Bradford, UK  
E. [louisewilkinson@cbituk.org](mailto:louisewilkinson@cbituk.org)  
[www.cbituk.org](http://www.cbituk.org)

**British Paediatric Neurology Association Conference**  
26-28 January, 2011; Bolton, UK  
T. 01204 492888  
E. [info@bpna.org.uk](mailto:info@bpna.org.uk)

**Education**  
27 January, 2011; Leeds, UK  
E. [louisewilkinson@cbituk.org](mailto:louisewilkinson@cbituk.org)  
[www.cbituk.org](http://www.cbituk.org)

**Specialist Rehabilitation Course**  
27-28 January, 2011; Derby, UK  
T. 01332 724735  
E. [Amy.Harte@nottingham.ac.uk](mailto:Amy.Harte@nottingham.ac.uk)

**4th Edition of the European Neurological Conference on Clinical Practices**  
28-30 January, 2011; Lisbon, Portugal  
E. [sdinenson@paragon-conventions.com](mailto:sdinenson@paragon-conventions.com)

**How to do Cognitive Rehabilitation**  
29 January, 2011; Gatwick Airport, London, UK  
E. [enquiries@braintreetraining.co.uk](mailto:enquiries@braintreetraining.co.uk)  
[www.braintreetraining.co.uk](http://www.braintreetraining.co.uk)

## February

**Education**  
1 February, 2011; Shrewsbury, UK  
E. [louisewilkinson@cbituk.org](mailto:louisewilkinson@cbituk.org)  
[www.cbituk.org](http://www.cbituk.org)

**Electrotherapy Update: Current Concepts in Electrical Stimulation (Study Day 1)**  
5 February, 2011; Elstree, UK  
[www.physiouk.co.uk](http://www.physiouk.co.uk)

**Electrotherapy Update: Current Concepts in Tissue Repair (Study Day 2)**  
6 February, 2011; Elstree, UK  
[www.physiouk.co.uk](http://www.physiouk.co.uk)

**International Stroke Conference 2011 and State-of-the-Art Stroke Nursing Symposium**  
8-11 February, 2011; Los Angeles, USA  
[www.strokeconference.org](http://www.strokeconference.org)

**Education**  
8 February, 2011; Newcastle, UK  
E. [louisewilkinson@cbituk.org](mailto:louisewilkinson@cbituk.org)  
[www.cbituk.org](http://www.cbituk.org)

**Dementias 2011: 13th National Conference**  
10-11 February, 2011; London, UK  
E. [anne.haylock@markallengroup.com](mailto:anne.haylock@markallengroup.com)

**OZC – Measuring Outcomes of Rehabilitation**  
11 February, 2011; Ely, UK  
T. 01353 652173  
E. [Rachel.everett@ozc.nhs.uk](mailto:Rachel.everett@ozc.nhs.uk)

**CME 2011 Young Neurosurgeons Meeting**  
11-14 February, 2011; Innsbruck, Austria  
E. [imundigl@kenes.com](mailto:imundigl@kenes.com)  
[www.kenes.com/eans-cme](http://www.kenes.com/eans-cme)

**Health & Social Care**  
14 February, 2011; Bristol, UK  
E. [louisewilkinson@cbituk.org](mailto:louisewilkinson@cbituk.org)  
[www.cbituk.org](http://www.cbituk.org)

**Education**  
17 February, 2011; Plymouth, UK  
E. [louisewilkinson@cbituk.org](mailto:louisewilkinson@cbituk.org)  
[www.cbituk.org](http://www.cbituk.org)

**7th Annual Update Symposium on Clinical Neurology and Neurophysiology**  
21-22 February, 2011; Tel Aviv, Israel  
E. [conventions@isas.co.il](mailto:conventions@isas.co.il)  
[www.neurophysiology-symposium.com](http://www.neurophysiology-symposium.com)

**The Society for Research in Rehabilitation 2011 Winter Conference**  
22 February, 2011; Cardiff, UK  
T. 0115 8230244  
E. [patricia.dziunka@srr.org.uk](mailto:patricia.dziunka@srr.org.uk)

**Youth Offending**  
22 February, 2011; Milton Keynes, UK  
E. [louisewilkinson@cbituk.org](mailto:louisewilkinson@cbituk.org)  
[www.cbituk.org](http://www.cbituk.org)

**European Traumatic Brain Injury Conference: TBI-Challenge. (EU 2011)**  
23-26 February, 2011; Vienna, Austria  
E. [nikolaus.steinhoff@hocheggknoe.at](mailto:nikolaus.steinhoff@hocheggknoe.at)

**Ear, nose and throat: Expert opinion in otorhinolaryngology, head and neck surgery**  
24-25 February, 2011; London, UK  
E. [anne.haylock@markallengroup.com](mailto:anne.haylock@markallengroup.com)

## March

**Education**  
1 March, 2011; Tunbridge Wells, UK  
E. [louisewilkinson@cbituk.org](mailto:louisewilkinson@cbituk.org)  
[www.cbituk.org](http://www.cbituk.org)

**Perfecting the ELISPOT - a time for answers**  
4 March, 2011; London, UK  
E. [enquiries@euroscicon.com](mailto:enquiries@euroscicon.com)  
[www.regonline.co.uk/workshopELISPOT2011](http://www.regonline.co.uk/workshopELISPOT2011)

**UK ILAE EEG Course**  
4-5 March, 2011; Cambridge, UK  
T. 01223 216376  
E. [ikb39@medschl.cam.ac.uk](mailto:ikb39@medschl.cam.ac.uk)

**Insight Workshop**  
4-5 March, 2011; London, UK  
E. [enquiries@braintreetraining.co.uk](mailto:enquiries@braintreetraining.co.uk)  
[www.braintreetraining.co.uk](http://www.braintreetraining.co.uk)

**Education**  
9 March, 2011; Sheffield, UK  
E. [louisewilkinson@cbituk.org](mailto:louisewilkinson@cbituk.org)  
[www.cbituk.org](http://www.cbituk.org)

**International Conference on Alzheimer's & Parkinson's Diseases (ADPD 2011)**  
9-13 March, 2011; Barcelona, Spain  
E. [adpd@kenes.com](mailto:adpd@kenes.com)  
[www.kenes.com/adpd](http://www.kenes.com/adpd)

**British Neurosurgical Research Group Meeting**  
10-11 March, 2011; Dundee, Scotland  
[www.ncl.ac.uk/bnrg](http://www.ncl.ac.uk/bnrg)

**Analysing and moderating the function of regulatory T cells in Autoimmunity**  
11 March, 2011; Welwyn Garden City, UK  
E. [enquiries@euroscicon.com](mailto:enquiries@euroscicon.com)  
[www.regonline.co.uk/autoimmunity11](http://www.regonline.co.uk/autoimmunity11)

**Understanding Brain Injury**  
11 March 2011; Cambridge, UK  
T. 01353 652173  
E. [Rachel.everett@ozc.nhs.uk](mailto:Rachel.everett@ozc.nhs.uk)

**Epilepsy 2011 (RSM 2011)**  
11 March, 2011; Dublin, Ireland  
[www.rsm.ac.uk](http://www.rsm.ac.uk)

**Third Annual Knock Out Stroke Symposium**  
12 March, 2011; Coral Gables, USA  
E. [juliez@baptisthealth.net](mailto:juliez@baptisthealth.net)  
[www.baptisthealth.net/cme](http://www.baptisthealth.net/cme)

**SIGAM 11th Advanced Prosthetic & Amputee Rehabilitation Course**  
14-16 March, 2011; Stanmore, UK  
T. 01992 638865  
E. [admin@bsrm.co.uk](mailto:admin@bsrm.co.uk)

**Cognitive Rehabilitation Workshop**  
14-15 March, 2011; Auckland, New Zealand  
E. [workshops@iphltd.co.nz](mailto:workshops@iphltd.co.nz)  
[www.braintreetraining.co.uk](http://www.braintreetraining.co.uk)

**9th Austrian Society of Neurology (ÖGN) Annual Congress**  
March 16-19, 2011; Vienna, Austria  
E. [weinhart@oegn.at](mailto:weinhart@oegn.at)  
[www.oegn.at/kongress2011](http://www.oegn.at/kongress2011)

**Insight Workshop**  
21-22 March, 2011; Auckland, New Zealand  
E. [workshops@iphltd.co.nz](mailto:workshops@iphltd.co.nz)  
[www.braintreetraining.co.uk](http://www.braintreetraining.co.uk)

**No Limits - Exploring adolescent behaviour following childhood acquired brain injury**  
23 March, 2011; Birmingham, UK  
T. 01869 341075  
E. [Lisaturan@cbituk.org](mailto:Lisaturan@cbituk.org)

**10th International Eating Disorders Conference**  
29-31 March, 2011; London, UK  
E. [anne.haylock@markallengroup.com](mailto:anne.haylock@markallengroup.com)

**British Neuropsychological Society Spring Meeting**  
30-31 March, 2011; London, UK  
E. [dana.samson@nottingham.ac.uk](mailto:dana.samson@nottingham.ac.uk)

**No Mind Left Behind: International Conference on Autism, ADHD and other early onset neurodevelopmental disorders**  
29-30 March, 2011; Glasgow, UK  
E. [nomindleftbehind@congreg.com](mailto:nomindleftbehind@congreg.com)  
[www.mindroom.org/nomindleftbehind](http://www.mindroom.org/nomindleftbehind)

**Society of British Neurological Surgeons Spring Meeting 2011 (SBNS 2011)**  
30 March – 1 April 2011; Bristol, UK  
[www.sbn.org.uk/](http://www.sbn.org.uk/)

**Education**  
31 March, 2011; Belfast, UK  
E. [louisewilkinson@cbituk.org](mailto:louisewilkinson@cbituk.org)  
[www.cbituk.org](http://www.cbituk.org)

## April

**ABN Joint Annual Meeting with the Neurology Section of the Cuban Society of Neurology and Neurosurgery**  
4-6 April, 2011; Cuba, Havana  
[www.theabn.org](http://www.theabn.org)

**Education**  
5 April, 2011; Stoke on Trent, UK  
E. [louisewilkinson@cbituk.org](mailto:louisewilkinson@cbituk.org)  
[www.cbituk.org](http://www.cbituk.org)

**Education**  
7 April, 2011; New Malden, UK  
E. [louisewilkinson@cbituk.org](mailto:louisewilkinson@cbituk.org)  
[www.cbituk.org](http://www.cbituk.org)

## Centre for Community Neurological Studies



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- Stroke Care (All 45 credits at level 6)

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

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### Contact Details

For more detailed information on our courses please contact:  
The Centre Administrator, Tel: 0113 812 5918, Fax: 0113 812 3440  
Email: [ccnsequiries@leedsmet.ac.uk](mailto:ccnsequiries@leedsmet.ac.uk)

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

Twenty-first Meeting of the  
European Neurological Society








28 – 31 May 2011

Lisbon, Portugal

*Neurology: Learning, knowledge, progress and the future*

**Key symposia:**

-  Treatment of muscle diseases: the future is already here
-  Molecular and cellular mechanisms of ischaemic stroke
-  Psychiatric aspects of neurological disorders
-  Metals and movement disorders
-  Biomarkers for diagnosis, prognosis and response to treatment in MS

The congress programme includes 22 teaching courses, 15 workshops, practical sessions in clinical neurophysiology, interactive case presentations and selected scientific sessions in the form of oral and poster sessions.

**Early Registration Deadline: 15 April 2011**

**For further information please contact:**

ENS 2011, c/o Congrex Switzerland Ltd.

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[www.ensinfo.org](http://www.ensinfo.org)

# 2nd Parkinson's UK Research Conference

**Conference details:** 1-2 November, 2010; York, UK. **Reviewed by:** Laura Parkkinen, Oxford Parkinson's Disease Centre, University of Oxford.

The second Parkinson's UK Research Conference took place in picturesque, autumnal York. Following the success of the first conference in 2008, Dr Kieran Breen, Research Director of Parkinson's UK, welcomed now almost 200 researchers from across the UK to share ideas, discuss challenges and work together towards a cure for Parkinson's disease. The conference opened with a key note speaker, Dr Deniz Kirik from Lund University in Sweden, discussing progress towards a new generation of treatments, cell and gene therapies, whether they are "science fiction or reality to patients". Dr Kirik assured us that both treatment methods hold great promise for future treatment of Parkinson's. To date, there are approximately 350 patients who have received embryonic stem cell transplants and probably an equal number that have not been scientifically reported, according to Dr Kirik. Furthermore, gene therapies are now entering clinical trial phases and Dr Kirik is hopeful: "If gene therapy will work, it will work in the brain and especially it will work in Parkinson's disease". Dr Kirik and his research group are vigorously working to resolve some problems that the stem cell therapies still face such as the role of serotonin in L-dopa induced dyskinesias.<sup>1</sup> Other problems highlighted by the audience included the treatment of non-motor symptoms of Parkinson's that are likely to derive from other systems than targeted dopaminergic circuitry. In addition, the optimal origin of stem cells remains an unresolved issue and search for the best possible candidates was emphasised throughout the conference. In regard to this, it was fascinating to hear from Dr Maya Sieber-Blum (Newcastle University) how multipotent stem cells from bulges of human hair can be differentiated into dopaminergic neurons.<sup>2</sup>

Another highlight of the first day was the presentation by Dr Lydia Alvarez from University College London who talked about the possible mechanisms by which  $\alpha$ -synuclein protein can be transmitted from one cell to another. The possibility that  $\alpha$ -synuclein pathology in Parkinson's disease may be spreading via a prion-like mechanism is a hot topic and is endorsed by the finding of Lewy bodies in long surviving fetal grafts implanted into the brains of patients with Parkinson's disease.<sup>3</sup> A number of researchers are now trying to dissect the mechanism of this propagation by using cell and animal models but we still do not know whether the  $\alpha$ -synuclein in the grafted cells has really been transferred from the host tissue or if the grafts are somehow reacting to the hostile environment. In addition, as raised by questions from the audience, it is unclear which  $\alpha$ -synuclein species exactly can



Dr Rosemary Fricker-Gates introducing keynote speaker Dr Mark Cookson of the National Institute of Health in Bethesda.



Dr Deniz Kirik, Head of the Brain Repair and Imaging in Neural Systems (BRAINS) Unit, and co-director of the Bioimaging Center at Lund University in Sweden.



Parkinson's UK Research Associate, Gerda Drutyte, with the Parkinson's UK poster "A Community-Based Study of Parkinson's Non-Motor Symptoms".

spread (e.g. oligomeric, phosphorylated forms etc.) and why this transmission would be along specific neural connections. Despite many unresolved questions, this intriguing research has great potential to shed light on the fundamental cellular basis of Parkinson's disease.

In the afternoon, we heard from the second keynote speaker, Dr Valerie Voon from the University of Cambridge, whose research focuses on neuropsychiatric symptoms such as pathological gambling, hypersexuality, compulsive shopping and binge eating that can affect up to 13% of people with Parkinson's.<sup>4</sup> These impulse control disorders are likely to stem from changes in dopamine release inside the brain. Dr Vladimir Buchman from Cardiff University introduced a mouse model that carries inactivating mutations in all three synuclein genes. As the normal physiological function of  $\alpha$ -synuclein remains unknown it was intriguing to see that these triple synuclein mutant mice perform fairly well without any structural changes. Some compromised performance in the behavioural tasks was detected however, along with changes in dopamine release. How the ageing process will affect these mice is still work in progress.

The second conference day began with a comprehensive review on the genetic architecture of Parkinson's by a final keynote speaker Dr Mark Cookson from the National Institute of Ageing.<sup>5</sup> Over the past 15 years, researchers have found changes in a number of different genes that affect the risk of a person developing Parkinson's and Dr Cookson emphasised the importance of now turning this information into therapeutic leads. He also described his own research with leucine-rich repeat kinase 2 (LRRK2), in which over 20 pathogenic mutations have been identified to date representing the most common genetic cause of Parkinson's disease. Continuing the genetic theme, Dr Patrick Lewis (University College London) described how his group is using artificial mutations in LRRK2 in order to understand how they affect the folding and enzymatic properties of the protein. The morning session ended with a

refreshing jump from molecules to neural networks and action potentials by Dr Peter Magill, explaining how Parkinson's disease is accompanied by inappropriately firing neurons i.e. excessive beta oscillations in the basal ganglia. In the final session of the meeting we heard from researchers on physiotherapy, potential new treatments for dyskinesias, and the long-term effects of taking levodopa. We also heard a fascinating report from Dr Lynn Bedford (University of Nottingham) on transcriptome changes detected in the animal model of PD.

Apart from the many enthusiastic and knowledgeable presentations, I was impressed by the high-quality of over 100 posters, many by the most talented, young researchers in the field. This reassures of the great future for Parkinson's research in UK and that we will continue to live

up to our excellent reputation worldwide. It must have been an extremely tough job for the judges to select the 3 poster prize winners: Lara Lourenco Venda (University of Oxford) dissecting the complex role of  $\alpha$ -synuclein in dopamine homeostasis; Zhi Yao (University College London) studying the effect of PINK1 deficiency to mitochondrial function and Paula McCandless (University of Central Lancashire) describing a laser cane as an effective cueing device in helping to overcome freezing.

Once again, I found the conference an inspiring and friendly forum to meet colleagues. Although the PD research community in UK is scientifically vibrant and expanding, it is still small enough to be friendly, collegiate and welcoming to junior members and the Parkinson's UK Research Conference plays a significant role in this. ♦

#### Acknowledgements

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## UKABIF Annual Conference Review

**Conference details:** 11 November, 2010; London, UK. **Reviewed by:** Michael P Barnes, MD FRCP, Chair, UKABIF.

The United Kingdom Acquired Brain Injury Forum presented yet another hugely successful conference this year entitled Acquired Brain Injury Behind Closed Doors: Unspoken Issues and Possible Solutions. The aim of the programme was to highlight the less visible aspects of acquired brain injury (ABI) – of which there are many – and to explore how individuals and clinicians deal with the problems.

The programme included a variety of academics, clinicians, survivors and relatives – each giving a personal slant to what proved to be an educational and enjoyable day for all.

Professor Mike Barnes, Consultant in Rehabilitation at Hunters Moor Neuro-rehab and Chair of UKABIF welcomed the delegates – a mix of professionals from health and social services, case managers, legal professionals, care providers and survivors.

Dr Hermano Igo Krebs from the US delivered the keynote talk on Robots and Rehabilitation. The issue addressed by Dr Krebs and his co-workers is that of the labour intensity of therapy for neuro-rehabilitation. The premise that they work on is that plasticity of the brain allows remapping of new pathways and that by combining robotics and information technology they can deliver an efficient and effective tool for clinical therapy to maximise recovery.

One of the highlights of the programme was the presentation from 15-year-old Louise Poole from Devon who talked about the fatigue issues that she experiences following meningitis. Louise explained that in addition to blurred vision and slurred speech she also becomes very irritable when tired. These symptoms are all invisible and to the untrained eye



Professor Mike Barnes opens the conference at The Russell Hotel.

are often interpreted as laziness – 'I can be a different person depending on the time of day' said Louise, something that many survivors, clinicians and families recognise. Louise's family support has been invaluable – they factor fatigue into everything they do. Louise also highlighted a problem she has with assessing and realising risk. She finds this terrifying as she could make a bad decision which would adversely affect herself or someone close to her. She asked all those present to remember that teenagers with a brain injury try their best on the whole - even though their experience has been scary and frustrating.

Penny Weekes, an OT from South Devon complemented Louise's talk by discussing how she helps teenagers with ABI. She has developed a six-week programme to help them to identify their personal triggers and areas which cause them problems. They are shown how to pace themselves and how to make priorities. The programme also takes into account the reactions of friends, teachers and family and encourages teenagers to review themselves regularly.

The next session also saw another duet of clinician and first hand experience from a relative. Mr Antonio Belli, a neurologist from Southampton talked through the lesser explored area of hormonal imbalances following TBI looking particularly at post traumatic hypopituitarism. The research shows that 30% of fatal head injuries show pituitary atrophy. Given the high levels of acquired brain injury many of the physical, cognitive and psychosocial consequences of TBI can be related to hormonal imbalances. Mr Belli asked how can we anticipate who is likely to be affected? There have been a few studies which have looked at this which show that a) there is a relationship between the severity of the Glasgow Coma Scale score and PTHP b) that hypoxia and hypotension may be associated with growth hormone deficiency and lastly c) there is no association with radiological evacuation. Mr Belli then addressed the validity of screening. Although it is worthwhile given the prevalence and severity it is questionable whether the cost of screening and effectiveness of treatment would make the process worthwhile. The natural history needs to be better understood together with the validity of the test used in early screening. If

screening is pursued it must be decided how problems should be treated.

Joanna Lane then gave an account of her son Christopher who had a head injury aged seven then committed suicide at the age of 28. Joanna Lane came across hypopituitarism following Christopher's death and investigated it further when it seemed to reflect Christopher's experience. She has since campaigned to raise the profile of hypopituitarism and encourages widespread screening after TBI as a requirement. More information about her research can be found at her website: [www.headinjuryhypo.org.uk](http://www.headinjuryhypo.org.uk).

Dr Barbara Chandler, Consultant in Rehabilitation Medicine Walkergate Park in Newcastle proceeded with the programme to discuss Sex and Relationship Problems after ABI. Dr Chandler cited research that 50% of men reported sexual dysfunction four years post TBI. Predictors included milder injury, depression, age and endocrine disorders. She also highlighted the change in relationships where roles change post TBI caused a shift in equal standing between the partners. Dr Chandler quoted Lezac's study from 1978 which highlights some of the issues of characterological alteration. These include self centre behaviour, impaired self monitoring, lack of initiative, lability, irritability and lack of self learning and insight. Dr Chandler stated that these are compounded by neuro-behavioural problems highlighted by Wood Williams in 2008 which include lack of empathy, saying the right things, but acting differently, lack of ability to exhibit warmth, and egocentricity. When addressing the issue of what can be done to help, the research has looked to those families who have coped well. Sex and relationship therapy and counselling are key as well as relieving the carer burden.

The conference programme then took a break while the UKABIF Awards for Innovation were presented by Professor Colin Blakemore. This is the first year of the awards and judging by the quantity and quality of the entries was a great success.

After an enjoyable break, during which time delegates networked and visited the exhibition, the afternoon's sessions resumed.

Edinburgh-based psychologist, David Johnson presented on prognosis problems with children post ABI. He highlighted the many cases where reports of complete recovery are made following serious head injury. However, he cited studies which show inability to progress in school later on in adolescence and pointed to the fact that his experience shows that complete recovery is rare. Dr Johnson pointed to the need for reha-



Dr Barbara Chandler, Consultant in Rehabilitation Medicine at the International Centre for Neuro-Rehabilitation and Neuro-Psychiatry, Walkergate Park in Newcastle talks about Sex and relationship problems.

bilitation and that this should include individual supervision, extra teaching, rest and exercise, avoidance of stress and vocational guidance.

Dr Howard Jackson has extensive experience of working with people who have or have had alcohol and drug problems before and after a brain injury. He highlighted the main issues, which are: that people who have had a brain injury do not recover as much; brain injuries cause problems in balance, walking or talking that get worse when a person uses alcohol or other drugs; people who have had a brain injury often say or do things without thinking first, a problem that is made worse by using alcohol and other drugs; people who abuse alcohol render themselves more likely to encounter undesirable influences; brain injury increases vulnerability to further brain injury as a result of intoxication; excessive intoxication may cause further brain injury. Situations are further complicated by access to services – people with drug and alcohol problems are often denied access to ABI services and vice versa. Dr Jackson went through the six stage programme he has developed to help people within his organisation: engagement, detoxification, establishing operations (an alternative “substance-free” life-style), addressing functional value of substance abuse (and substituting), addressing false attributions/attitudes, helping the client take control (relapse prevention).

Finally Associate Professor Huw Williams

talked about new research carried out by the University of Exeter on traumatic brain injury in prison populations – the first study focused on prevalence and the risk for reoffending, the second on the correlation between TBI in young offenders and the risk for re-offending, mental health and violence. He highlighted the need for new policies relating to TBI in prisoners and reaffirmed David Johnson's points from the previous presentation about the long term effects of brain injury in childhood. These included persisting personality and emotional deficits and lack of moral reasoning. The studies concluded that brain injury is not necessary for crime, but that brain injury may contribute to “expression of violence” and increase the risk “threshold” in vulnerable people.

Huw called for screening and better rehabilitation within the criminal justice system. UKABIF is teaming up with the Child Brain Injury Trust and the University of Exeter to pull together a special interest group to address the issues raised by the research. ♦

The website [www.ukabif.org.uk](http://www.ukabif.org.uk) has links to the presentations and gives more information about UKABIF and its work.

UKABIF will hold the 2011 Conference on Thursday 10th November at the National Motorcycle Museum in Birmingham. Please see [www.ukabif.org.uk](http://www.ukabif.org.uk) for details.

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# American Epilepsy Society Annual Meeting

*Conference details:* 3-7 December, 2010; San Antonio, Texas, USA. *Reviewed by:* Mark Manfred.

I had no idea what San Antonio in Texas was like before leaving the frozen wastes of Terminal 5, but it was a delight to be walking around in shirtsleeves. The centre of the city has a narrow, branching and meandering river, at basement level to the buildings. It has been pedestrianised and the cars are on the roadways above. The banks are lined with side-by-side food outlets throughout its length, serving portions designed to increase the revenue of the gastric banders. According to the paper delivered to my hotel room, they have just been authorised to operate on slightly less obese Americans, apparently a mere 12 million of them. It was relaxing to take the quiet, ten minute morning walk along the Riverwalk door-to-door from hotel to conference centre. Later on, the hive of tourist activity, Christmas lights on every tree and endless tourist boats mean that it tips into Disneyland tweedom.

I haven't been to the AES for a while and they seem to have abandoned breakfast meetings and the large number of parallel platform sessions in favour of more posters and fewer, high impact platforms. It is certainly more manageable and this was an excellent meeting. On the first day was a session on psychogenic non-epileptic seizures. The speakers agreed that patients came from a background where emotion was difficult to express in the usual way and so manifested them with somatic symptoms, in what was neatly termed alexithymia. Management is difficult but a seamless, multidisciplinary approach from diagnosis to treatment and providing patients with the language for emotional expression was felt to be part of the solution.

Non-lesional cases for epilepsy surgery were discussed in an open forum. The quality of MRI seems to vary and some cases would not necessarily be non-lesional everywhere. There is increasing use of new technology and magnetoencephalography appears particularly valuable in selected cases, as does tractography for mapping visual pathways, to try to avoid field defects in planning posterior resections. Very closely spaced extracranial EEG, with enormous numbers of electrodes has shown promise in a pilot study to look at its predictive power for more invasive studies. Whether it can replace intracranial EEG remains to be seen.

I was particularly pleased to see that in the Presidential Session, Simon Shorvon was presented with the AES lifetime achievement award, although in the long list of his merits they did not mention his most challenging feat – to guide me to achieving an MD. So this is my opportunity to give my thanks in writing. The afternoon went on to GABA and ion channels. GABA receptors are increasingly recognised to be complex beasts with two subtypes. KCC1 is



excitatory and dominates in infants and KCC2 is inhibitory and dominates in older individuals. Consequently drugs such as phenobarbital do not work in seizures in very young children but the drug bumetanide (remember it as a loop diuretic?) block KCC1 receptors and is theoretically a useful adjunct, which may allow GABA agonists to be anti-epileptic in the right setting. However, phenobarbital causes neuronal apoptosis in young animals and bumetanide causes inhibition of neuronal sprouting so use of both of these drugs needs to be considered carefully in the young. In status epilepticus, GABA receptors are internalised into the cell, which is at least partly why status becomes refractory to benzodiazepines and needs to be treated aggressively and early. Moreover, there is a loss of dental hilar cells and a redistribution of GABA receptors in chronic temporal lobe epilepsy, which may also contribute to the refractoriness of the condition. The story may be made more complicated by the chemical milieu, since alterations in glucose and in ketones may impact on the function of ion channels. Dr Berkovic from Melbourne discussed sodium channel genetic defects and epilepsy. He explained how abnormalities of the SCIN gene may be associated with quite mild forms of epilepsy (GEFS+) or Dravet syndrome (severe myoclonic epilepsy of infancy). Although the phenotypic heterogeneity has not been fully explained, there are some clues, in that the mutations may exhibit mosaicism and their effect may be either a gain of function or a loss of function. The genetic basis of Dravet syndrome may explain the clinical observation that sodium channel blockers can exacerbate the condition. In another talk he told us that most cases with so-called post-vaccination encephalopathy have genetically confirmed Dravet syndrome. Similarly, potassium channel abnormalities may manifest with a gain or a loss of function and they

overlap genetic abnormalities associated with cardiac arrhythmia. In fact some genetic abnormalities previously thought exclusively cardiac, have been shown to be expressed in the brain. Such a close relationship may underpin some cases of SUDEP. It seems that these channels are expressed on the initial segment of the axon, a particularly important part of the cell neurophysiologically, in terms of impulse propagation.

The theme of development and age-related differences was continued in another major session. As well as childhood changes in neuronal sprouting, electrical activity and GABA receptor function, the conference looked at the other end of life. This is much less well explored, but it seems that beta-amyloid may have a specific effect on decreasing neuronal function and predisposing to abnormal neuronal synchronisation. As well as different causes of seizures, the neurobiological effects of seizures appear to differ with age, so that in older animals for example, there tends to be more neuronal damage but less cell death from seizures than in neonates. The widely quoted demise of neurons with age, seems to be a misrepresentation and the changes are of compaction and loss of dendritic spines, with reduction in long term potentiation – at least I think that is what they said, but I can't quite remember. On a more optimistic note, studies tend to confirm that epilepsy in the elderly has a high remission rate. This increasing understanding of age-related differences in basic science means that we should be looking more closely at treatment trials in different age groups, rather than assuming homogeneity. Such clinical evidence is sadly lacking.

As well as basic science, there was a presentation on the problems of epilepsy in adolescence. Social dysfunction, measured as education failure, having children outside a stable relationship, criminal activity or unemploy-

ment affected 75% of individuals with epilepsy in adolescence. Those with JME, or a more benign IGE with GTCS and a high remission rate had equal problems. For example, unplanned pregnancy was seen in one third of young women, compared to 3% of matched controls with juvenile arthritis. In another presentation, a slightly contradictory view was presented, in which the social function of adults who had developed epilepsy as children was related to duration of epilepsy and seizure frequency. The key ameliorating factor was parental support. Either way, psychobehavioural issues need to be addressed independently of epilepsy in adolescent transition clinics.

If it moves, stick an electrode in it was the lesson of an evening session which, with the music of the president's dinner in the background, was devoted to new stimulation techniques. In the evaluation of any of these, there is an important effect of just having the operation, even before stimulation starts and this was the factor confounding one of the studies into anterior thalamic stimulation. Responsive nerve stimulation is an intellectually more appealing technique in which there are two wires attached to a box of tricks in the head. The afferent wire from the seizure zone detects a predetermined neurophysiological abnormality, and the efferent wire sends out an impulse to the seizure zone, to try and prevent

seizures. Patients have to be evaluated fully to work out this zone before the treatment can be tried. Prof Martha Morell (winning the award for the smartest dressed woman at the meeting, which bore no relation to the fact that she was both principal investigator and medical director to the manufacturers of the device) presented data from 190 refractory patients, where the technique has had some benefit, although disappointingly not that much and it is before the FDA at the moment. Trigeminal stimulation was proven in laboratory rats to block seizures and some elegant animal studies showed how the stimulus created a refractory period in the cerebral cortex, blocking aberrant activity. It has been tried with extracranial stimulation of the supraorbital electrode in 13 patients with very significant reduction in seizure numbers. What this does beyond the sensorimotor cortex is for debate and I think the science of these techniques is questionable – but if they truly work.....watch this space.

The annual course was devoted to inflammation in the nervous system and started with an excellent exposition of the bewildering array of auto-immune neurological diseases which will send me scurrying guiltily back to some review articles. More specifically, the autoimmune encephalopathies were discussed and there was a basic science session explaining how Interleukin-1  $\beta$  mediates seizures in the context

of lipopolysaccharide and how caspase and TOLL 4 receptors (which recognise certain antigens) are also involved. Clearly these findings have potential therapeutic relevance in the context of the extremely refractory cases of autoimmune status that we all see from time-to-time. The management of status remains a problem and Matthew Walker (Queen Square) delighted an American audience with a term familiar to UK neurologists: "evidence-free zone". The panel discussing the case had little new to say perhaps because of this. There were also reviews of tropical infections and viral encephalitides and systemic autoimmune diseases affecting the brain. The management of neurocysticercosis is complex and when to give cysticidal treatment remains controversial, especially as some patients seem to have recurrent oedema round the lesions of uncertain cause – ask your local infectious diseases doctor.

There were over a thousand posters on all areas but undoubted highlights were a study showing that cuddly toys in the telemetry unit were associated with psychogenic non-epileptic seizures but did not exclude epilepsy and an analysis of the 1950 Cary Grant film "Crisis" in which a despot kidnaps a neurosurgeon to operate on his tumour. Putnam, a famed American epileptologist, was adviser and one of his scrub nurses participated in the film (\$39.95 from Amazon). ♦



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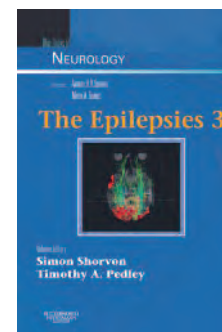
## The Epilepsies 3 (Blue Books of Neurology)

As the great Telly Savalas (inter alia) wisely said, rather than sang, "if a picture paints a thousand words then why can't I paint." And if I have one gripe with this otherwise super book it is this. Why oh why is there no more user-friendly way of presenting what is interesting, important, and relevant information than page upon page of text? Yes there are tables and these are helpful, EEGs spring up periodically (or should that be paroxysmally?) and coloured brain maps are included but there is a woeful paucity of images, forest plots or "blobograms" as I believe they are called, or diagrams and other 'at a glance' images that summarise the substantial data, lovingly laid out in text format,

into a single digestible picture that tells the story, the thousand words, in a way that would firstly aid retention and secondly could be shown, to take one example, to a "woman of child-bearing potential" facing a discussion about which anticonvulsant is "best" for her in the clinic. Gripe over.

This is a fine piece of work. Multi-authored chapters on a wide range of topics (21) ranging from pre-conception to resurrection (almost). Pregnancy, febrile seizures, through epileptic encephalopathies of childhood, and seizures in the elderly. Highly informative and balanced chapters including, in addition to those mentioned, the psychoses of epilepsy, SUDEP, and drug interac-

tions are sandwiched between a fascinating introduction (for me at least!) to the concept of seizure prediction and a chapter on the vexed question of early treatment and its influence of long term outcome. A welcome chapter on sleep and epilepsy could have a little more on the differentiation between parasomnias and seizures which has come a long way in recent times. To wrap up, this particular blue book concludes with chapters on temporal lobe surgery the good, the bad, and the ugly, and whither DBS? I paraphrase. Top notch 'ologists write these books for the non-'ologists and as one of the latter this is certainly good value for a fistful of dollars. ♦



Editors: S Shorvon and TA Pedley  
Published by: Butterworth Heinemann Elsevier (2009)  
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ISBN: 9781416061717

Reviewed by:  
John Bowen,  
Lincoln County Hospital.

## Following Charcot: a forgotten history of neurology and psychiatry (Frontiers of Neurology and Neuroscience volume 29)

More than 100 years after his death, Jean-Martin Charcot (1825-1893) continues to be a subject of fascination to many neurologists (a neurological colleague even named the family cat after him). Perhaps this is because he was the first professor of neurological diseases, perhaps because of the aura which developed around him and his department at the Salpêtrière hospital in Paris which boasted many alumni who made significant and sometimes eponymous contributions to the developing discipline. Many of these contributions have already been the subject of significant studies, such as Goetz et al.'s *Charcot: Constructing Neurology* (OUP, 1995).

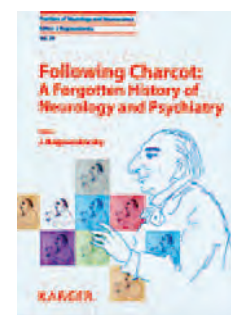
The current volume, beautifully produced, focuses particularly on Charcot's contributions to psychiatry (or alienism, as it was then widely known), directly and indirectly through the work of his protégés.

There is a complete listing of all Charcot's (32) house officers (*internes*) and descriptions of the contributions of many of them, likewise his *chefs de clinique*. Many instantly recognisable names are here (Bouchard, Marie, Babinski, Gilles de la Tourette), as well as others perhaps less familiar (Brissaud, Raymond, Richer, Joffroy, Féré, Bourneville, Sollier, Proust senior), and those working in Paris at around the same time who made neurological contributions (Déjerine, Luys). The tangled history of the succession to Charcot's chair is recounted, as well as Bouchard's actions which stymied the careers of Gilles de la Tourette and, particularly, Babinski.

Bogousslavsky is at particular pains to point out that Charcot had a major influence on psychiatry, though professing no interest in this field, through the successive appointment of three of his trainees

to the chair of mental and brain diseases: Ball, Joffroy and Ballet. Charcot's formulation of hysteria as a "dynamic lesion", resistant to definition by means of the clinico-anatomical method which had proved so fruitful in Charcot's hands for other neurological disorders such as multiple sclerosis and motor neurone disease, ultimately proved incorrect, and his teachings were eventually rejected by some of his followers, notably Babinski. Freud also visited the Salpêtrière, albeit he was only very briefly in Charcot's ambit (October 1885-February 1886). A comparison of his contributions with those of Pierre Janet and their respective reception, both contemporaneous and by posterity, makes for interesting reading.

This well illustrated volume will surely delight all those who retain an interest in the life and work of Charcot. ♦



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ISBN: 9783805595568

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

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## EDITOR'S CHOICE

## Myasthenia gravis: immunoglobulins or plasma exchange – are we any wiser?

The choice of immunomodulatory therapy for neuromuscular respiratory failure following Guillain-Barré syndrome or myasthenia gravis (MG) crisis has always been between intravenous immunoglobulins (IVIG) and plasma exchange (PLEX). Evidence from small institutional series has looked at small numbers of patients, with no discernible difference between the two. It is in this context that this 6-year retrospective population-based cohort study looking into over 1600 MG patients by Mandawat et al, gains importance. The authors did an inpatient database search from 1000 acute-care hospitals in the United States from 2000 to 2005, identifying 6034 patients with MG or MG crisis, based on the ICD-9 coding system. After excluding patients who were transferred between hospitals (thus avoiding duplicate data), and those with a prolonged hospital stay for more than a year, 1606 patients (900 in MG crisis) were identified who received either IVIG or PLEX. Patients who received both treatments were not included in the analysis. Although MG patients not in crisis were similar in age, gender and comorbidities between the IVIG and PLEX groups, patients with MG crisis receiving PLEX were more likely to be male (45.37% vs 29.59%,  $p < 0.001$ ), likely to stay in hospital longer (10 vs 5 days,  $p < 0.001$ ) and were more likely to have been discharged to a rehabilitation facility (18.34% vs 11.24%,  $p < 0.001$ ). The authors ascertain that patients in MG crisis who receive PLEX had a significantly higher unadjusted mortality rate than those given IVIG (5.67% vs 0.59%,  $p < 0.01$ ). However, when this was adjusted for covariates, there was no difference in the mortality or complication rates. Acute respiratory failure, cardiac complications and acute renal failure were associated with an increase in mortality. IVIG was better

tolerated in the elderly and in those with complex comorbid conditions, including acute respiratory failure. The authors conclude that patients receiving IVIG have a shorter hospital stay and less total inpatient costs.

Essentially, this tells us what we already know – IVIG and PLEX are as effective as each other and the choice depends on availability and comorbid diseases. Economically, IVIG has always been thought to be more expensive at the point of delivery, and although the prices have come down recently, supply can be erratic. This study suggests that IVIG is cheaper based on the overall hospital costs. But there is an inherent bias in reaching this assumption – since there were almost 9 times more patients in the PLEX group who had acute respiratory failure than in the IVIG group (181 vs 21,  $p < 0.0001$ ). It is possible that the most unwell patients were more likely to receive PLEX than IVIG and would have had a longer length of stay irrespective of the treatment given. This reinforces the common perception among neurologists that PLEX may be marginally superior to IVIG in MG crisis, when the patient is severely unwell. This remains a gut feeling and robust Class I evidence comparing the overall clinical effect and economical impact of these two therapies is unlikely to materialize in the near future.

– **Saiju Jacob, Consultant Neurologist, Queen Elizabeth Neurosciences Centre, University Hospitals of Birmingham NHS Foundation Trust, Edgbaston, Birmingham, UK.**  
**Mandawat A, et al. Comparative analysis of therapeutic options used for myasthenia gravis.**  
**ANNALS OF NEUROLOGY 2010;68:797-805.**

## Parkinson's disease: nature and neurturin

As the disease progresses, patients accumulate motor disability due to nigrostriatal degeneration, typically developing dyskinesias due in part to increasing levodopa requirements. In recent years, many researchers have turned their attention to developing therapies capable of minimising these long-term motor complications, either by surgically implanting dopamine-producing neurones into the striatum or by changing the genetics of the neurons involved in the damaged circuitry. Gene delivery is exciting because it has the potential to deliver long-lasting expression of a particular protein or growth factor to the brain following a single surgical procedure. One such growth factor is neurturin, an analogue of glial cell line derived neurotrophic factor (GDNF), that has been shown to protect dopaminergic neurones in animal models of Parkinson's disease (PD). A vector capable of carrying the gene for neurturin (adeno-associated vector type 2; AAV2) was studied in a recent double-blind, randomised trial published in *Lancet Neurology*.

A North American collaboration, supported by the company Ceregene, reported the safety and efficacy of stereotactic injection of AAV2-neurturin versus sham surgery in patients with advanced PD (disease duration around 10 years, Hoehn and Yahr stage 3). The vector genomes were delivered to the putamen bilaterally through frontal burr holes, with the expectation that some of the protein would be transported from the striatum to nigral neurones. Patients undergoing sham surgery underwent an identical procedure, except the dura was not breached and the intracranial injections were not done.

The study found that AAV2-neurturin treated patients ( $n=38$ ) and sham surgery patients ( $n=20$ ) did not differ in terms of the primary study

endpoint – change in motor subscore of Unified Parkinson's Disease Rating Scale (UPDRS III) from baseline to 12 months. However, the treatment group did show a modest, but significant, improvement compared with the sham surgery group at 18 months in a subgroup analysis (least squares mean change from baseline to 18 months of -11.96 in the AAV2-neurturin group compared with -4.34 in the sham surgery group). After looking at available autopsy specimens, the authors proposed that the delayed improvement may be due to impaired or delayed transport of the trophic factor to the substantia nigra. As well as longer-term follow-up, the authors plan to carry out further trials using direct injections into the substantia nigra, perhaps combined with higher putaminal concentrations.

This trial is an important early step in establishing whether gene therapy has a place in the long-term treatment of motor complications in PD. Future results will need to show improved outcomes if this approach is to compete with deep brain stimulation and cell transplantation, not only in terms of effectiveness – clinical and cost – but also safety. The risk of tumour induction using trophic factors is a particular concern. Whilst one patient treated with AAV2-neurturin in this study was found to have a glioblastoma, this was later felt to have been present on brain imaging prior to study entry and probably unrelated to the AAV2-neurturin (although the potential for accelerated tumour growth due to the trophic factor must be considered). Other serious adverse events related to the surgical procedure in the AAV2-neurturin group – all of which were self-limiting – included confusion, seizure, haemorrhage, cerebral oedema, and caudate nucleus infarct (all in one patient), transient mental change (in one patient), and urinary retention (in two patients).

Over the next few years, it will be fascinating to see how successful each of the surgical interventions will be in demonstrating and communicating their efficacy and safety record. Deep brain stimulation has a head-start but research funding and pharmaceutical backing will help cell transplantation and gene therapy to stake their claim. This type of competition will only benefit PD patients in the long run. One must realise, however, that these treatments may never be able to treat the extra-nigral manifestations of PD (e.g. memory and neuropsychiatric problems) and we still need to better understand and treat these.

– **David P Breen, Clinical Research Fellow in Neurology, Cambridge Centre for Brain Repair, University of Cambridge.**  
**Marks WJ Jr, et al. Gene delivery of AAV2-neurturin for Parkinson's disease: a double-blind, randomised, controlled trial. LANCET NEUROLOGY 2010;9:1164-72.**

## Pathogenic antibodies to intracellular antigens?

Over the last ten years, there has been an increase in the number of neurological syndromes associated with highly specific autoantibodies directed against proteins expressed in the central nervous system, with well-established antigenic targets such as ionotropic receptors (eg. NMDA receptors) and components of the voltage-gated potassium channel complex (Lgi1, Caspr2). The antibodies bind to cell-surface exposed determinants and are presumed to be pathogenic. By contrast, current dogma suggests that antibodies to intracellular targets, such as typical onconeural antigens, are not pathogenic since the antigen will be unavailable to circulating antibodies. However, Geis et al studied antibodies to amphiphysin, an intracellular antigen involved in synaptic vesicle recycling, in the pathogenesis of paraneoplastic stiff person syndrome (SPS). Immunoglobulin fractions from two patients with SPS were intrathecally infused for 15 days, thus circumventing the blood brain barrier. Rats developed some of the clinical features of the disease including muscle stiffness and spasms, and these features were not seen in appropriate control animals. Electrophysiological investigations showed reduction of the Hoffman reflex and dorsal root potential amplitudes. In vitro neuronal preparations demonstrated highly specific uptake of amphiphysin antibodies into the nerve terminals, and a reduction in stimulated GABA release, and to a lesser extent, glutamate release. These extensive findings provide strong evidence for the pathogenicity of amphiphysin antibodies in SPS, but interesting questions arise: amphiphysin antibodies were derived from the patients' plasma, would it be possible to recapitulate the pathophysiological features by peripheral administration of immunoglobulins? And what is the mechanism by which the antibodies are taken up into the nerve terminals? This study sets a benchmark for further demonstrations of pathogenic effects of antibodies to both intracellular and extracellular antigens in neurological disease.

– **Philippa Pettingil, Research Fellow, Department of Clinical Neurology, Oxford University.**  
**Geis C, et al. Stiff person syndrome-associated autoantibodies to amphiphysin mediate reduced GABAergic inhibition. BRAIN 2010;133:3166-80, with editorial by Angela Vincent, BRAIN 2010;133:3164-5.**

## Alzheimer's Disease: evidence for a neuroprotective effect of an apolipoprotein E genetic polymorphism

The association between APOE genetic polymorphism and differing risks of developing Alzheimer's disease has been well documented. While APOE4 allele, which is present in 25% of the general population, has been associated with more rapid rates of memory decline, the reports regarding the role of much less prevalent (5% of population) APOE2

allele have been inconsistent. One study has reported a protective role for this allele due perhaps to greater entorhinal cortical thickness in the adolescents studied, whereas a few others have associated APOE2 carrier status with increased loss of mnemonic neural substrates. Armed with the neuroimaging data and CSF analysis results of the Alzheimer's Disease Neuroimaging Initiative (ADNI), this study aimed to test the hypothesis that compared to cognitively normal APOE3/3 carriers, APOE2/2 and APOE2/3 carriers demonstrate reduced rates of hippocampal atrophy and episodic memory decline and less immunobiochemical evidence of Alzheimer's related pathological processes in their CSF. Analysis of the longitudinal data obtained from 1.5 T MRI scans using Freesurfer software showed evidence of hippocampal volume loss in both groups with a statistically significant greater degree of atrophy in APOE3/3 carriers. The MRI findings were not supported by the neuropathological evidence as there was a longitudinal improvement in the performance of both groups which was attributed to practice effect. CSF findings however, were compatible with the assumed neuroprotective role of APOE2 carrier status.

The authors discuss that the findings of their study support the assumed neuroprotective role for APOE2. They postulate that decreased Alzheimer's neuropathological changes, evidenced by the CSF findings, might be the mechanism behind the reduced hippocampal atrophy in APOE2 carriers. Two major caveats to this hypothesis are also presented: i) a recent post mortem study among a population aged greater than 90 found increased Alzheimer's pathology but a reduced risk of clinical dementia amongst APOE2 carriers which suggests a mechanism other than decreased neuropathological changes for the reduced risk of dementia in this group; and ii) APOE2 has been associated with an increased risk of cerebral amyloid angiopathy leading to lobar haemorrhage, and the authors remind us that such patients would have been excluded from the ADNI study due to abnormal screening MRI which in turn could have confounded the inferences made. Regardless of mechanisms involved the study provides objective evidence of reduced hippocampal atrophy rates amongst carriers of APOE2 allele compared to the prevalent APOE3/3 carrier status.

– **Sayed Sajjadi, Clinical Research Fellow and Honorary SpR in Neurology, Herchel Smith Building for Brain and Mind Sciences and Neurology Unit, Addenbrooke's Hospital.**  
**Chiang et al. Hippocampal atrophy rates and CSF biomarkers in elderly APOE2 normal subjects. NEUROLOGY 2010;75:1976-81.**

## Tourette Syndrome: habit reversal therapy

There is a new vogue for behavioural therapies in tic disorders which has been driven by Doug Woods from Milwaukee and supported primarily by the US Tourette Syndrome Association. A number of factors lie underneath this renaissance, the chief amongst which is the poor tolerability of most anti-tic medications, even though these drugs can definitely suppress tics (but then, so does a general anaesthetic). Extra-pyramidal side-effects, obesity, impaired glucose tolerance and school refusal are commonly encountered with dopamine blocking agents of all types. This has made the search for alternative forms of therapy more urgent. A further factor is a paradigm shift amongst Tourette doctors and lay organisations which has enabled the Tourette establishment to accept a "non-biological" form of treatment for the first time: much of the early campaigning work was based around using a biological model to prevent blaming of children and parents for the occurrence of tics. It is interesting to note the "rider" at the end of this paper which states "...acknowledging that behavioural and learning processes play a role in tic severity does not imply that tics have a purely psychological etiology or that patients can suppress tics by force of will". The authors are defending people with Tourette Syndrome (TS) against the charge that this is "just a bad habit" and "they could stop doing it if only they tried hard enough". This is ironic in that habit reversal (the basis of the behavioural therapy) is pretty much a technique for "trying really hard not to tic".

The trial itself is excellently constructed and executed. The basic finding of the RCT is that behavioural therapy (based on habit reversal) is

superior to supportive therapy (listening to patients talking about tics and generally supporting them) in around 120 patients with mild to moderate TS. Habit reversal involves performing a competing movement to the tic and holding this until the urge to tic subsides. The therapy also involves concentrating on the “urge” feelings and trying to develop a mastery over them. Effect sizes are reasonable (slightly below those of the drug trials) with a much better tolerability than the drugs in other trials.

There are some quibbles about the methodology, it's difficult to see how the trial was blinded. For instance it would be interesting to see how the two arms of the trial were presented in the patient information sheet. The behavioural treatment appears to be much more intense and time-consuming than the control intervention and, therefore, vulnerable to bias. Habit reversal is clearly not a treatment for the workers. Around 80% of all the trial participants came from a higher professional background (which may reflect access to US health insurance). The treatment and control groups did not appear to be well-matched for anti-psychotic use (13.1% in the treatment group compared to 4.6% in the control group). Perhaps the most valid outcome in the trial is the “impairment” score on the Yale Global Tourette Syndrome Severity Scale. This is only one question worth 50 marks covering the effect on school, occupation and social function. The treated group improved from a score of 25 to 12.2 over 10 weeks. The control group improved from 23.4 to 16.4. The improvements in both groups suggest a strong placebo component but the effect size of 0.57 is reasonable.

Behavioural therapy is clearly developing a place in the management of tic disorders and this trial is a further building block in that process. Clinics seeking to provide specialist services for people with tic disorders should be aiming to provide behavioural therapy as part of a range of treatment options. However, this requires the training and supervision of allied health professionals. At the moment I know of only 3 such practitioners in the UK.

– **Hugh Rickards, Hon. Reader in Neuropsychiatry, Birmingham University and Consultant in Neuropsychiatry, Birmingham and Solihull Mental Health Foundation Trust.**

**Piacentini J, et al. Behavioural Therapy for Children with Tourette Disorder: A Randomised Controlled Trial.**

**JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION 2010;303:1929-37.**

## Tourette Syndrome: greying on top

Brain imaging research in neuropsychiatric research is an esoteric and problematic field. Adequate controls are difficult to find, biases are common, particularly in relation to ascertainment, multiple comparisons, medication and co-morbidity, and causative chains are hard to establish. Finally, one can sometimes get the feeling that a “new piece of kit” is routinely tried out on a series of complex conditions, which may not be a bad thing. This paper is no exception. The authors used two different methods for examining brain structure in Tourette Syndrome (TS): cortical thickness estimation and voxel-based morphometry. They chose adults with TS and healthy controls to compare with and found a reduction in grey matter in the orbito-frontal, anterior cingulate and ventrolateral prefrontal cortices. The cortex also appeared thinner in the mesial temporal lobe. Cortical volume was increased in the primary somatosensory cortex associated with higher premonitory sensation intensity.

There are some limitations to this paper. The sample are adults, who represent the few children with TS who didn't grow out of it, and attend a hyper-specialised clinic where previous research has indicated a high level of personality disorder, also associated with structural brain abnormalities. Over half of the sample had been medicated (probably chronically in most cases). The authors have made some assumptions in relation to causation which are not supported by their data. For instance, they have argued that the reductions in grey matter are “primary” (i.e. reflecting developmental abnormality) and the increases (for instance in the somatosensory cortex) are a reflection of neural plasticity. This implies a causal relationship and is not warranted. In the end, this paper does not tell us much that is new, only that adult TS brains are somehow different to controls. Whether these differences are the primary cause of the disorder, a reflection of the disorder or an epiphenomenon remains to be seen. But, this is not to dismiss the findings out of hand. The data represent a starting point for

understanding the shape of the brain in TS. They need careful replication. The whole field of TS needs longitudinal cohort studies to tease out the causal relationships. Ideally, we should explore the longitudinal study of those people at risk of developing the disorder (i.e. those with affected first degree relatives). Until that happens, progress will probably be slow.

– **Hugh Rickards, Hon. Reader in Neuropsychiatry, Birmingham University and Consultant in Neuropsychiatry, Birmingham and Solihull Mental Health Foundation Trust.**

**Draganski B, et al. Multispectral brain morphometry in Tourette syndrome persisting into adulthood. BRAIN 2010;133:3661-75.**

## BDNF or not BDNF – that is the question in Huntington's Disease

The cause of Huntington's disease (HD) is known to be due to expression of mutant huntingtin, but how this causes the actual cell loss is less clear especially given that whilst all cells express the mutant protein, only a few develop pathology. In the early part of this century, Elena Cattaneo and colleagues showed that the mutant gene may be exerting its effects through BDNF expression in the corticostriatal pathway. The evidence supporting this hypothesis has slowly accumulated over the years, and part of the attraction of the theory is that abnormalities in BDNF expression are known to occur in patients with HD and that abnormalities in its expression could help explain some of the regional pathology seen in the brains of patients with this disorder. In this new paper, Xie et al show that they can rescue the phenotype on the YAC128 mouse model of HD by overexpressing BDNF in the forebrain using a double transgenic approach, in which BDNF is put in under the promoter for the alpha subunit of Ca<sup>2+</sup>/calmodulin dependent protein kinase II. They show that this overexpression not only rescues the behavioural phenotype but also rescues the mouse at the histological and biochemical level. This study therefore adds further weight to the theory that abnormalities in BDNF signalling are critical to the expression of some features of HD. Whether it accounts for all of them is less clear as is the route by which we can exploit this fact for therapeutic gain in patients. However, knowing this means there is hope for patients with HD. The challenge now is knowing how we can do this effectively as has been tried to some extent using exercise and diet – both of which are known to effect levels of this neurotrophic factor in the CNS.

– **Roger Barker.**

**Xie Y, Hayden MR, Xu B. BDNF overexpression in the forebrain rescues Huntington's Disease phenotypes in YAC128 mice. J NEUROSCIENCE 2010;30:14708-18.**

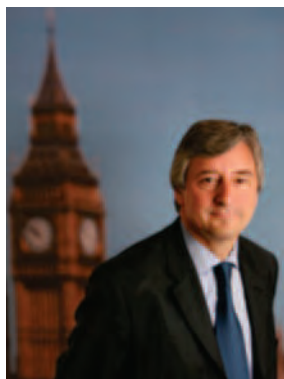
## The Lynx1 effect

These authors from Harvard have identified a novel restrictor of CNS plasticity (akin to the axonal growth inhibiting chondroitin sulfate proteoglycans) relevant to visual cortex, which could be a therapeutic target for amblyopia, with potential for the method to be taken further afield. The molecule, Lynx1, is structurally similar to  $\alpha$ -bungarotoxin, and binds directly to nicotinic acetylcholine receptors. Importantly, the protein was identified through analysis of a transcriptome of mouse V1 visual cortex (16,209 full-length cDNA clones: for light reading turn to Plessy et al. PLoS ONE 2008), with special attention to the binocular zone of V1 and for molecules expressed later than the early ‘critical period’ of visual plasticity. Lynx1 knockout mice deprived of monocular vision for a short or long time in maturity (>postnatal day 60) demonstrated electrophysiological evidence of reorganisation and plasticity that wildtype mice did not, and return of normal visual acuity measured by visual evoked potentials. The plasticity was not at the structural level of perineural nets or increased myelination, and was achieved also purely by cholinergic agonism in wildtypes, leading the authors to hypothesise that the mechanism is at the level of attentional control.

– **Mike Zandi.**

**Morishita, H. et al. Lynx1, a Cholinergic Brake, Limits Plasticity in Adult Visual Cortex. SCIENCE 2010;330:1238-40.**

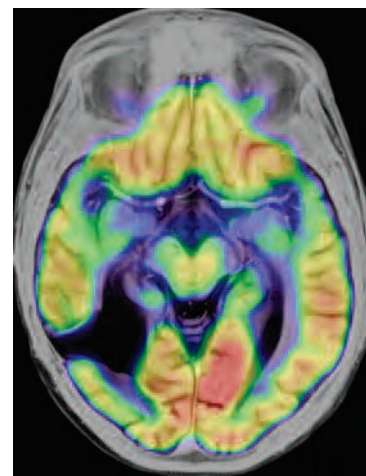
## Trigeminal Neuralgia discussed in House Of Commons Adjournment Debate



On 27th July 2010 Jim Fitzpatrick, MP for Poplar and Limehouse, raised the subject of Trigeminal Neuralgia (TN) in the final Adjournment Debate in the House of Commons. Mr Fitzpatrick is himself a sufferer of TN and member of the active support group TNA UK. Responding, Minister of State for the Department of Health, Paul Burstow, agreed that there was a need for better understanding by policymakers, the general public and clinical staff. He informed the House that he would ask his officials to "look carefully at pain management in the context of the framework for long-term neurological conditions," and announced his intention to meet the Neurological Alliance, an umbrella group representing more than 50 neurological charities and organisations, including the Trigeminal Neuralgia Association UK.

For more information see [www.tna.org.uk](http://www.tna.org.uk)

## World's first molecular MR system unveiled



The Biograph mMR gives spectacular visualisation of organs, their function as well as their metabolism, in a single image. This one shows Brain cancer.

For the first time, a Magnetic Resonance (MR) scanner and PET (Positron Emission Tomography) detection system have been combined to simultaneously capture tissue and cellular data from inside the human body. The Biograph mMR\* system from Siemens Healthcare is a new concept in diagnostic imaging that will revolutionise whole-body scanning. The first clinical installation has just been announced in Germany. The 3 Tesla MR provides exquisite morphological and functional details in human tissue and PET goes further to investigate the human body at the level of cellular activity and metabolism. The innovative system has the potential to be a valuable tool for identifying neurological, oncological and cardiac conditions of disease and in supporting the planning of appropriate therapies. As MRI does not emit ionising radiation, the Biograph mMR may also provide an added benefit of lower-dose imaging. The system also opens new opportunities for research, such as the development of new biomarkers or new therapeutic approaches.

For more information see [www.siemens.com/press/healthcare/Biograph-mMR](http://www.siemens.com/press/healthcare/Biograph-mMR)

## Extension of FDA Priority Review Period for Cladribine Tablets

Merck Serono announced recently that the U.S. Food and Drug Administration (FDA) has extended its review period for Cladribine Tablets as a therapy for relapsing forms of multiple sclerosis (MS) by three months to February 28, 2011.

The FDA granted Priority Review status for Cladribine Tablets in July of 2010, reducing the standard 10-month review period to six months,

which was set to end on November 28, 2010. The FDA extended the review period to provide additional time for a full review of additional information provided under the new drug application (NDA).

For more information contact Merck Serono on T. +44 (0)20 8818 7200.

## SMC approves Zebinix – once daily anti-epileptic treatment

Zebinix® (eslicarbazepine acetate), a treatment for epilepsy, has been accepted for restricted use in Scotland after a decision by The Scottish Medicines Consortium (SMC). Following the new clinical and cost effectiveness decision, Zebinix can now be used as an add-on (adjunctive) therapy in adults with partial-onset seizures, with or without secondary generalisation (where the seizure spreads to both sides of the brain). The Committee adds that Zebinix use should be restricted to patients with hard-to-treat (highly refractory) epilepsy who have been heavily pre-treated and remain uncontrolled with

existing anti-epileptic drugs, contingent upon the continuing availability of the patient access scheme in Scotland.

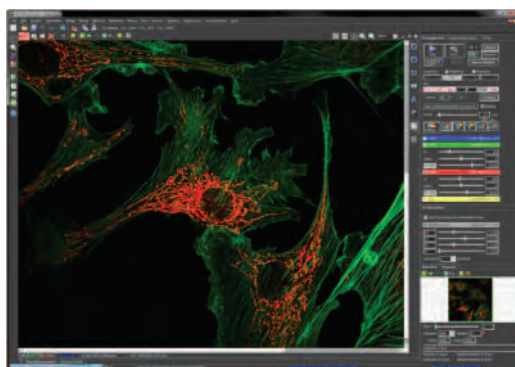
Zebinix was approved for use by the European Medicines Agency in April 2009 for the treatment of adults with partial-onset seizures with or without secondary generalisation. In its first year Zebinix has had over 9,000 months of patient exposure.

Scottish Medical Consortium advice on Zebinix available at: [www.scottishmedicines.org.uk/Home](http://www.scottishmedicines.org.uk/Home).

## Nikon launches NIS-Elements upgrade

Nikon Instruments has introduced version 3.2 of its comprehensive imaging software, NIS-Elements. Following the launch of Microsoft's Windows® 7 operating system, Nikon has developed its software to incorporate many unique features, including improved instrument control combined with enhanced image acquisition and data analysis. Version 3.2 includes updated core features to facilitate customised experiments and evolving protocols and comes with optional software upgrade agreements for easier access to future software updates.

NIS-Elements provides complete control over Nikon motorised microscopes and other devices in four distinct packages scaled to address specific application requirements: AR



– optimised for advanced research applications, with fully automated 6D image acquisition and device control; BR – suitable for standard research applications, such as analysis and photodocumentation of fluorescent imaging through 4D image acquisition; C – enables full integration of confocal specific acquisition controls together with advanced image analysis functionality; and version D which supports colour documentation requirements in bioresearch, clinical and industrial applications with basic measuring and reporting capabilities.

For more information on Nikon microscopes T: +44 (0)20 82471718, E. [info@nikoninstruments.eu](mailto:info@nikoninstruments.eu), [www.nikoninstruments.eu/niselements](http://www.nikoninstruments.eu/niselements)



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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](http://www.yellowcard.gov.uk).  
Adverse events should also be reported to  
Teva Pharmaceuticals Ltd on  
telephone number: 01296 719768.

Date of Preparation: May 2010

C0210/610a

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