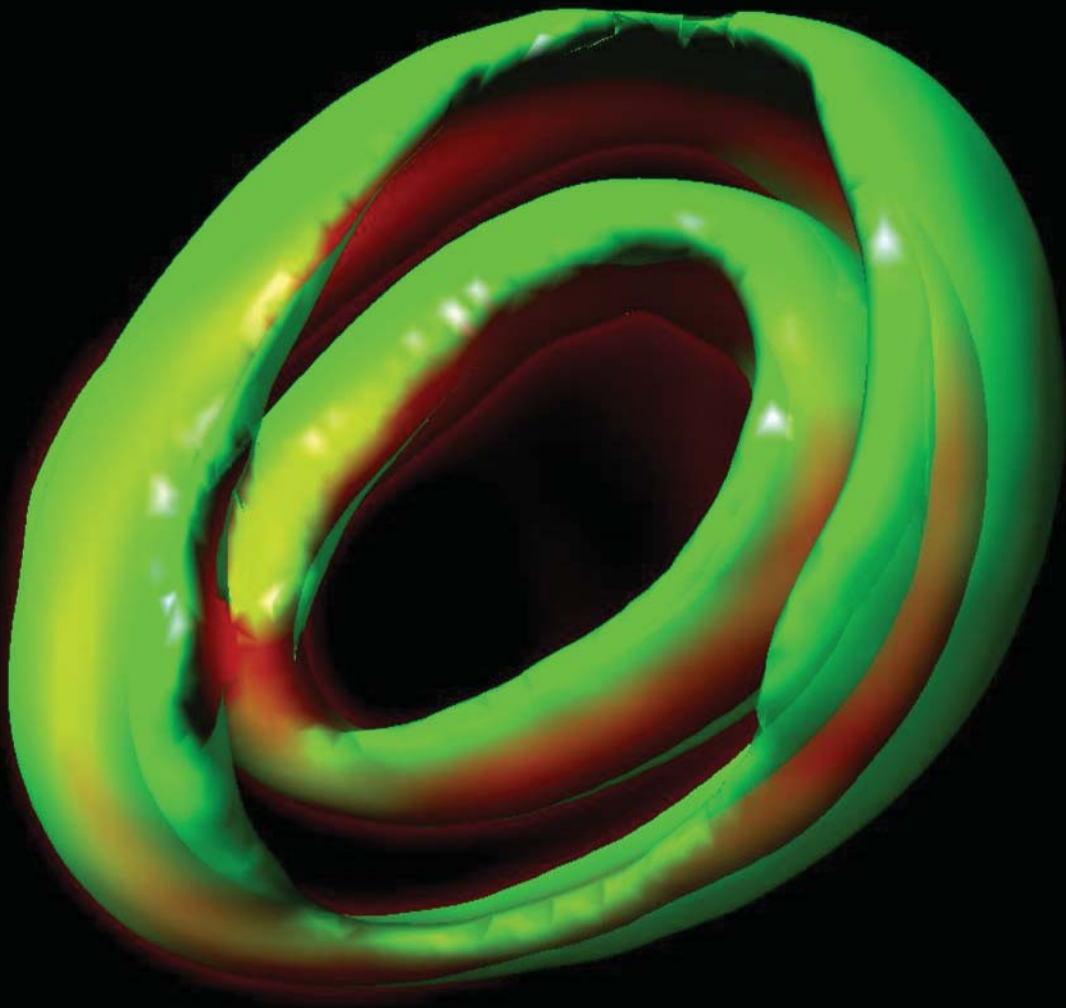


# ACNR

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**Advances in Clinical Neuroscience & Rehabilitation**



## **John Stein**

Dyslexia

## **Phil Cowen**

Treatment of Major Depression: Beyond Generalised Serotonin Potentiation

## **Louis Lemieux**

EEG, fMRI and Their Combination in the Study of Epilepsy

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John Stein argues the case for dyslexia being a distinct neurological entity with a plethora of data to support its diagnosis and a rationale for how to treat it. This is a clear, thought provoking account by an acknowledged expert in this area and will be of great interest to neurologists and neuroscientists alike.

Simon Hammans reviews the approach to patients with mitochondrial disease in this supremely comprehensive and comprehensible account of this group of disorders. Simon, who worked with the late Anita Harding when the field was in its infancy, uses that perspective to distil the critical issues that are of value clinically as well as of interest scientifically.

Depression is common and its aetiology and treatment varied and complex. Professor Philip Cowan in his review takes us through the serotonin system and its fourteen different receptors to give us a clear account on the way in which 5HT could be best manipulated for maximal efficacy and for treating this condition with minimal side effects.

The origins of neuropathology can be traced back to Herophilus of Chalcidion in Greece around 300 years BC, according to Roy Weller in his article entitled "Neuropathology in Context". Roy, who initially edited our neuropathology series, takes us through the history of this discipline and includes a discussion of its current standing and future position in neurological practice.

Katharine Symons in her article in the rehabilitation section discusses what happens with standing up patients with minimal conscious states or the vegetative state in terms of their behavioural capabilities. She comments that "this study demonstrates that simple interventions can enhance behavioural repertoires in some low awareness patients", and thus highlights that assessments of such patients should involve relatively 'low tech' manoeuvres as much more 'high tech' assessments including functional imaging (see ACNR 7.2).

The management of chronic migraine, often in the context of analgesia



abuse, is enough to induce a headache in all but the most robust of neurologists. It is therefore very useful to have Paul Shanahan and Manjit Matharu take us through their approach to this problem and how best to manage such patients in our sponsored Drugs in Neurology feature.

Dinesh Nayak and Kurupath Radhakrishnan, in their fascinating account on epilepsy in India, begin with the sobering fact that if all cases of epilepsy were seen by neurologists in this country then each neurologist would have to care for about 5,000 people with this condition! However, given that most of

the population live in rural areas (away from tertiary centres and neurologists) then this is not the case but consequently they are seen by non-specialists who tend to favour expensive sub-therapeutic polypharmacy. This, coupled to the social stigma of having epilepsy (especially if you are a woman), makes management of this condition particularly difficult, when the only drug free of cost to patients is phenobarbitone.

In the neurophysiology series, Professor Louis Lemieux explores the potential of EEG coupled to fMRI in the assessment of epilepsy. This novel technique has now developed to the point that interesting data is emerging which suggests it can provide more information on the origin of focal seizures and so could become a more mainline tool in the assessment of epilepsy patients in the future.

Andrew Larner in the fourth of his series on headache concentrates on its descriptions in the ancient world. In the course of his typically illuminating discussions he informs us that "wisdom is born of headache by way of unsafe sex" as well as revealing that Aristotle felt "that those with lousy heads are "less than ordinarily troubled with headache""

We have our usual regular items including journal, book and conference reviews, and don't forget our website.

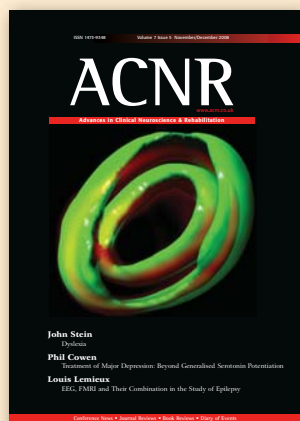
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Bridging clinical and basic aspects**  
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Tuesday July 1 – Queen Square, London

Clinical Aspects  
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Muscle and nerve neuropathology  
Deep brain stimulation experience  
Syndromes related to NA including Huntington's disease, Huntington's disease –like 2, PKAN, FAPED and chronic granulomatous disease  
Caudate nucleus pathology and obsessive-compulsive disorder.  
Coach transportation to and from Queen Square

Wednesday July 2 – Oxford

Basic science of neuroacanthocytosis  
Chorein/VPS13 proteins,  
XK abd Kell genes proteins  
Animal models of neurodegenerative basal ganglia diseases  
Mechanisms of red cell membrane shape changes.

For details on participation including oral presentations or posters covering new material contact:  
Glenn Irvine, Advocacy for Neuroacanthocytosis Patients  
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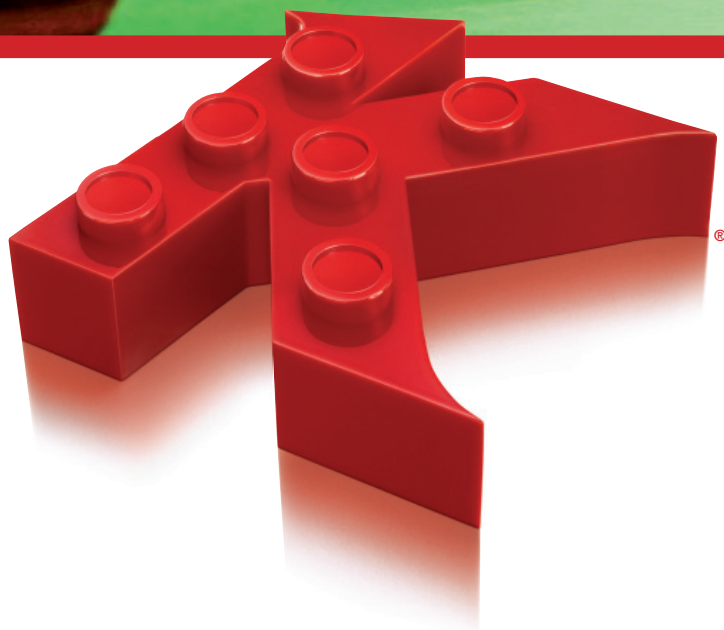
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# Dyslexia

The word dyslexia comes from the Greek, 'disordered words'; it was coined by an ophthalmologist, Berlin, in 1887 to describe patients who had lost the ability to read due to a stroke dividing visual processing from language areas in the left hemisphere. We would now call this 'acquired dyslexia'. Acquired dyslexia can take many forms depending on the precise areas lesioned. The features described separately below are combined to greater or lesser extents in most patients; 'pure' examples are extremely rare because strokes do not respect functional borders in the brain.

Both acquired and developmental dyslexias are most easily understood by reference to the two main routes by which we read words. The phonological or 'sublexical' route converts seen letters into their sounds. This process is essential for children reading new words and even experienced readers reading words they've never seen before, such as made up nonsense words like 'tegwop'. We can read this word by translating its letters into sounds, even though it has no meaning.

The second route to reading is the visual, semantic or 'lexical' route whereby the whole visual form of words is recognised, hence their meaning is understood very quickly, because slow translation of the separate letters into their sounds is not required. This enables familiar and irregular words to be read quickly.

'Phonological' acquired dyslexia is when the patient's sublexical, phonological route is most affected. He will have particular problems with letter to sound translation; and will not be able to read nonsense words like tegwop at all; because he has never seen them before, they are not represented in his visual lexicon. Hence he cannot use the other visual route for reading which may still be intact. This kind of acquired dyslexia occurs when the stroke involves the left supramarginal gyrus and also it is often combined with Broca's motor dysphasia when the left inferior frontal gyrus is damaged.

Visual, 'letter by letter' or 'surface' varieties of acquired dyslexia are seen when the alternative visual lexical reading route is damaged. Here the patients have particular difficulties with reading irregular words, such as 'yacht' or 'bough', where the letter sounds give little help to its pronunciation and the visual form of the word has to be learnt as a whole in order to read it correctly. Phonological 'regularisation errors' are therefore common, whereby the patient has to sound out each letter in the word, bough, and perhaps read it as 'bog'. The most common site for lesions causing visual acquired dyslexia is in the 'visual word form area' that is situated in the anterior part of the left fusiform gyrus on the under surface of the occipito-temporal junction.

The third main kind of acquired dyslexia, 'deep' dyslexia, is when the patients' misreading is semantically related, eg 'ship' is read as 'boat'; the misreading has only a similar meaning, with no visual/orthographic or phonological resemblance to the target word.<sup>1</sup> This occurs when there is partial disconnection between the semantic store of word meanings and their visual/orthographic and phonological representations, again often following lesions in the left angular gyrus. Normally when reading, both these are activated so that the word retrieved can be checked for accuracy against its phonological and orthographic forms.

## Developmental Dyslexia

Deep acquired dyslexia is the most interesting kind from a theoretical linguistic point of view. But semantic errors of this kind are seen less often in 'developmental' dyslexia because this occurs in children learning to read, before they have acquired many visual or detailed phonemic representations of words. However phonological and visual

versions of developmental dyslexia are frequently found, which is why considering acquired, is helpful for understanding developmental, dyslexia.

Developmental dyslexia (hereafter called simply 'dyslexia') is much more common than acquired. It affects perhaps 10% of all children, particularly boys, and is a potent source of individual and family misery. These children with normal or high intelligence unexpectedly find it very difficult to learn to read despite normal schooling and other opportunity. Most neurologists now view this condition as a neurodevelopmental syndrome, because its effects are not confined to reading, but instead reveal more fundamental underlying sensory, motor and attentional features. However, there is still fierce debate. Many psychologists still take the view that dyslexia is a specifically linguistic phonological condition without more basic underlying neurological causes.<sup>2</sup>

## Aetiology

The neurological case rests on many kinds of evidence: genetic, neuropathological, functional imaging, physiological, psychophysiological and behavioural. First dyslexia has a strong genetic basis. Comparing dizygotic and monozygotic twins has shown that 60% of the variability in dyslexics' reading can be attributed to the particular alleles they have inherited.<sup>3</sup> Recent high resolution linkage studies have identified at least 6 chromosomal sites associated with reading difficulties. None seem to make any distinction between visual or phonological problems. Recently 4 genes, ROBO1, KIAA 0319, DYX1C1 and DCDC2 have attracted particular interest because they have all been implicated in the way in which neuronal migration is controlled early in brain development and with how new connections are formed later in development.<sup>4</sup> For example, using RNA interference techniques, KIAA 0319 has been shown to provide essential surface active signals that control neuronal migration from the germinal ventricular plate up the radial glia to form the 6 layers of the mature cerebral cortex.<sup>5</sup> However the slight underexpression of this gene that has been found in dyslexics is probably balanced by slightly increased expression of other genes that may explain the talents in areas other than reading that many dyslexics demonstrate.

The few dyslexic brains that have been examined in detail neuropathologically have confirmed that they contain many sites of mild mismigration of neurones, that must have occurred in utero early in brain development. They show surface 'ectopias' which are small (c. 1 mm) outgrowths beyond the cortical surface where large migrating neurones seem to have failed to observe stop signals at the surface.<sup>6</sup> These ectopias are particularly common in the homotypical association areas that form the language network in the left hemisphere. They are associated with disorganised connectivity of these neurones not only in the cortex immediately below them but also in the homotopic areas connected to them via the corpus callosum in the opposite right hemisphere.

In addition mild abnormalities have been detected in subcortical structures. For example the large neurones that should be confined to the magnocellular layers of the main visual relay in the thalamus, the lateral geniculate nucleus, were found to be 30% smaller and more disorganised than in control brains.<sup>7</sup> Again they seem to have failed to observe stop signals, so that they had infiltrated the parvocellular layers of the LGN. Likewise in the left medial geniculate (auditory relay) nucleus of the thalamus the neurones were found to be smaller and more disorganised. To summarise the neuropathological findings, large, 'magnocellular' neurones in both subcortical and cortical structures tend to be mildly abnormal and disor-



**Prof John Stein** teaches Neuroscience at Oxford. He first studied medicine at Oxford and St Thomas's Hospital. Now his research focuses on the guidance of eye and limb movements by the visual magnocellular system in animals, neurological patients and dyslexics. He doesn't cook fish; his brother, Rick Stein, doesn't do neuroscience!

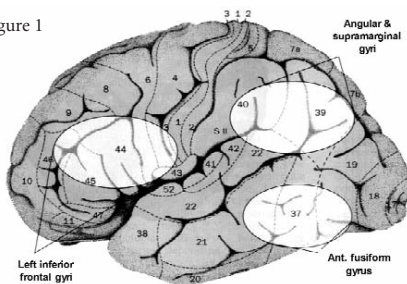
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ganised in dyslexic brains. But it must be admitted that only a small number of dyslexic brains have been examined in this detail and these could have been exceptional.

However recent functional imaging studies in live subjects have corroborated this neuropathological story to a large extent. Figure 1 shows that the same areas that showed ectopias in the language network in the left hemisphere, namely the left anterior fusiform, angular and supramarginal and inferior frontal gyri, are found to be less activated when dyslexics read compared with good readers, whereas, perhaps in compensation, language area homologues in the right hemisphere together with the left middle frontal gyrus seem to be relatively overactive in dyslexics.<sup>8</sup>

Figure 1



Neurophysiological studies have shown that visual, auditory and language related event related potentials are slower and smaller in many dyslexics, providing further evidence that dyslexia may be due to mild abnormalities in the overall development of the brain.<sup>9</sup> But this conclusion is still hotly disputed because not all dyslexics show them. So they have been dismissed as 'epiphenomena' and not causal. But such thinking exhibits the logical fallacy known as the 'undistributed middle' - like saying that because not all diabetics suffer eye problems, eye problems are never caused by diabetes.

A fifth strand of evidence is behavioural. Developmental dyslexics have difficulty with reading of course. Although they make both visual and phonological errors most have the most trouble with splitting down the sounds of words into their constituent phonemes, so, like phonological acquired dyslexics, they make more errors trying to read nonsense words. They also tend to have poor short term phonological memory, so that they are also poor at repeating nonsense words read out to them. Others are more like visual acquired dyslexics; they have particular problems with reading irregular words, making characteristic visual errors such as continuing to confuse bs and ds and misreading god for dog or was for saw.

However in addition all developmental dyslexics are characterised by a variety of non-reading problems.<sup>10</sup> They often report other members of the family who were affected. During development they may have been late crawlers or walkers, failed to learn to ride a bicycle easily and been generally clumsy. They tend to have difficulty distinguishing their left from their right sides. They usually have big problems with recalling a string of digits read out to them, particularly if they are asked to repeat them backwards. They tend to have difficulty with focusing attention and concentration, so that they are slow at reading out a simple list of digits, or naming a sequence of pic-

tures, or reciting the days of the week or months of the year in the right order. None of these features are particularly dependent upon reading experience; hence they suggest that dyslexics tend to have a general problem with rapid linear sequencing, again suggesting a more fundamental neurological causation and casting doubt on a purely linguistic explanation.

This doubt is reinforced by the large number of studies that have shown low level sensory anomalies in dyslexics. Many have reduced visual sensitivity to flickering coarse black and white stripes, ie they have lowered contrast sensitivity to low spatial and high temporal frequency 'gratings'. In line with their histological magnocellular abnormalities this is the hallmark of a selective impairment of the visual magnocellular system. This hypothesis that dyslexics have slightly impaired visual magnocellular function has been supported by numerous studies that have demonstrated that many dyslexics have reduced visual motion sensitivity, since this is mainly mediated by the visual magnocellular system.<sup>11</sup>

Likewise dyslexics tend to have reduced auditory sensitivity to changes in the frequency and amplitude of simple acoustic stimuli; identifying these is thought to be carried out mainly by large neurones in the auditory system. Since these temporal changes mediate our ability to distinguish between the different sounds of letters, this is further evidence that dyslexics may have mild impairments in basic sensory processing that underlie their phonological reading problems.<sup>12</sup>

Again however, since not all dyslexics can be shown to have these impairments, it is vigorously argued that their basic problem is not sensory but at a higher phonological level. Nevertheless it is likely that many psychophysical tests lack the sensitivity required to detect the mild deficits characterising most dyslexics, but that together these slight auditory and visual deficits compound to make it difficult for them to learn to read.

## Diagnosis

It is not surprising, given the amount of disagreement about its aetiology, that there is little agreement about how to identify developmental dyslexia reliably. Its hall mark is difficulty with reading, despite normal intelligence. But thereafter agreement ends. Those who believe that a linguistic phonological deficit is paramount argue that it is only necessary to demonstrate this to diagnose dyslexia. Yet children of low average intelligence experience the same kinds of difficulties with acquiring the phonological skills required for reading. So an influential body of opinion has concluded that there is no real difference between dyslexia and poor reading due to low intelligence, often known as 'garden variety reading difficulty'. The logical conclusion to all this is that there is no such thing as specific reading difficulty or developmental dyslexia.<sup>13</sup>

However this argument ignores the genetic, neurological and physiological evidence that dyslexia is a neurological syndrome. We can argue from this point of view that dyslexia should be diagnosed whenever there is a discrepancy between reading performance and general intelligence in the presence of many of the non-reading symptoms discussed above, such as family histo-

ry, clumsiness, poor recall of digits, slow naming, poor sequencing, visual errors, and it is this discrepancy/ syndromic approach that neurologists should follow.

## Treatment

As might be expected there is great controversy about the best means of treating dyslexics. Everybody agrees however that the most important issue is to recognise the problem as early as possible, by the age of 8 before the child loses all self confidence, and descends into a downward spiral of misery and depression, even suicide, or frustration, anger and delinquency. Those who survive their usually horrible educational experiences, later develop the compensating talents that many dyslexics turn out to possess, regularly reporting that what made all the difference was someone, often a grandparent, who recognised their talents and gave them unstinting support.

Although the mainstay of treatment according to the phonological view is to train children in phonics, this is not always successful by itself. The most successful treatment regimes adopt a multi-sensory, visual, auditory and motor, approach,<sup>14</sup> tacitly accepting that dyslexia is more than just a phonological problem. There is also evidence, some supported by randomised controlled trials, that basic visual or auditory perceptual training can often be highly cost effective for some dyslexics.<sup>15,16</sup> There is much that we can do to help dyslexics, but they must be identified as early as possible, because all these treatments are more effective the younger the child, and will abort the negative emotional consequences of failure.

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# Treatment of Major Depression: Beyond Generalised Serotonin Potentiation

Increasing recognition of the burden of disability associated with recurrent depression led the authors of a recent article in the *Lancet* to conclude that worldwide, depression produces greater overall health impairment than diseases such as angina, arthritis, asthma and diabetes.<sup>1</sup> Part of the reason for the substantial impact of depression on global health burden is its high life-time prevalence (somewhere between 10-20%). Furthermore, patients with angina, arthritis, asthma and diabetes have a greatly increased risk of experiencing co-morbid depression with correspondingly greater health and social disabilities. Indeed depression itself has been linked to an increased risk of a number of medical conditions such as cardiovascular disease and obesity.<sup>2</sup>

## Treatment of depression

One of the reasons for the large health burden of depression is that community surveys suggest that only a minority of patients receive effective treatment with psychotherapy and antidepressants. Generic selective serotonin re-uptake inhibitors (SSRIs) such as fluoxetine and citalopram are recommended as first line treatment of moderate depression by the National Institute for Clinical Excellence. However, a recent large investigation in the United States (the STAR\*D study) which assessed the response of over 2500 depressed patients to first line treatment with citalopram found that only about one third reached symptomatic remission.<sup>3</sup> In clinical terms, remission means being almost completely free of depressive symptoms and it is an important endpoint because patients who reach this goal show better social and occupation function and have a greater chance of staying well than those with lesser degrees of improvement.

As well as limited efficacy, SSRIs also have a number of adverse effects which limit their acceptability. Early in treatment patients can experience nausea, agitation and insomnia while later problems include sexual dysfunction and persistent sweating. A more recently described problem is an increased risk of gastro-intestinal (GI) bleeding, possibly because SSRIs inhibit the function of blood platelets through lowering platelet serotonin levels. When SSRIs are used as a sole therapy the risk of significant GI bleeding is increased about threefold but in combination with non-steroidal anti-inflammatory drugs (NSAIDs) the risk is much greater (about twelvefold) and prophylaxis with gastro-protective agents has been recommended.<sup>4</sup>

## Pharmacology of SSRIs

The key pharmacological action of SSRIs is confined to blockade of the re-uptake of synaptic serotonin (5-HT) into pre-synaptic 5-HT nerve terminals. This increases the availability of serotonin in the synapse and produces a general activation of all post-synaptic serotonin receptors. Research over the last two decades has shown that serotonin receptors exist in multiple subtypes that have distinct biochemical and functional properties. The identification of these receptor subtypes and the development of selective ligands for them is currently a focus of intense activity in academic and industrial research.

At present researchers have described four main families of 5-HT receptors (5-HT<sub>1-4</sub>) and some of the families have themselves been subdivided into further receptor subtypes; at present at least 14 pharmacologically

distinct 5-HT receptors have been identified. While this is a rapidly developing area, there is already some useful knowledge about the pharmacological correlates of many of these different receptor subtypes and how they may contribute to the therapeutic and adverse effects of antidepressant drugs.

## 5-HT receptors, antidepressant action and adverse effects

The antidepressant effect of SSRIs can be reversed by manipulations such as tryptophan depletion, which lower brain 5-HT synthesis.<sup>5</sup> This indicates that sustained activation of post-synaptic 5-HT receptors is required for the therapeutic effect of SSRIs. However, the specific post-synaptic 5-HT receptors involved in the antidepressant action have not been identified definitively. Post-synaptic 5-HT<sub>1A</sub> receptors may play a role and selective 5-HT<sub>1A</sub> agonists such as buspirone and gepirone have antidepressant properties in clinical trials.<sup>6</sup> However, the latter agents do not seem as useful in the treatment of depression as SSRIs because of restricted antidepressant efficacy and relatively poor tolerance. Overall if post-synaptic 5-HT<sub>1A</sub> receptors do play a role in the antidepressant action of SSRIs, it is likely to be in combination with other 5-HT receptor subtypes.

More progress has been made in understanding the 5-HT receptor subtypes involved in the adverse effects of SSRIs. For example it seems likely that stimulation of 5-HT<sub>3</sub> receptors may be involved in the nausea that often accompanies the introduction of SSRI treatment.<sup>6</sup> It is also possible that a number of the adverse effects of SSRIs could be mediated by activation of post-synaptic 5-HT<sub>2C</sub> receptors. For example, in both humans and animals, the 5-HT<sub>2C</sub> receptor agonist, m-chlorophenylpiperazine (mCPP), produces anxiety and sleep disruption.<sup>7</sup> As well as reducing sleep continuity, mCPP lowers slow wave sleep, a stage of sleep important for memory consolidation.<sup>8</sup> In contrast, drugs with 5-HT<sub>2C</sub> receptor blocking properties such as the antidepressant, mirtazapine and the atypical antipsychotic agent, olanzapine, increase slow wave sleep and sleep continuity.<sup>9,10</sup> In animal models, acute administration of SSRIs increases anxiety and this effect can be blocked by a selective 5-HT<sub>2C</sub> receptor antagonist.<sup>11</sup>

Taken together these data suggests that the early effects of SSRIs to produce anxiety, agitation and sleep disturbance are probably mediated through activation of 5-HT<sub>2C</sub> receptors. Another troublesome adverse effect of SSRIs in longer-term treatment is inhibition of ejaculation and orgasm. Animal studies suggest that this effect too may well be mediated in part by activation of 5-HT<sub>2C</sub> receptors.<sup>6,12</sup>

## Antidepressants with 5-HT<sub>2C</sub> receptor blocking properties

The role of 5-HT<sub>2C</sub> receptors in the adverse effects of SSRIs suggests that combination of 5-HT<sub>2C</sub> receptor antagonists with SSRIs might be a useful therapeutic strategy from the



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**Table 1: Clinical profile of some commonly used antidepressant medications**

Drug	Insomnia	Sedation	Nausea	Weight gain	Sexual dysfunction	Toxicity in Overdose
SSRI	++	0	++	+	++	0
Venlafaxine	++	0	++	+	++	+
TCA	0	++	0	++	+	++
Mirtazapine	0	++	0	++	0	0

0 = not present, + = sometimes, ++ = common, TCA = TriCyclic Antidepressants and SSRI = Selective Serotonin Reuptake Inhibitors





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20 cm<sup>2</sup> patch contains 9.0 mg rotigotine.

**Neupro 6 mg/24 h transdermal patch:**

Releases 6 mg rotigotine over 24 hours.

30 cm<sup>2</sup> patch contains 13.5 mg rotigotine.

**Neupro 8 mg/24 h transdermal patch:**

Releases 8 mg rotigotine over 24 hours.

40 cm<sup>2</sup> patch contains 18.0 mg rotigotine.

**Indications:** To treat the signs and symptoms of idiopathic Parkinson's disease, either with or without concomitant levodopa therapy. **Dosage:** Neupro is applied to the skin once a day. The patch remains on the skin for 24 hours and will then be replaced by a new one at a different application site. In monotherapy,

treatment is initiated with a single daily dose of 2 mg/24 h. Dose increased by 2 mg/24 h each week (e.g. 2 mg/24 h in Week 1, 4 mg/24 h in Week 2, 6 mg/24 h in Week 3 and 8 mg/24 h in Week 4), until an effective dose is reached. Maximal dose is 8 mg/24 h. In combination with levodopa, treatment initiation is at 4 mg/24 h and increased weekly in 2 mg increments, up to a maximum dose of 16 mg. **Contraindications:** Hypersensitivity to rotigotine or to any of the excipients. Neupro should be removed prior to Magnetic Resonance Imaging (MRI) or cardioversion to avoid burns. **Warnings and Precautions:** External heat should not be applied to the patch. Dopamine agonists are known to cause hypotension, and monitoring of blood pressure is recommended. Where somnolence or sudden sleep onset occurs, or where there is persistent, spreading or serious skin rash at the application site, consider dose reduction or termination of therapy. Rotate the site of patch application to minimise the risk of skin reactions. In case of generalised skin reaction associated with

use of Neupro, discontinue treatment. Avoid exposure to direct sunlight until the skin is healed. If treatment is to be withdrawn, it should be gradually reduced to avoid symptoms of neuroleptic malignant syndrome. Compulsive behaviours and hallucinations have been reported in patients treated with Neupro. Do not administer neuroleptics or dopamine antagonists to patients taking dopamine agonists. Caution is advised when treating patients with severe hepatic impairment, and in patients taking sedating medicines or other depressants in combination with rotigotine. Switching to another dopamine agonist may be beneficial for those patients who are insufficiently controlled by rotigotine. **Undesirable effects:** Very common side effects include nausea, vomiting, somnolence, dizziness and application site reactions. Common side effects include anorexia, hallucinations, sleep attacks, insomnia, abnormal dreams, headache, dyskinesia, lethargy, orthostatic hypotension, hypertension, hiccup, cough, constipation, diarrhoea, dry mouth, dyspepsia, hyperhidrosis, erythema, pruritus, asthenic

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point of view of easing the side effect burden of SSRIs therapy. However, might selective 5-HT<sub>2C</sub> receptor antagonists have potential as antidepressants in their own right?

The tetracyclic antidepressants, mianserin and mirtazapine, do not inhibit the re-uptake of noradrenaline or 5-HT but have antagonist properties at 5-HT<sub>2C</sub> receptors. Both these drugs are relatively free from sexual dysfunction and, as noted above, promote sleep. However, they are complex molecules with several other pharmacological actions which makes analysis of the specific effects of 5-HT<sub>2C</sub> blockade difficult to assess. For example, both are strong histamine H<sub>1</sub> receptor antagonists which may well contribute to their ability to improve sleep in depressed patients. H<sub>1</sub> receptor antagonism may also cause the weight gain associated with mianserin and mirtazapine treatment. Mirtazapine and mianserin are also  $\alpha$ <sub>2</sub>-adrenoreceptor antagonists which would be expected to result in increased noradrenaline release from pre-synaptic noradrenergic terminals. This action, rather than 5-HT<sub>2C</sub> receptor antagonism might therefore account for their antidepressant effects.

There is, however, evidence from basic studies that 5-HT<sub>2C</sub> receptor antagonism might have antidepressant potential. 5-HT pathways have inhibitory effects on dopamine and noradrenaline release through post-synaptic 5-HT<sub>2C</sub> receptors. In animal studies blockade of these receptors leads to increased release of both noradrenaline and dopamine, an action which might be expected to be associated with antidepressant effects.<sup>13</sup>

Agomelatine is a recently described molecule which combines melatonin agonist properties with 5-HT<sub>2C</sub> receptor blockade. Agomelatine is active in animal models of depression and also has proved efficacious in depressed patients in a number of placebo controlled trials.<sup>13,14</sup> Interestingly the adverse effect profile of agomelatine does not include early anxiety and insomnia;<sup>13</sup> in fact sleep continuity in depressed patients is improved and slow wave sleep increased.<sup>15</sup> These early data suggest that 5-HT<sub>2C</sub> receptor antagonists and melatonergic agonist are worth exploring as antidepressant agents. If effective such drugs would be expected to have a much lower adverse effect burden than SSRIs and could be particularly helpful for patients troubled by sleep disturbance and sexual dysfunction during SSRI treatment.

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# Mitochondrial Disease: Old and New

The mitochondrion is an intracellular organelle with the primary function of generating ATP, the energy currency of the cell, by oxidative phosphorylation. It also hosts beta oxidation, the Krebs cycle and other pathways. Mitochondrial dysfunction is particularly prominent in the energy dependent tissues brain and muscle. In some diseases, mitochondrial dysfunction is part of the pathophysiology (e.g. Parkinson's disease); in others a mitochondrial enzyme deficiency is the primary cause of the disease.

The complexity of mitochondrial disease is increased by the presence of copies of mitochondrial DNA (mtDNA) within the organelle. Human mtDNA is a 16.6 kb circular double stranded DNA molecule. It contains 13 genes for protein subunits of the mitochondrial respiratory chain. A further 2 genes encode ribosomal RNA, and there is a complete set of 22 tRNAs. The mtDNA encoded proteins are subunits of respiratory chain complexes I, III, IV and V, while the subunits of complex II are entirely nuclear encoded. Because there are multiple copies of mtDNA within each mitochondrion, cell and tissue, the concept of heteroplasmy arises, in which there is a mix of different mtDNAs. In mitochondrial disease heteroplasmy is common, with normal mtDNA coexisting with abnormal mtDNA.

This article is necessarily selective and describes:

- a scheme of investigation for classical mitochondrial respiratory chain disease (often easy to diagnose)
- a discussion of more recently described mitochondrial disorders and those more difficult to diagnose

## Classical mitochondrial encephalomyopathies

It is often stated that mitochondrial disease is clinically and genetically heterogeneous, and is protean in its manifestations. It would therefore be expected that the diagnosis of mitochondrial disease is often overlooked and misdiagnosed. Whereas this may happen, most experienced neurologists meeting a patient with mitochondrial disease will consider the diagnosis in timely fashion, although genetic classification may take somewhat longer. The reason for the diagnostic success lies in the fact that although presentations are highly variable, mitochondrial disease is usually suggested by the cardinal features of classical mitochondrial encephalomyopathies (Table 1).

Mitochondrial disease is not rare, having a prevalence of approximately 10/100000,<sup>1</sup> which ensures that patients appear in general neurology clinics fairly regularly. Although the presenting complaint may be ataxia, ptosis, seizures or one of the other manifestations, these rarely

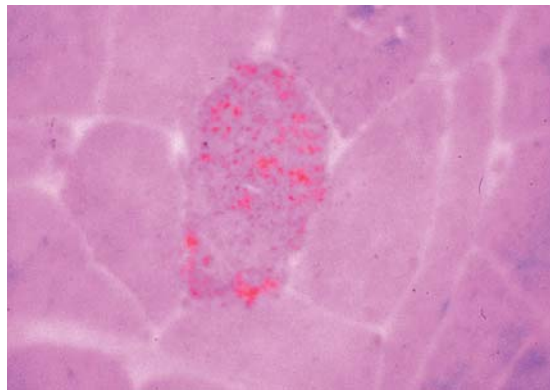


Figure 1: A muscle biopsy of a patient with a heteroplasmic mtDNA deletion. In situ hybridization using a probe detecting deleted mtDNA species showing them to be concentrated within ragged red fibres (RRF).

occur in isolation. For example, a patient may present with ataxia. If additional deafness or ptosis is noted, mitochondrial disease rises to the top of the differential diagnosis. This should lead to a comprehensive review to look for further features in the patient and their family. When the diagnosis is suspected, it may usually be confirmed by the appropriate use of genetic analysis of blood or muscle, and histochemical examination of muscle. Table 2 details the usual scheme of investigation. A genetic diagnosis from blood may be possible, but if not muscle biopsy usually shows focal histochemical abnormalities, with proliferation of mitochondria seen as ragged red fibres on the modified Gomori trichrome reaction. Research techniques such as in situ hybridisation show these abnormal fibres to be populated by mutant DNA (Figure 1). Such fibres react heavily with succinic hydrogenase, which is not mtDNA encoded, but are usually deficient in cytochrome oxidase (COX), which is.

## Mitochondrial encephalopathies

Mitochondrial encephalopathies can present at any age. Presentations in childhood have a higher incidence of multisystem disease, with short stature, bone marrow, cardiac and renal involvement often seen. Mitochondrial encephalopathies sometimes conform to the acronyms MERRF (myoclonic epilepsy with ragged red fibres) or MELAS (mitochondrial encephalopathy with lactic acidosis and stroke-like episodes), but more often do not. The value of the acronyms is to provide a mnemonic for some of the more common manifestations of mitochondrial encephalopathy, and the clinical features have an approximate correlation with the two commonest mtDNA point mutations (mtDNA 8344 tRNA<sup>Leu</sup> and 3243 tRNA<sup>Leu</sup>(UUR) respectively). However, dementia, ataxia and deafness are also common CNS features and even within families the clinical features vary qualitatively and



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**Table 1: Common features of classical mitochondrial disease**

Eyes	Ptosis and ophthalmoplegia Retinopathy
Somatic	Diabetes Deafness Short stature
	Cardiac, renal involvement Sideroblastic anaemia
CNS	Dementia Ataxia Myoclonus Seizures Stroke-like episodes

**Table 2: Investigation of mtDNA disorders**

Presentation	First investigation	Further investigation
PEO, KSS or myopathy	Muscle biopsy	Muscle mtDNA analysis including deletions
Encephalopathies	mtDNA analysis (blood) for common point mutations	Muscle biopsy
Leber's hereditary optic neuropathy	mtDNA analysis (blood)	
NARP/MILS	mtDNA analysis (blood)	

KSS = Kearns Sayre syndrome, NARP = Neurogenic weakness, ataxia, retinitis pigmentosa, MILS = maternally inherited Leigh's syndrome.

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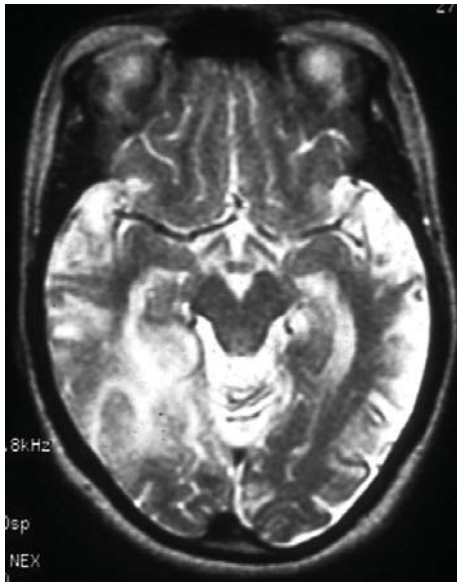


Figure 2: A T2 weighted magnetic resonance brain scan image showing atrophy and infarction in a young adult with MELAS.



Figure 3: A patient with Progressive external ophthalmoplegia (PEO), showing asymmetrical ptosis and squint.

quantitatively. Although screening for the common mutations in blood is suggested as a first investigation, if these are negative a muscle biopsy is required.

In modern practice diagnostic suspicion of mitochondrial encephalopathy may be generated by brain imaging. CT may show basal ganglia calcification. Stroke-like episodes appear on MRI as high signal change on T2 weighted images, particularly posteriorly, not necessarily following arterial territories (Figure 2). Atrophy of the cerebellum and/or cerebrum is common.

**Mitochondrial myopathies**

Mitochondrial disease may have its major manifestation in muscle. The commonest muscles affected are those of the eyes, with a progressive external ophthalmoplegia (PEO), often consisting of an asymmetrical ptosis and weakness of the extraocular muscles (Figure 3).

PEO is often combined with other clinical features, and can range from late onset pure PEO to more severe variants such as the Kearns-Sayre syndrome. Although some degree of proximal limb weakness is common, a pure limb girdle syndrome without clues such as PEO, deafness, or somatic features is relatively rare. Petty et al<sup>2</sup> pointed out that if the patient has no CNS manifestations of disease within 5 years of onset, then these are unlikely and the prognosis correspondingly much better than the mitochondrial encephalomyopathies. Muscle involvement rarely causes severe weakness, and loss of mobility secondary to muscle weakness alone is rare.

PEO can be sporadic with very low recurrence risk (single large heteroplasmic mtDNA deletion), or with maternal (heteroplasmic mtDNA mutation), or autosomal inheritance (see below). Thus genetic investigation is important to define recurrence risks.

The commonest abnormality causing mitochondrial PEO is a single large mtDNA deletion. This is present in much larger proportion in muscle, and a muscle biopsy remains the definitive investigation for histochemical studies and genetic analysis.

**Therapeutics in mitochondrial disease**

A Cochrane review concluded that there was no clear evidence supporting any therapeutic intervention in mitochondrial disorders.<sup>3</sup> Exercise training appears to help patients and is probably safe.<sup>4</sup> Some patients report subjective improvement in muscle symptoms on Coenzyme Q10 or creatine supplements. The author has observed abrupt improvement in treating stroke-like episodes acutely with dexamethasone, but this is unlikely to be trialled. Supportive treatment for the many other manifestations of these disorders remains valuable.

**New and more difficult mitochondrial disease**

The characteristics of classical mitochondrial disease establish useful guidelines to the clinician and scientist. Maternal inheritance, multi-system disease, focal histochemical abnormalities on muscle biopsy, and heteroplasmic mtDNA are all typical of these diseases. Clinical and molecular diagnosis becomes more challenging when these features are not present. Examples of such patients not conforming to the classical model are increasingly described, and are summarised here

**Absence of typical histochemistry**

Mitochondrial encephalomyopathies are historically defined by the presence of ragged red fibres (RRF) in muscle, an indicator of pathological focal mitochondrial proliferation.

Diseases without this hallmark or without any histochemical markers of mitochondrial dysfunction are more difficult to identify. The characteristic phenotype of Leber's hereditary optic neuropathy is not associated with mitochondrial histochemical defects, and similarly RRF are not found in the biopsies of NARP patients (which usually show evidence of denervation). More difficult are the few patients with classical mitochondrial phenotypes such as MELAS and others. Such phenotypes are usually associated with mtDNA tRNA mutations, but less commonly can be associated with mutations in protein coding genes. Mutations in protein coding genes such as mtDNA ND5, often do not cause histochemical abnormalities on muscle biopsy.<sup>5</sup> When abnormalities are found, they are subtle, with increased staining of the succinic dehydrogenase reaction in cytochrome oxidase positive fibres.

**Absence of family history or multisystem disease**

Some patients with muscle symptoms such as fatigue and exercise intolerance (sometimes with episodic myoglobinuria) also have mutations in mtDNA protein coding genes. Such patients are difficult to identify because there may be no maternal family history and no manifestations outside muscle.<sup>6</sup> This group of patients do have abnormalities on muscle biopsy which often acts as a spur to more directed mtDNA analysis. Unless the mtDNA mutation involves COX genes, the RRF are COX positive, which is an additional clue.

**Absence of mtDNA heteroplasmy**

LHON is more often due to mutations in the homoplasmic rather than heteroplasmic state. Homoplasmic mtDNA mutations causing other mitochondrial disease are rare, but has now been described in several families, although the pathogenicity of the mutation is always harder to prove.<sup>7</sup>

**No mtDNA defect**

MtDNA encodes only 13 of the 90 (approximately) proteins of the respiratory chain, leaving much scope for respiratory chain defects secondary to nuclear gene defects, as well as many other mitochondrial proteins. These disorders may have similar clinical and biochemical features to mtDNA disease and may be difficult to define in molecular terms. Many of these mutations cause severe or fatal early onset disorders, such as SURF1 mutations which are the commonest cause of typical Leigh's disease. These numerous disorders are beyond the scope of this review.

**Intergenicomic disease**

Whereas the initial thrust of research and understanding of mitochondrial disease was largely confined to the primary disorders of mitochondrial DNA, a more recent research priority has been the elucidation of disorders arising from defects in the interaction of the two genomes. These disorders are caused by nuclear gene defects involved in mtDNA maintenance; consequently Mendelian inheritance is observed. These defects give rise to direct or

Table 3: MtDNA disorders without RRF or histochemical deficit.	
Phenotype	Genetic abnormality
LHON	3 mtDNA mutations account for ~95% of disease
NARP/MILS	mtDNA ATPase mutations
Some patients with MELAS and other encephalopathies	mtDNA mutations in ND5 and other protein coding genes

LHON = Leber's hereditary optic neuropathy.

Table 4

Gene	Protein	MtDNA defect	Clinical syndrome
POLG1	polymerase $\gamma$ -alpha subunit catalytic subunit p140	Multiple deletions and depletion	See text ad/arPEO, ad/ar multisystemic syndromes Alpers syndrome
POLG2	polymerase $\gamma$ -alpha subunit accessory subunit p55	Multiple deletions and depletion	adPEO
C10orf2	mitochondrial helicase PEO1 (Twinkle)	Multiple deletions	adPEO, arIOSCA, ar hepatocerebral syndrome
ANT1	adenine nucleotide translocator 1	Multiple deletions	ad/arPEO
TP	Thymidine phosphorylase	multiple deletions and depletion	MNGIE
dGK	deoxyguanosine kinase	Depletion	Hepato-cerebral syndrome
SUCLA2	beta subunit of the ADP-forming succinyl-CoA synthetase ligase	Depletion	Encephalomyopathy and anaemia
MPV17	MPV17 inner mitochondrial membrane protein	Depletion	Hepato-cerebral syndrome
TK2	thymidine kinase 2	Depletion	Myopathic syndrome
RRM2B	P53 controlled ribonucleotide reductase	Depletion	Fatal infantile multisystem disease

ad/ar = autosomal dominant/autosomal recessive, IOSCA = infantile onset spinocerebellar ataxia.

Table 5: Clinical features suggestive of POLG mutations

• Onset at any age but neurological features commonly in teens
• Epilepsy is the most frequent presenting symptom (often with headache and sometimes resulting in status epilepticus)
• Axonal neuropathy is present in most patients
• Myopathy, ataxia, PEO are also common
• PEO is not invariably present and usually appears after age 20
• Alper's disease is caused by POLG mutations, and valproate may precipitate hepatic failure in neurological patients carrying POLG mutations

indirect injury to mtDNA through different pathways, either quantitative or qualitative. However, as might be predicted, the biochemical, pathological and clinical consequences are often suggestive of mitochondrial disease.

MtDNA is continuously recycled. Replication is performed by a number of nuclear encoded proteins. MtDNA polymerase gamma (POLG) is the only DNA polymerase present in mammalian mitochondria. It is a heterodimer with a catalytic subunit (coded by POLG) and two identical accessory subunits (coded by POLG2). The accessory subunit is a DNA binding factor required to increase the affinity of the heterotrimer for template DNA. POLG together with other nuclear encoded proteins is central to the synthesis of mtDNA. Other proteins involved in mtDNA maintenance and associated with human disease are tabulated (Table 4).

## POLG mutations

### Autosomal dominant disease

POLG came to attention when pathogenic mutations were discovered to cause autosomal dominant PEO (adPEO). It is now apparent that POLG defects account for about half of adPEO. In such patients, multiple defects are found in mtDNA with muscle biopsy findings indicating a mitochondrial myopathy. PEO is accompanied by a variable number of other clinical manifestations. Clinically patients with adPEO may have a similar phenotype to patients with PEO due to a single deletion or a mtDNA mutation. Some additional features such as deafness and neuropathy are common accompaniments of mitochondrial disease, but

some families show an excess of cataracts, parkinsonism and psychiatric disorders. POLG or other nuclear mutations may be suspected if autosomal inheritance is present, or if mtDNA analysis raises the possibility of multiple deletions or depletion.

### Autosomal recessive disease

Compound heterozygotes for POLG mutations may also show ophthalmoparesis. However, neuropathy and ataxia are common additional features, giving rise to the acronym SANDO (sensory ataxic neuropathy with dysarthria and ophthalmoparesis). Recessive POLG mutations may also cause adult onset ataxia without ophthalmoplegia (mitochondrial recessive ataxia syndrome or MIRAS).

POLG mutations are not a rare cause of mitochondrial disease and the phenotype is expanding, ranging from fatal childhood hepatopathy (Alpers syndrome) to milder clinical syndromes in later life.<sup>8</sup> Whereas the diagnosis is often suggested by the muscle biopsy, biochemical and mtDNA findings, clinicians may suspect the diagnosis when autosomal inheritance is evident or clinical features match those tabulated (Table 5).

The phenotype of POLG gene variants is still expanding. There are several reports of deterioration on initiation of valproate, and it is prudent to avoid this medication if POLG associated disease is suspected.

### Other nuclear mutations causing mtDNA deletions and depletion

This is currently an active area of research, with an increasing number of genes implicated (Table 4). The latest gene investigated is RRM2B, which accounts for the depletion syn-

drome in further families.<sup>9</sup> More causative genes are likely to be identified as some families with deletions/depletion do not have a known causative gene.

### Thymidine phosphorylase mutations

Mitochondrial neurogastrointestinal encephalopathy (MNGIE) is an autosomal recessive disorder caused by mutations in the thymidine phosphorylase gene. The phenotype is relatively stereotyped with onset often in late childhood with PEO, and cachexia secondary to gastrointestinal dysmotility. A demyelinating neuropathy may be initially asymptomatic or may be the presenting feature, mimicking CIDP.<sup>10</sup> A striking leucoencephalopathy seen on magnetic resonance imaging of the brain remains asymptomatic.<sup>11</sup>

Disability results from the neuropathy as well as myopathy, but the gastrointestinal manifestations cause cachexia and life threatening complications. As a consequence of loss of function of thymidine phosphorylase, blood levels of thymidine and deoxyuridine are raised. Alterations of nucleoside metabolism cause preferential impairment of mtDNA replication, leading to both depletion and deletions on mtDNA.

Elucidation of the biochemical disturbance has led to the possibility of therapeutic intervention, by restoring thymidine phosphorylase function. Allogeneic stem cell transplantation is one approach, already shown to be capable of improving the plasma levels of nucleosides, but it is not clear whether this will have a beneficial effect on cellular function. This approach has not yet been shown to produce significant clinical improvement.

### Co-enzyme Q10 deficiency

Coenzyme Q10 is a respiratory chain cofactor. Deficiency states would be predicted to cause respiratory chain dysfunction. Co-enzyme Q10 deficiency has been reported in association with diverse presentations from early onset encephalomyopathy often with fatal renal involvement, to later onset and milder myopathic presentations. This heterogeneous condition is now being elucidated. Nine enzymes are involved in Co-enzyme Q10 biosynthesis. To date pathogenic mutations have been described in three of these enzymes, PDSS1, PDSS2, and COQ2.<sup>12</sup> It has been shown that what has been described as the myopathic form of co-enzyme Q10 deficiency is a presentation of late onset glutaric aciduria. Recessive mutations in the electron transferring flavoprotein dehydrogenase gene (ETFDH) have been identified.<sup>13</sup>

The importance of these disorders is the potential response to Co-enzyme Q10 supplementation, including the secondary deficiency seen in glutaric aciduria. High doses may be needed, and the case of the myopathic presentations additional riboflavin may be required. Whereas the myopathic presentation may be suggested by lipid accumulation and mitochondrial changes on muscle biopsy, the primary deficiencies showed no such clues, and Co-enzyme Q10 assay on muscle or fibroblasts may be advisable in suggestive phenotypes in order to detect therapeutic possibilities.

### Conclusion

Classical mitochondrial disorders affecting the nervous system are often diagnosed promptly by neurologists, but this article has shown that mitochondrial disease may not always be associated with expected patterns of inheritance, muscle histochemistry, and molecular genetic abnormalities. Consequently, mitochondrial disease must be considered beyond the classical mitochondrial phenotypes. Recent therapeutic attempts with respect to MNGIE and coenzyme Q10 deficiency are still being evaluated and may herald the start of a new era of therapeutic options in mitochondrial disease.

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## “Neurological literature”: Headache (Part 4)

“Existence is just an ache in the head” –

Margiad Evans, diary entry for 23rd November 1949

That headache has been a feature of the human condition since prehistory may be inferred by the finding of skulls with holes cut in them. Such trepanations date from as far back as the Neolithic era, and have been found in Europe, Asia, the Americas, and north Africa.<sup>1</sup> Although their purpose will be forever obscure to us, the possibility that they were undertaken to relieve headache, perhaps through a perception that such surgery would release malign spirits from inside the head, seems at least plausible. Recourse to such extreme, life-threatening, measures may suggest the presence of severe symptoms.

That no record of headache is to be found, as far as I am aware, in the doings of the numinous, extracorporeal, God of the Jews and Christians is perhaps no surprise. Nor that the domestic soap opera of the Olympian gods of ancient Greece, amounting at times almost to farce (e.g. in the Homeric epics *Iliad* and *Odyssey*), should give an example of something so quotidian as headache, specifically in one of the myths of the birth of Athene, the goddess of wisdom.<sup>2,3</sup> Zeus, ruler of the gods, lusted after Metis the Titaness; she has been identified with the planet Mercury, itself associated with wisdom. Having gained his wicked way with Metis, Zeus was warned by a prophecy that she would bear a son strong enough to depose him, in the same way that Zeus himself had deposed his father Cronos with the assistance of Metis. To avoid this eventuality, Zeus swallowed Metis. However, this was not the end of the matter: “In due process of time, he was seized by a raging headache ... so that his skull seemed about to burst, and he howled for rage until the whole firmament echoed.” Hermes divined the cause of Zeus’s discomfort and summoned Hephaestus, the blacksmith god, who with his wedge made a breach in Zeus’s skull, from which sprang forth Athene, the goddess of wisdom. Hence, our evidence-based conclusion is clear: wisdom is born of headache by way of unsafe sex.

The early Socratic dialogue *Charmides*, named for Plato’s maternal uncle, is ostensibly a search for the definition of *sophrosune* (Σωφροσύνη), variously translated as soundness of mind, self-knowledge, or self-control. Internal evidence dates the action of this dialogue to 432 B.C. It begins with Socrates trying to gain the attention of Charmides by means of suggesting a remedy for the headaches Charmides has been having recently on getting up in the morning (155b). The remedy is a leaf and a charm: chanting the charm at the same time as using the leaf will produce a complete cure, but the leaf on its own is no use at all. Socrates learned the secret from a Thracian doctor whilst on military duty (156d). However, before he will disclose it, the discussion of *sophrosune* must be undertaken. The dialogue ends inconclusively, with the characteristic Socratic aporia; we learn neither the definition of *sophrosune*, nor the headache remedy.<sup>4</sup> Perhaps the implicit suggestion is that philosophy is the best treatment for headache.

Socrates also makes a passing reference to headache when discussing the subject of education in Plato’s *Republic* (407c):

*If you are always wondering if you’ve got a headache or are feeling giddy, and blaming your philosophical studies for it, you will always be prevented from exercising and proving your talents.*<sup>5</sup>

Charms, with their appeal to the supernatural, may be one of the most ancient forms of headache treatment. John Kirk, medical officer on David Livingstone’s expedition to the Zambesi between 1858 and 1863,<sup>6</sup> noted amongst the indigenous people the use of charms, such as fruit, for treatment of, amongst other things, headache.<sup>7</sup>

Unlike Plato’s transcendentalism, we may rely on Aristotle for sound empirical observation. In the *Historia animalia*, he reports (Book 5, chapter 31) that those with lousy heads are “less than ordinarily troubled with headache”, but sadly proposes no mechanism for this beneficial effect of the humble head louse. Later, he reports (Book 7, chapter 4) that after conception women experience a sensation of headache in front of the eyes and suffer also from heaviness throughout the body and darkness before the eyes, these symptoms occurring as early as the tenth day. A humoral mechanism is adduced (“according as the patient be more or less burthened with superfluous humours”).

Saints may perhaps have taken the place of charms in Christian iconography. As mentioned in a previous article,<sup>8</sup> St Stephen, the first Christian martyr, was invoked against headaches because of the manner of his death by stoning. He was not alone: in Brittany, legend has it that there are 7777 local saints, enough to intercede for every eventuality, including Saint Livertin for headaches.<sup>9</sup> In the Koran (Chapter LVI), when the “inevitable” happens, the “foremost” shall enjoy a cup of flowing wine and “no headache shall they feel therefrom, nor shall their wits be dimmed”.

The abbess Hildegard of Bingen (1098-1179) was a woman of extraordinary intellectual ability, whose works include volumes dealing with illness and medical treatment, the *Causae et curae* and *Physica*.<sup>10</sup> Throughout her long life she had visions, which she believed to be divinely inspired and which she used to inform and illustrate her theological works (e.g. *Scivias*, *Liber divinorum operum*). Writing on “The visions of Hildegard of Bingen”, Charles Singer suggested that “the medical reader or the sufferer from migraine will ... easily recognize the symptoms of ‘scintillating scotoma’”,<sup>11</sup> a theme later taken up by Oliver Sacks who found the visions to be “indisputably migrainous in nature”.<sup>12</sup> Indeed, perhaps as a consequence of this, she has attracted the label of “The most distinguished migraine sufferer” (see [www.fordham.edu/halsall/med/hildegarde.html](http://www.fordham.edu/halsall/med/hildegarde.html)).

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# Neuropathology in Context

## Introduction

Neuropathology is the naked eye (macroscopic) and microscopic study of the nervous system and its diseases. Its main purpose is to determine the causes and effects of disease in the nervous system; in this way neuropathology plays a major role in the multidisciplinary team of clinicians caring for and investigating patients with neurological disease.

But how did it all start? In this article, I trace the origins of neuropathology, its development through the centuries and its evolution into the 21st Century.

## Neuroscience in ancient times

Records of interest in the nervous system date back to Ancient Greece but it was probably Herophilus of Chalcedon (335-280 BC) who first proposed that the brain is the centre of intelligence rather than just a cooling system to chill the ardours of the heart, as taught by Aristotle. Subsequently, Galen, in the second century AD, expanded the then popular pneumatic theory of the brain. This theory proposed that the vital spirit entered through the eyes and was purified in the ventricular system of the brain to form the animal spirit which in turn was distributed around the body by the arteries and nerves. Waste products from this refining process were dispersed into the nose or the sinuses. According to the pneumatic theory, the major functions of imagination, cogitation (thinking) and memory resided in the different parts of the cerebral ventricular system.

These views were still prevalent in the 16th Century in Europe at the dawn of Modern Neuroscience when Vesalius published detailed anatomical drawings of the brain (Figure 1) in his book *De humani corporis fabrica* in 1543. Vesalius also described neuropathological conditions such as hydrocephalus in children with enlargement of the head and attenuation of the cerebral brain tissue around expanded ventricles that contained excessive amounts of fluid quantified in "Augsburg wine measures".

## Early development of neuropathology

With the increasing availability of microscopes during the 19th century, peripheral nerves were the first parts of the nervous system to be studied in detail. Robert Remak described non-myelinated nerve fibres and ganglion cells in 1838.<sup>1</sup> He recounted how he prayed for sunshine in the Berlin winter as microscopes relied upon natural light, so on cloudy days he saw nothing. Remak's contemporary in Berlin, Theodore Schwann, is credited with the description of Schwann cells in 1839, although he described them as a syncytium rather than separate cells surrounding a continuous axon. Augustus Waller, in London, followed with his description of axonal (Wallerian) degeneration in 1850. Detailed descriptions of the anatomy and pathology of separated "teased" nerve fibres were published in 1878 by Ranvier in Paris. One of his suggestions for the function of *étranglements annulaires* (nodes of Ranvier) was that they prevented the semi-liquid myelin from flowing down the nerve while standing. Many neurological syndromes were described in France in the last decades of the 19th century, perhaps most famously by Charcot who also described the pathology of *sclérose en plaque* (multiple sclerosis).

Development of histological techniques to separate the closely interwoven elements of the nervous system began in earnest in the 1880s with stains to define astrocytes and other cells and with the tinctorial stain for neurons devised by Franz Nissl (1892) while still a medical student (Figure 2). With the introduction of techniques using salts of silver to stain neurons and axons and other cells, Golgi in Italy,

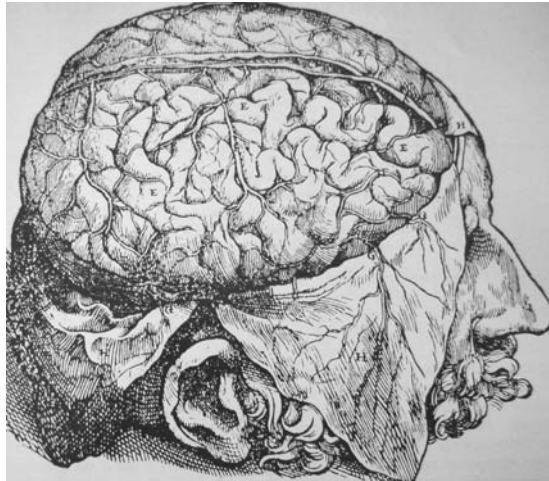


Figure 1: A drawing of the external aspect of the brain by Vesalius in *De Humani Corporis Fabrica* published in 1543.

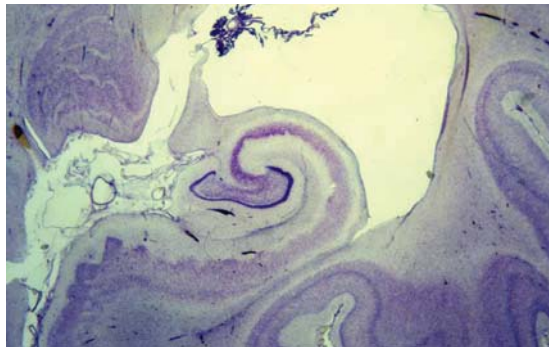
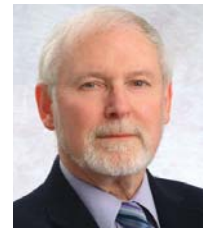


Figure 2: A Nissl stain demonstrating layers of neurons in the hippocampus (centre), cerebral cortex (bottom right) and lateral geniculate body (top left).

Cajal in Spain and Bielschowski in Germany led the way to defining individual neurons, their dendrites and axons and their connections in the nervous system. This allowed close correlation with neurophysiological observations that defined neuronal function. As a direct result of silver staining techniques, Alzheimer (1907) described the histological picture of plaques and neurofibrillary tangles that still form the basis for the pathological diagnosis of Alzheimer's disease 100 years later.

Following the first operation for a brain tumour in the 1890s in London, neurosurgery developed rapidly and so did a closer interest in the classification and diagnosis of brain tumours. This is exemplified by the histological descriptions by Bailey and Cushing in 1926. They based their classification on resemblance of the cytological and histological patterns in tumours to various cell types in the mature and immature nervous system. However, the number of different names for brain tumours expanded so much that in 1949 Kernohan simplified the classification by introducing a Grading System for brain tumours based on their predicted behaviour with Grade 1 at the benign end of the spectrum and Grade 4 at the more malignant end.<sup>2</sup> A similar but modified Grading System has been used in all the World Health Organisation Classifications of Tumours of the Nervous system published between 1973 and 2007.<sup>3</sup>

Descriptive neuropathology flourished during the first half of the 20th century in Europe and the USA and resulted in the first major English language text book of neuropathology, published by Greenfield and colleagues in London in 1958. At that time many diseases carried long



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eponymous titles that are gradually disappearing as the causes or genetic backgrounds of neurological diseases have been defined.

**Neuropathology in the second half of the 20th century**

This era witnessed an explosion of new technology for investigation and research into nervous system pathology. Electron microscopy was introduced in the 1950s and immunocytochemistry in the 1970s; these two techniques have probably had the greatest direct impact on neuropathology. Electron microscopy revealed the fine detail of brain cytology, showed the arrangement of neuronal and glial structures in the previously featureless neuropil and defined the tight junctions between endothelial cells associated with the blood-brain barrier (Figures 3 & 4). Scanning electron microscopy visualized the three dimensional relationships of many structures in the nervous system and the associated meninges (Figure 5). The introduction of immunocytochemistry allowed the chemical definition of many of the structures discovered by

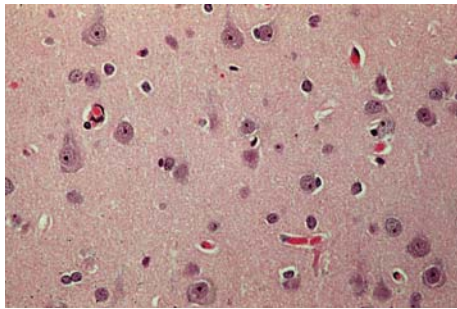


Figure 3: A Haematoxylin and Eosin stained section of cerebral cortex. Neuronal and glial cell bodies are embedded in a featureless pink neuropil.

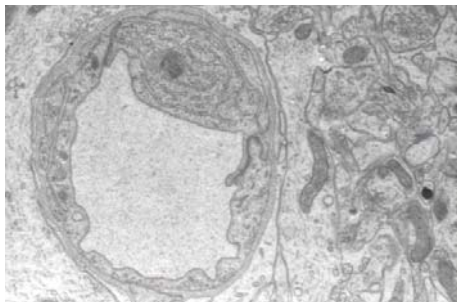


Figure 4: An electron micrograph showing closely packed neuronal and glial processes in the neuropil (right) and a capillary with darkly stained tight junctions between the endothelial cells.

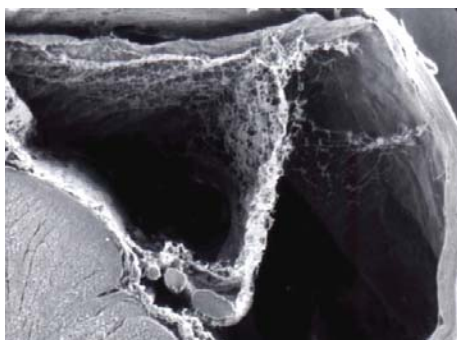


Figure 5: A scanning electron micrograph showing a three dimensional image of a highly perforated, lace-like dorso-lateral ligament of arachnoid cells extending from the spinal cord (bottom left) to the parietal arachnoid (top right).

electron microscopy and the more reliable identification of the different types of cell in the normal and diseased nervous system (Figures 6 & 7).

With the introduction of computerised tomography (CT) and magnetic resonance imaging (MRI) neuropathology became visible in the living patient. The pathological identities of the lesions seen in CT and MRI scans were determined by correlating the appearances in scans with the histological analysis of biopsies and post-mortem brains. Many thought that the need for neuropathology as a clinical diagnostic service would decline and perhaps disappear altogether and be supplanted by CT and MRI. This did not happen as the gold standard for diagnosis still largely rests upon histological diagnosis, especially for tumours.

**Neuropathology in the 21st Century**

The 21st century has seen an increasing role for neuropathology in a wide range of disciplines within neuroscience, ranging from the diagnosis of lesions in individual patients and monitoring the effects of therapy to research into the causes and mechanisms of disease.

Why does it take more than five years or more of postgraduate study to train a consultant neuropathologist? The main reason is the complexity of the nervous system and the wide spectrum of its pathology, ranging from focal disease in the brain and spinal cord (e.g. tumours, infarcts, abscesses and multiple sclerosis plaques) to the more diffuse diseases of the brain such as the many different types of dementia, movement disorders and hereditary diseases. Interpretation of neuropathological specimens requires an in-depth knowledge of the structure and function of the nervous system and a very good working knowledge of clinical diagnostic neurology, neurosurgery and psychiatry.

Much of the work load of a consultant neuropathologist in one of the Regional Neurological and Neurosurgical Centres in Britain is the diagnosis of lesions in the brain, spinal cord, muscle or peripheral nerve in biopsy specimens removed at surgery. Intra-operative diagnosis of tumours, by the use of smear preparations and cryostat sections, is often required. This is followed by a final diagnosis based on paraffin sections stained by histological and immunohistochemical techniques and the correlation of histological findings with the clinical and radiological data.<sup>2</sup> The neuropathological diagnosis usually forms the basis for discussion at the Multidisciplinary Team (MDT) Meetings involving a wide variety of clinicians and scientists (Figure 8). Communication, audit, education and quality control at MDT meetings form a basis for Clinical Governance and the maintenance of high quality care for patients.

The neuropathology of neurological, psychiatric and forensic disorders is usually investigated in post-mortem brains with close correlation between pathology and clinical findings. This process is particularly important for the investigation of dementias, movement disorders and infections. Working with coroners and the police on the examination of medico-legal cases may entail appearances in court, often to argue a case in the face of differing opinions.

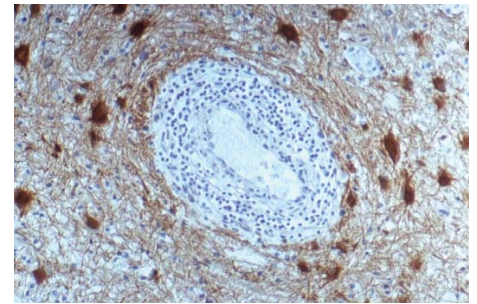


Figure 6: Reactive astrocytes and their processes stained brown by immunocytochemistry for glial fibrillary acidic protein (GFAP). From a case of multiple sclerosis.

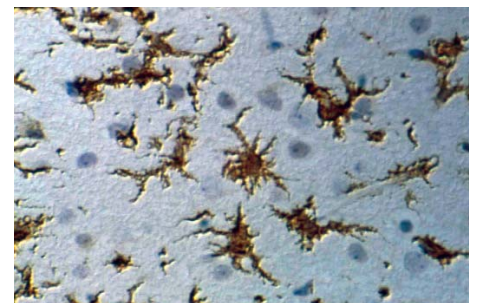


Figure 7: Activated microglia in rat cerebral cortex stained by immunocytochemistry for MHC class II.

**Neuropathology in the future**

What does the future offer? As long as there are unresolved problems in the causes, diagnosis and treatment of neurological disease, there will be a need for information on the structural aspects and cell pathology of the nervous system. Neuropathology will remain a very important lynch-pin in clinical management and in research. Knowledge of the pathology of the human nervous system will always be required to guide research efforts in experimental neuroscience to the most relevant areas of investigation.

Borders between disciplines in medicine are often blurred and this applies to neuropathology and closely related disciplines in clinical and basic neuroscience. Many neuropathology laboratories combine structural, molecular biological and genetic analyses of tissue samples to gain a complete picture of the disease process affecting the patient. This trend is likely to grow and produce an increasingly integrated approach based on the cell biology of diseases of the nervous system.



Figure 8: Neuropathology in context with other members of the Multidisciplinary Team involved in the diagnosis, treatment and management of patients with neurological disease.

# EEG, fMRI and Their Combination in the Study of Epilepsy

Electroencephalography (EEG) and Functional Magnetic Resonance Imaging (fMRI) are two important techniques for the study of the human brain, healthy or diseased. For example, EEG is of primary importance in the clinical evaluation of patients with epilepsy, by allowing the visualisation of very brief (order of ms) electrophysiological abnormalities during seizures and between seizures, such as interictal spikes (focal epileptic spikes).<sup>1</sup> EEG can therefore provide specific markers of epilepsy containing some localising information in relation to an underlying brain abnormality responsible for the epilepsy. EEG is also capable of recording patterns linked to specific external (visual, sensorial, etc) stimuli, in the form of evoked responses. Salient features of the scalp EEG, such as spikes or rhythms, reflect increased synchronisation of cortical activity at various spatial scales, ranging from sub-lobar to the entire brain. Simulations and experimental data have shown that such EEG features must involve a patch of cortex with an area of at least 10cm<sup>2</sup>. Crucially, scalp EEG is most sensitive to superficial cortical activity with limited or no sensitivity to events taking place deeper in the brain such as on the medial aspect of the temporal lobe, which are only detectable via propagation to more superficial cortex.

Some localising information on the generators of EEG features can be derived qualitatively from visual inspection of the recordings by experienced observers, mainly based on consideration of the feature's amplitude in relation to the various channels particularly for discharges such as focal epileptic spikes. In patients with drug-resistant epilepsy who may benefit from surgery EEG recordings combined with careful examination of

the clinical manifestations observed during seizures (such as recorded on video-EEG telemetry) are capable of providing very useful information, but at the lobar level. Focal spikes being much more common than seizures, a great effort has been made to use these for localisation purposes. Although in general spikes may originate from outside the epileptic focus itself (their generator is called the irritative zone), in many cases there is considerable overlap. In theory, spike generator localisation can be improved on using computational EEG source reconstruction methods based on assumptions on the form of the EEG generators.<sup>2</sup> The simplest and commonest assumption is that EEG generators can be represented as electrical dipoles, consisting of combined positive and negative sources. Although widely used in research this type of localisation has had limited impact on clinical practice in large part due to uncertainties in the modelling assumptions.

## Functional MRI

Therefore, EEG-based localisation remains limited in accuracy and clinical utility. On the other hand functional MRI, in the form of activation maps derived from series of scans, is a powerful tool for visualising changes linked to epochs of specific brain activity contrasted to a control state.<sup>3</sup> Two great advantages of fMRI are its more or less equal sensitivity irrespective of location in the brain and sampling down to a few mm. Although fMRI-based localisation does not suffer from the same type of uncertainties as EEG-based localisation as highlighted above, it is limited by other factors such as poor temporal resolution (of the order of seconds) and is subject to numerous artefacts (particularly at high field strengths such as 3T and above). Perhaps more impor-



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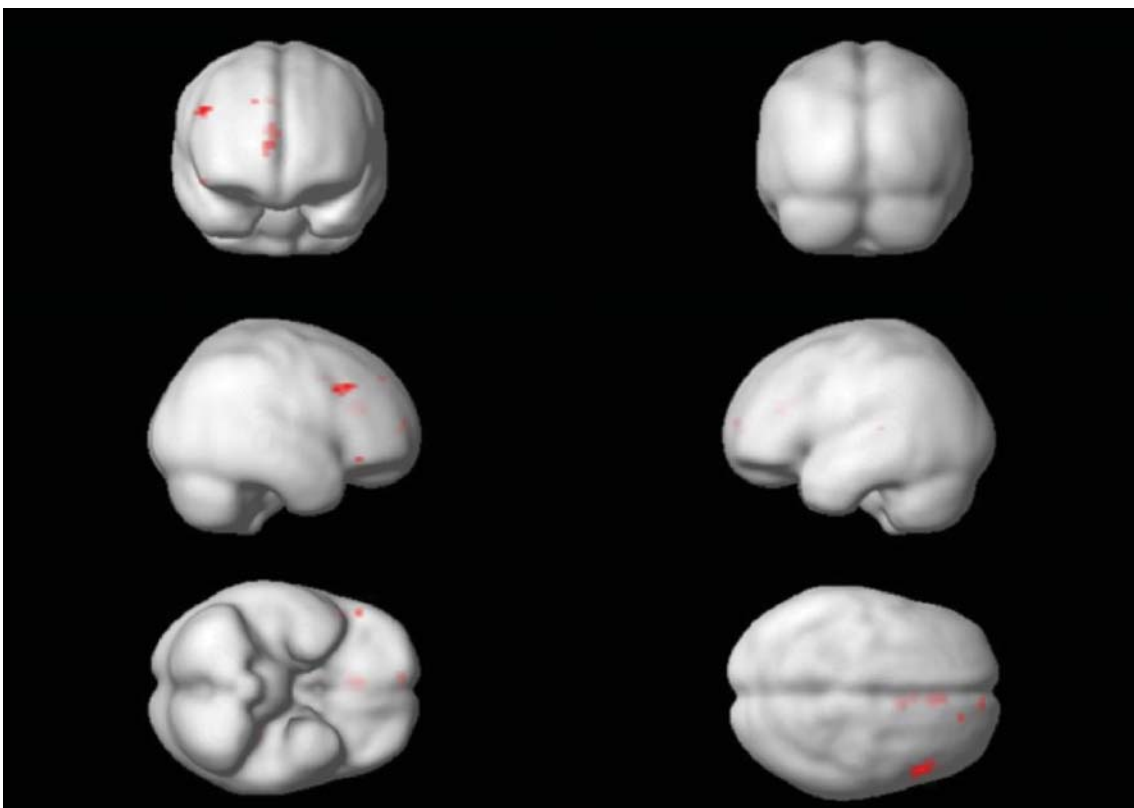


Figure: Spike-related activation pattern (BOLD increase, in red) derived from combined EEG-fMRI experiment, associated with frequent focal spikes originating in the right frontal lobe in a patient with drug-resistant epilepsy. There are clusters in the mesial and lateral aspect of the frontal lobe.

## ...there are already signs that EEG-fMRI can provide additional information in the pre-surgical evaluation of patients with drug-resistant epilepsy

tantly, fMRI reflects neuronal activity only indirectly, in the form of signals related to the haemodynamic changes that are associated with neuronal activity. The most commonly used form of fMRI signal is the Blood Oxygen-Level Dependent (BOLD) effect. The spatio-temporal relationship between the BOLD signal and neuronal activity in general remains the subject of intense investigation.<sup>4</sup> One of the main features of the BOLD signal is that it develops (grows and resolves) over a period of 15-20 seconds following a brief external stimulus. In some circumstances, the BOLD signal decreases following an event; this is thought to reflect mainly local decreases in blood flow and neuronal activity. This means that fMRI activation maps, although often extremely revealing and compelling, can present the investigator with an interpretation challenge. This may also reflect the fact that fMRI is novel compared to EEG, about which much remains to be understood. An important aspect of fMRI, quite distinct from most EEG, is its reliance on correlation with an independent factor, such as external stimulus or task, i.e. precisely timed queues, for acquisition and interpretation. Therefore most fMRI is acquired and analysed in a fashion similar to evoked potential EEG experiments rather than free-running as in most routine EEG.

### The combination of EEG and fMRI and its application in the study of Epilepsy

A question that arose in the early 1990s was whether paroxysmal activity of the type encountered in patients with epilepsy, such as seizures and focal spikes, could be imaged using fMRI. In view of the way fMRI is analysed, this requires data to be collected in two states, normal background (control state) and paroxysmal ('active' state), such that each scan in the time series can be labelled as either. Therefore imaging seizures may be possible based on behavioural manifestations in some cases. However, in most cases it is neither practical (because of the rarity of ictal events on one hand and the image artefacts caused by head movement on the other) nor safe to aim to image seizures in an MR scanner, although there have been a few attempts at imaging focal seizures.<sup>5</sup> In generalised epilepsy, absence seizures (which are usually devoid of motion) are interesting candidates for imaging. Interictal events, such as focal spikes, occur much more commonly but by definition are devoid of clinical manifestations. Therefore, imaging this type of activity requires the recording of EEG during the fMRI acquisition; this type of experiment is called EEG-correlated fMRI or EEG-fMRI. This EEG-fMRI represents a technical challenge because of interactions between the MR scanner and EEG recording equipment, which can result in degradation of image and EEG data quality, and because of patient safety concerns. These have been largely addressed over the last 10 years, although combined EEG-fMRI experiments remain some of the most technically challenging in the field of neuroimaging.

In a typical EEG-fMRI experiment, as performed in our centre, EEG electrodes in a cap are attached to the patient's scalp and to a specially designed MR-compatible EEG recording system, and the patient is asked to keep their eyes closed and to relax during the 20 to 40 minute scan. One of the main features of this type of EEG recording system is that the lack of ferrous components to avoid mechanical forces turning it into a dangerous projectile and minimise image quality degradation, and the very high sampling signal rate (and synchronization link to the scanner) necessary to get rid of the artefacts caused in the EEG by the scanning process.

No experimental task or stimulus is therefore imposed; this type of experiment is called resting-state fMRI. As noted previously, the experimental state at any given time is determined based on the simultaneously recorded EEG. Scans acquired during or following an EEG event

of interest (focal spike, spike-wave complex or run of events) are compared to those acquired during periods of background activity and activation maps obtained following the application of statistical tests to assess the likelihood of genuine correlation at any given location in the brain.

The application of EEG-fMRI in epilepsy remains largely exploratory, focusing on investigating the technique's ability to reveal activations in relation to various types of EEG abnormalities and syndromes (see Figure). The technique has now been applied in hundreds of patients with focal epilepsy in many centres throughout the world. The main findings are: fMRI provides localising information (i.e. statistically significant regional BOLD changes) in roughly 60% of cases in which focal spikes are captured; regions of positive BOLD changes tend to co-localise with the presumed focus; regions of negative BOLD changes tend to be more remote from the presumed focus; activation of the ipsilateral hippocampus and deactivation of the precuneus commonly observed in relation to temporal spikes; a time course of BOLD signal increase similar to that observed following brief external stimuli or tasks in healthy subjects.<sup>6</sup> Although much more work needs to be done to assess the technique's potential added clinical value, effectively taking the technique into a more clinical hypothesis-driven phase, there are already signs that EEG-fMRI can provide additional information in the pre-surgical evaluation of patients with drug-resistant epilepsy.<sup>7</sup> An interesting potential role for EEG-fMRI is that of providing implantation targets for intra-cranial EEG investigation.

In the generalised epilepsies, absence seizures and interictal generalised spike-wave discharges have been shown to be characterised by thalamic activation and widespread (though rather variable) cortical deactivation, including a set of regions comprising the precuneus, labelled 'default mode network' which is altered in relation to variations in brain state away from restful wakefulness.<sup>8</sup> These new and unique observations highlight EEG-fMRI's great potential as a scientific tool.

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# An Indian Perspective of the Epilepsies

Developing countries, where ~90% of the people with epilepsy reside, are least equipped to cope with the burden of care of these patients because of an unequal distribution of medical facilities and an inability of a major segment of the population to afford them.<sup>1</sup> Nevertheless, during the last one and one-half decades, considerable progress has been made in the management of people with epilepsy in India. Investigational facilities such as electroencephalography (EEG), computed tomography (CT) and magnetic resonance imaging (MRI) scans are available in most major cities. Antiepileptic drugs (AEDs), including several of the new ones are widely available. Over 1500 surgeries for medically refractory epilepsy have been performed during the last 10 years, which is several fold more than those undertaken during the previous 50 years.

## The burden of epilepsy

Recent community-based surveys have shown that epidemiological indices of epilepsy in India are comparable to those from developed countries, with a prevalence rate of ~5 per 1000<sup>2,3</sup> and incidence rate of ~50 per 100,000.<sup>4</sup> With around 1000 neurologists and ~5 million people with epilepsy, in India, there would be approximately 1 neurologist to take care of ~5000 persons with epilepsy. While 70% of the Indian population resides in rural areas, nearly all neurologists practice at or close to big cities and towns. A majority of people with epilepsy in India are therefore managed by primary and secondary care physicians with very little knowledge of the present day management of the epilepsies. In general, patients in India pay for medical care from their own resources. Epidemiological studies from rural parts of India have found that the medical treatment gap, which is defined as the proportion of persons with active epilepsy in the population who have never received AED treatment, is around 70%.<sup>4,5</sup> Lack of medical facilities, failure to diagnose epilepsy, reluctance on the part of the patient and family to accept the diagnosis, and non-availability or non-affordability of AEDs contribute to this enormous treatment gap among the rural population.

## Geographically specific epilepsy syndromes

Two epilepsy syndromes, hot water epilepsy and single small enhancing CT lesions in patients presenting with new onset focal seizures, are almost unique to India.

### Hot water epilepsy

A reflex epilepsy precipitated by the act of pouring hot water over the head occurs almost exclusively in certain geographical regions of the south Indian state of Karnataka.<sup>6,7</sup> The seizures are usually complex partial, characterized by a sense of fear, dazed look, visual or auditory hallucinations, and limb automatisms with or without secondary generalisation. A positive family history is found in one-fifth of patients.<sup>7</sup> The role of an aberrant thermoregulatory system

sensitive to rapid increases in temperature, coupled to a genetic susceptibility for this disorder is currently being investigated.<sup>7</sup> The majority of patients remit spontaneously within few years, but spontaneous non-reflex seizures may develop in a quarter of patients. Clobazam taken orally 1-2 hours before a hot water bath has been shown to be effective in preventing the reflex seizures.<sup>7</sup>

### Single small enhancing lesions

Although cerebral cysticercosis is widely prevalent in several parts of the world, a single cyst seen as a small ring-enhancing CT lesion in patients presenting with new onset focal seizures, occurs almost exclusively in India.<sup>8</sup> Whether this is related to low parasite load or enhanced immune status of the host is uncertain. While the majority of lesions resolve spontaneously within 3 to 6 months without any specific treatment, some may calcify leading to chronic partial epilepsy. Treatment with a single standard AED is recommended for a period of 6 months or till the lesion disappears. The role of cysticidal drugs is controversial; albendazole was not found to be beneficial in one double-blind randomized placebo-controlled study.<sup>9</sup>

### Diagnostic facilities

Technical standards of EEG recording and interpretation are generally poor in India because of the lack of qualified technicians and adequately trained electroencephalographers. Widespread availability of MRI in recent years has resulted in its indiscriminate usage. Many of the MRIs performed outside the selected tertiary epilepsy referral centers in India do not conform to the required technical standards and are often performed without proper indication.

### Treatment of the epilepsies

#### Medical treatment

Among the standard AEDs, only phenobarbitone is provided free of cost to patients through government dispensaries. Most new AEDs such as lamotrigine, topiramate, levetiracetam, and zonisamide are available and widely promoted by pharmaceutical companies among primary and secondary care physicians, whose knowledge about pharmacotherapy of epilepsy is limited. This frequently results in indiscriminate treatment with these expensive AEDs in patients who cannot afford them. Unnecessary AED polypharmacy is widely prevalent. In a study conducted at a tertiary referral center, 58% of the 972 patients referred from primary and secondary care facilities were receiving multiple AEDs simultaneously at the time of referral.<sup>10</sup> More than 95% of these patients were on inadequate dosages of the AEDs. Over the next two years, 72% of them were converted to monotherapy, with better seizure control, fewer side effects and reduced expenditure.<sup>10</sup>

#### Surgical Treatment

Although the majority of patients with epilepsy are



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Epidemiological studies from rural parts of India have found that the medical treatment gap, which is defined as the proportion of persons with active epilepsy in the population who have never received AED treatment, is around 70%

responsive to presently available AEDs, nearly 30% of them continue to exhibit recurrent seizures, despite optimal AED therapy, resulting in reduced quality of life and substantially increased risk of morbidity and mortality.<sup>11</sup> Epilepsy surgery is a useful option in selected patients with AED-resistant focal epilepsies.

The first epilepsy surgery in India was performed in 1951 by Dr Jacob Chandy at the Christian Medical College, Vellore.<sup>12</sup> During the last 10 years, there has been a revival of interest in the surgical treatment of epilepsies, with a few major centers regularly performing epilepsy surgery. Over 850 epilepsy surgeries have been undertaken at the R. Madhavan Nayar Center for Comprehensive Epilepsy Care, Trivandrum, during the last 12 years, nearly three-quarters of them for refractory temporal lobe epilepsy. The majority of patients are selected for surgery based on non-invasive selection strategies at an affordable cost without compromising patient safety and seizure outcome.<sup>13</sup>

Those medically refractory epilepsy patients who are not candidates for resective epilepsy surgery, can be offered vagal nerve stimulation or a ketogenic diet. While the cost of vagus nerve stimulation can be afforded only by a minority of patients, there are very few centres in the country practicing ketogenic dietary treatment.

### Some social issues

Misunderstanding and lack of knowledge about epilepsy and the resultant discrimination against people with epilepsy are still widely

prevalent in India as in any other developing country. Since it is difficult for a woman with epilepsy to get married, parents often conceal the history of epilepsy at the time of marriage negotiations.<sup>14</sup> Preliminary data from the Kerala Registry of Epilepsy and Pregnancy revealed that nearly two-thirds of the women were not receiving folic acid supplementation at the time of conception and congenital fetal malformations occurred at a frequency of about 13%.<sup>15</sup>

### Conclusions

While tremendous progress in diagnosis and treatment of persons with epilepsy has been made in India in recent years, the distribution of epilepsy care is lopsided and concentrated in urban areas. More equitable distribution of services can be achieved by establishing more comprehensive epilepsy programs in different parts of the country to reduce the medical and surgical treatment gap, and to educate the public and primary health care providers about recent trends in the management of epilepsies.

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# Management of Chronic Migraine

Migraine is one of the commonest neurological disorders, and yet remains relatively underdiagnosed and undertreated. The World Health Organisation considers a day with severe migraine to be as disabling as tetraplegia,<sup>1</sup> and estimates suggest that disability due to migraine costs over €27 billion per annum across Europe.<sup>2</sup> A significant minority of migraine sufferers go on to develop chronic headache; this group constitutes an estimated 2-3% of the general population.

Chronic migraine was introduced as a diagnostic subcategory of migraine in the second edition of the International Classification of Headache Disorders (ICHD-2),<sup>3</sup> and describes a chronic daily headache (by definition, occurring more than fifteen days per month), occurring in patients who have met the diagnostic criteria for migraine. The introduction of this classification prompted debate about the diagnostic criteria required in this (often complicated) patient group, which in turn has led to the publication of a revised set of criteria (Table 1). The term "chronic migraine" is a descriptive one, suggesting a significant ongoing headache burden, and is a useful standardisation for research purposes, but it should be recognised that it represents an arbitrary distinction. Patients with chronic migraine are often very significantly disabled by their headaches, form a significant part of general neurology and subspecialty headache practice, and constitute an ongoing therapeutic challenge.

By the time patients with chronic migraine reach neurology or headache clinics, their headaches may have been present for months, years or even decades. There may be a preceding history of episodic migraine, with or without aura, which gradually became more frequent

over time. By the time such patients are seen at clinic, they have often been on a variety of medications and are often overusing acute therapies such as simple or compound analgesics and triptans. They may describe different headache types, not all with migrainous features, and tension-type headache and medication overuse headache may often coexist in such patients.

The first step towards effective treatment in 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) which may coexist. If there has been a recent or abrupt change in headache severity, character or pattern without apparent cause, consideration should always be given to the possibility of secondary headache.

Several studies<sup>4,5,6</sup> have identified factors including attack frequency, medication overuse, head injury, female sex, obesity, hypothyroidism, snoring, stressful life events and low socioeconomic status as risk factors associated with the progression from episodic to chronic migraine. These, of course, may not be causative, and no interventional studies have been carried out as yet to assess the effects of modifying these factors on headache chronicity. It has been shown, however, that obesity is not in itself associated with refractoriness to treatment.<sup>7</sup>

Although the ICHD criteria for chronic migraine specifically exclude concomitant medication overuse, in clinical practice the two frequently coexist. Patients who have found an analgesia regime that has worked well for previously infrequent episodic headaches understandably come to use these medications more often as their headaches become more frequent. When this occurs with any delay in initiating preventative therapy, or reluctance to take preventative treatment due to anticipated or actual side-effects, this situation may escalate to daily or near-daily usage of analgesia and/or triptans, even though the patient may offer that "the medication doesn't really help, but I need to take it every day anyway". The revised ICHD criteria<sup>8</sup> define medication overuse as usage of ergotamine, triptans, opioids or combination analgesic medications on 10 or more days per month on a regular basis for more than 3 months. In addition, the revised criteria have acknowledged that patients taking simple analgesics or any combination of ergotamine, triptans, analgesics or opioids on 15 or more days per month, on a regular basis for more than 3 months, without overuse of any single class alone, also warrant a diagnosis of medication overuse.

The issue of how to optimally treat analgesia 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 above. 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 preventative treatment.

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**Table 1: Revised International Headache Society criteria for chronic migraine<sup>8</sup>**

A. Headache (tension-type and/or migraine) on $\geq 15$ days per month for at least 3 months
B. Occurring in a patient who has had at least five attacks fulfilling criteria for migraine without aura
C. On $\geq 8$ days per month for at least 3 months headache has fulfilled C1 and/or C2 below, that is, has fulfilled criteria for pain and associated symptoms of migraine without aura <ol style="list-style-type: none"> <li>1. Has at least two of:               <ol style="list-style-type: none"> <li>(a) unilateral location</li> <li>(b) pulsating quality</li> <li>(c) moderate or severe pain intensity</li> <li>(d) aggravation by or causing avoidance of routine physical activity (e.g. walking or climbing stairs)</li> </ol> </li> <li>and at least one of:               <ol style="list-style-type: none"> <li>(a) nausea and/or vomiting</li> <li>(b) photophobia and phonophobia</li> </ol> </li> <li>2. Treated and relieved by triptan(s) or ergot before the expected development of C1 above</li> </ol>
D. No medication overuse and not attributed to another causative disorder

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This final point in particular is open to dispute, as it lacks well-controlled supportive data. While there is a good empirical argument to be made for removing any potential contributory factors (i.e. overused medication) prior to initiating preventative treatment, in practice this may not be so easy. Patients withdrawing from abortive medications may experience an increase in headache among other symptoms which, although usually self-limiting, can test compliance and without adequate support, can result in relapse. Strategies for minimising relapse 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 patients true underlying headache rather than a secondary, drug-induced one. Headache diaries kept during this period can help the assessment process. It is also important that the patient (and treating doctors) realise that all abortive medications when overused can exacerbate headache, to avoid the pitfall of substituting overuse of one agent for another.

Adjunctive therapy during the withdrawal period can be helpful in reducing discomfort and assisting compliance. It is our practice to use naproxen or similar long-acting NSAIDs (sparingly) to "take the edge off" headaches during the withdrawal period. In patients with significant tenderness over the greater occipital nerve, an injection of lidocaine and depot methylprednisolone over the nerve may provide a transient reduction in headache severity (typically lasting from two weeks) which can help to ease the withdrawal process. Some clinicians advocate the use of oral steroids during the withdrawal period, but a recent study of reducing doses of oral prednisolone (60mg tapering to zero over six days) did not show any reduction in rebound headache compared to placebo.<sup>9</sup>

Although many preventative drugs have been shown in placebo-controlled trials to be beneficial in episodic migraine, few studies have been conducted in chronic migraine. Treatment of chronic migraine, as with disabling episodic migraine, involves a combina-

tion of effective, abortive strategies in addition to a preventative agent such as those listed in Table 2.

Diener et al recently carried out a randomised, double blinded, placebo controlled trial of prophylactic topiramate in the setting of chronic migraine with and without medication overuse.<sup>10</sup> They found that in the group as a whole, topiramate reduced the number of headache days per month by  $3.5 \pm 6.3$ , compared to an increase in the placebo group of  $0.2 \pm 4.7$  ( $P=0.02$ ). In the medication-overuse subgroup, topiramate reduced headache days per month by  $3.5 \pm 7.1$  compared to an increase of  $0.8 \pm 4.8$  with placebo ( $P=0.03$ ). Although these figures are encouraging, there are a few caveats: the study was small, with 59 patients overall, 32 of whom received topiramate. Of these, only 23 were overusing medication. There was also a significant drop-out rate, with only 24 patients on topiramate completing the double-blind phase of the trial. There were differences in the baseline patterns of medication overuse between the treatment and placebo groups: 30% of the topiramate group were overusing analgesia compared to 9% in the placebo group, whereas 96% of the placebo group were overusing triptans compared to 61% of the topiramate group. It is also interesting to note that the significant reduction in headache days did not translate into a significant reduction in usage of acute medications in either the group as a whole or the medication-overuse subgroup. It is difficult, therefore, to conclude with certainty that initiating preventative treatment prior to withdrawing analgesia will make subsequent withdrawal any easier, and in our practise we still make every effort to eliminate medication overuse prior to any other interventions. Hopefully, future studies will clarify this issue further.

The complications arising from analgesia and triptan overuse also make a strong case for patient education while headache is still episodic. Patients and doctors alike need to be aware of the importance of initiating preventative treatment for frequent headache, and to realise that excessive use of abortive therapy becomes part of the problem rather than the solution.

Effective treatment for chronic migraine can reduce overall disability but has other advantages too. Silberstein et al have shown, in the case of topiramate, that preventative treatment over a 12 month period reduced resource utilisation,<sup>11</sup> with a 46% decrease in A&E visits, a 72% decrease in diagnostic procedures, a 61% decrease in hospital admissions, and a 35% decrease in visits to physicians, resulting in lower total healthcare costs compared with baseline, even allowing for the cost of treatment. One can therefore argue that aggressive treatment of troublesome migraine, with early intervention to avert chronicity if possible, together with avoidance of medication overuse and appropriate prophylaxis, benefits all those who deal with this common and disabling condition.

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**Table 2: Drugs used for prophylaxis in migraine\***

Beta-Blockers:	Atenolol, Metoprolol, Propranolol
Anticonvulsants:	Sodium Valproate, Topiramate, Gabapentin
Antidepressants:	Amitriptyline, Nortriptyline, Dosulepin, Venlafaxine, Phenelzine
Calcium Channel Blockers:	Flunarizine
5HT <sub>2B/2C</sub> antagonists:	Pizotifen, Methysergide
Others:	Coenzyme Q <sub>10</sub> , Riboflavin, Butterbur, Feverfew, Lisinopril, Candesartan
* Not all the agents in the above table are licensed for prophylaxis of migraine in the UK. Check individual Summaries of Product Characteristics (SPC) for more information regarding specific licensed indications for each agent prior to prescribing.	

If you would like to review books for ACNR, please contact Andrew Larner, Book Review Editor, c/o rachael@acnr.co.uk

## Neurobiology of Alzheimer's Disease (3rd edition)

I recall buying the first edition of this book (produced by Bios Scientific Publishers) when I was a struggling research registrar in 1996. Over 10+ years and two further editions the book has expanded (now 50% larger by pages) but many of the topics remain as before: neuropathology, genetics, APP metabolism, amyloid  $\beta$ -peptide and its cellular targets, tau and neurofibrillary pathology, animal models of AD (but no mention of flies), inflammation, neurotransmitters, neurotrophins. These are comprehensive accounts, heavily referenced throughout, on subjects central to the endeavour of understanding AD pathophysiology. There is a new chapter on (CSF) biomarkers, and therapy now has two chapters, one exclusively on amyloid based therapies. The chapter on clinical assessment sits somewhat uneasily within the neurobiological milieu (and neurologists may blench to read that dysphasia is "difficulty with articulation of speech", p335) and the chapter on neuroimaging has disappeared.

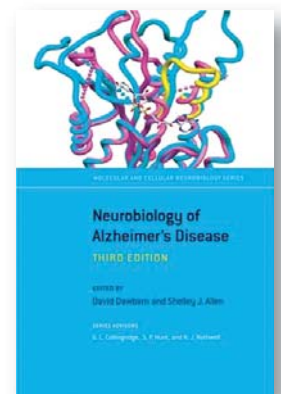
The preface points out that previous editions went to press just as significant new findings were breaking (linkage of familial AD to chromosomes 14 and 1 in 1995; characterisation of BACE in 1999), and it is possible that a similar thing has happened with this edition. Although sortilin is mentioned (p295) as a p75NTR binding part-

ner, it seems publication came too soon to include the recent excitement about a genetic association between the sortilin receptor SORL1 and AD (Rogaeva et al., *Nat Genet* 2007; 39: 168-77).

The scientific accent of the book means that a few clinical errors creep in: for example, FTDP is not "frontotemporal dementia of the Parkinson type" (p3), and the cerebellum is affected in AD (p235); there are well-described neuropathological and neurochemical changes.

Neurologists with an interest in dementia in general and AD in particular are presumably, following the 2006 NICE/SCIE guidelines, an endangered species threatened with extinction (PCTs and special health authorities apparently comprehend no role for neurologists in the management of this most quintessential of brain diseases), and so the principal market for this book will be amongst the growing numbers of neuroscientists with an interest in AD, and possibly those psychogeriatricians with more than simply a clinical interest. When one considers that the first edition cost me £65 in 1996, the current price of under £50 seems good value for money.

*AJ Larner, Cognitive Function Clinic, WCNN, Liverpool, UK.*



Dawbarn D, Allen SJ (eds)  
**Published by:** Oxford University Press  
 ISBN: 978-0-19-856661-8  
**Price:** £49.95

## Including People with Communication Disability in Stroke Research and Consultation – A Guide for Researchers and Service Providers

A concise, practical guide drawing on the authors' professional experiences of people with aphasia. Its aim is to increase inclusion in stroke research and consultation of people with communication disability. Aphasia is reported in 30% of first ever ischaemic stroke patients, whilst aphasic stroke patients tend to be older than their non-aphasic peers,<sup>1</sup> thus confirming aphasia to be a very common and important problem with an age-related dimension. Improving inclusivity is of course particularly topical given the current emphasis on 'user involvement' in health care and research.

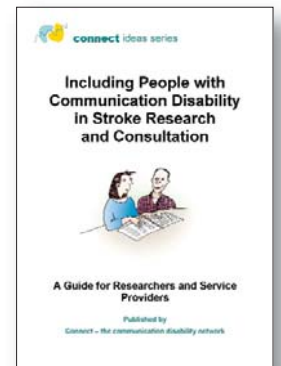
The authors are right to address the issue of communication impairment in this simple and accessible guide – although perhaps an overly simplistic style in places will not appeal to everyone. It has been published by Connect, the communication disability network (www.ukconnect.org) – a national charity based in London promoting effective services, new opportunities and a better quality of life for people living with aphasia.

The guide comprises seven short chapters, a resource list, bibliography, and a forty-nine page appendix containing extensive examples of documents considered by the authors to be accessible to people with aphasia. The guide includes an elementary introduction to communication impairment, suggestions for improving inclusivity and practical strategies for effective interviews, meetings, and dissemination of information in the context of communication impairment.

Overall a highly practical publication which can be readily and quickly absorbed – hopefully it will achieve its stated aims.

*Dr Hedley Emsley, Clinical Lecturer in Neurology, Division of Neuroscience, University of Liverpool, UK.*

- Engelter et al. *Epidemiology of aphasia attributable to first ischemic stroke: incidence, severity, fluency, etiology, and thrombolysis.* *Stroke* 2006;37:1397-84.



Swinburn, K  
**Published by:** Connect – the communication disability network  
 ISBN: 978-0-9536042-8-9  
**Price:** £21.99

## Encephalitis - a parent's handbook

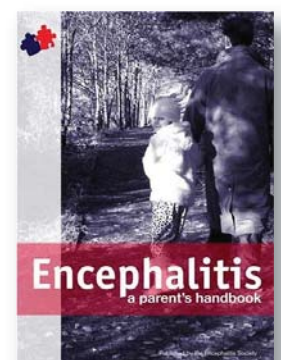
This guide to encephalitis in childhood is an extremely comprehensive, well thought out support for parents. The easy-to-read and thorough approach perfectly balances the complex scientific information necessary to make informed choices about the necessary services at the time of illness and following on into community care.

As a resource for dealing with the various sequelae and consequences of the illness, particularly with regards to potential behavioural difficulties and education, it is extremely useful for all members of an interdisciplinary team around the child.

It therefore fulfils its remit as a support tool for the child and family, but wider reading should be compulsory for all members of health, education and social teams that have dealings with children who have had encephalitis.

*Charlie Fairhurst, Chailey Heritage Clinical Services, Lewes, UK.*

**Compiled by:** Dowell, E. **Published by:** Encephalitis Society, 2006  
 www.encephalitis.info. **Price:** £10



# Standing Enhances the Behavioural Repertoire of Minimally Conscious and Vegetative State Patients

Developments in medical and surgical care have led to improved survival following injuries that would previously have been fatal, and means that those suffering with severe brain injuries (GCS<8) are more prevalent in our hospitals and rehabilitation units. The use of generally agreed terminology for unresponsive patients will allow study populations to be described more consistently, and their implications to be generalised with more confidence.<sup>1,2,3</sup> Functional MRI provides physiological evidence to support, or refute, clinical beliefs about patients awareness.<sup>4,5</sup> Assessments should be repeated regularly, and reports of all those participating in the care of the patient, including family, should be noted. Prognostic decisions should be made by physicians and professionals with experience working in assessment of those with impaired consciousness.<sup>1</sup>

Previous descriptions of the assessment and diagnosis of those in vegetative and minimally conscious states can be found in earlier editions of this journal. It is imperative that diagnosis is accurate and secure as this will affect decisions about rehabilitation potential and therefore the level of rehabilitation input. The question of where patients should go for further rehab or long-term care must be considered by the whole team. The importance of therapist input to this process has been recognised but, until recently there has been little evidence of effectiveness of rehabilitation in this patient group.

Early rehabilitation is accepted as having positive effects upon facilitating patient recovery.<sup>6,7</sup> Active therapy may reduce their stay in the critical care unit and avoid the secondary effects of spasticity and contractures, which will reduce cost of care overall.<sup>8</sup> Critical care units that have a therapeutic ethos can start observations of patients in low arousal states, and information about timing of emergence from coma has useful prognostic

value. The Glasgow Coma scale is not sensitive enough to detect change within this group, and more specific measures have been developed for this purpose: the Sensory Modality Assessment and Rehabilitation Technique (SMART), the JFK Coma recovery scale and the Wessex Head Injury Matrix (WHIM). In our experience the WHIM is sensitive to subtle behaviour changes and is easy for staff to learn to administer.<sup>9</sup>

Therapists may observe behaviours in response to passive movements as part of respiratory management<sup>7</sup> or maintaining joint range of movement. Often, rolling a patient is enough to stimulate some eye opening, or other behavioural response previously un-witnessed. This is presumed to be due to activation of the reticular system by patient movement.<sup>10</sup> These passive movements are usually accompanied by verbal or visual stimuli, which may provoke some responses. Positioning of the patient with a neutral and well supported posture will reduce tone and aid comfort,<sup>11</sup> but also augments the potential for interaction as active movement is more readily accessible.

Gradually standing patients from horizontal to vertical on a tilt table enhances visual stimuli, stretches calf muscles, and is thought to reduce loss of bone density.<sup>10,12</sup>

Tilt tabling also offers a number of key benefits to the assessment and therapeutic stimulation of patients with impaired consciousness. Pilot work by Elliott et al<sup>13</sup> found that standing patients using a tilt table revealed behaviours not observed in the supine position. This effect was significant in both vegetative and minimally conscious patients. However, the behaviours observed in vegetative patients remained reflexive and the act of standing patients did not reveal behaviours suggestive of awareness of self or environment.

We have now documented the outcome of tilt tabling in



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This research has been developed with the support of Dr Coleman, Mrs Baker (nee Elliott), Dr Shiel, Professor Wilson and Professor Pickard.



Results: VS Patient Group

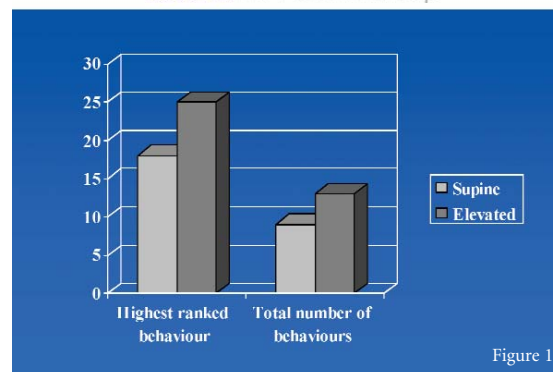


Figure 1

Results: MCS Patient Group

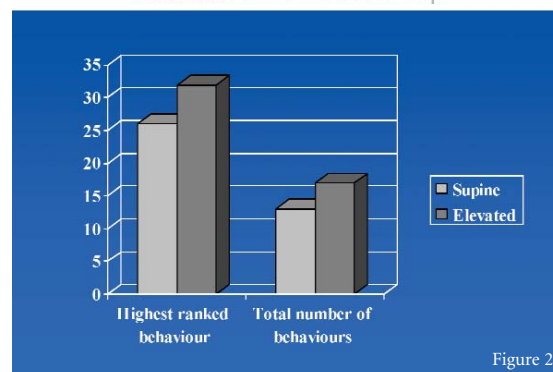


Figure 2

**Table 1: Highest ranked behaviours recorded in the supine and standing positions for each patient. Patient classification at the time of recruitment is denoted VS (vegetative state) or MCS (minimally conscious state).**

Patient	VS / MCS	Supine highest ranked score	Behaviour observed	Standing highest ranked score	Behaviour observed
1	VS	6	Volitional vocalisation to express feelings	6	As Supine
2	VS	43	Smiles	43	As Supine
3	VS	4	Attention held by dominant stimulus	4	As Supine
4	VS	43	Smiles	43	As Supine
5	VS	5	Looks at person briefly	26	Frowns, grimaces etc. to show dislike
6	VS	7	Eyes open briefly	49	Vocalises to attract attention
7	VS	14	Mechanical vocalisation (yawn, sigh)	26	Frowns, grimaces etc. to show dislike
8	VS	1	Eyes open briefly	1	As Supine
9	VS	14	Mechanical vocalisation (yawn, sigh)	14	As Supine
10	VS	43	Smiles	43	As Supine
11	VS	24	Maintains eye contact over 5 seconds	24	As Supine
12	MCS	57	Names or indicates left and right on self	57	As Supine
13	MCS	13	Looks at person giving attention	16	Turns head/eyes to look when someone is talking
14	MCS	20	Vocalises to express mood or needs	36	Switches gaze from one person to another, spontaneously
15	MCS	26	Frowns, grimaces etc. to show dislike	34	Monosyllabic or single words in response to questions
16	MCS	26	Frowns, grimaces etc. to show dislike	26	As Supine
17	MCS	15	Performs physical movement on verbal request	14	Mechanical vocalisation (yawn, sigh)
18	MCS	18	Tracks for 3-5 seconds	28	Looks at object when requested
19	MCS	8	Makes eye contact	23	Shows selective response to preferred people
20	MCS	42	Can find a specific playing card	43	Smiles
21	MCS	12	from a selection of four Eyes follow person moving in line of vision	24	Maintains eye contact over 5 seconds
22	MCS	26	Frowns, grimaces etc. to show dislike	26	As Supine
23	MCS	52	Uses one or two gestures	52	As Supine
24	MCS	33	Seeks eye contact	43	Smiles

a total of 24 patients (11 VS, 13 MCS, 15 male, average age 44, range 19-71; 11 TBI) in terms of the behaviours observed in the supine and standing position. These results incorporate the 12 patients in Elliott et al, 2005. Patients were assessed whilst lying in bed, during a 20-minute stand in a tilt-table at 85°, and again whilst lying in bed. The patient's behaviour was assessed using the WHIM.<sup>9</sup> These observations were repeated over a one-week period, at 6 & 12 months post ictus, and the median highest ranked behaviour and median total number of behaviours observed, were recorded (Table 1).

Eleven patients (3 VS and 8 MCS) showed greater highest ranked behaviours (p=0.004) and total number of behaviours (p=0.001) in the standing position (Figures 1 and 2). Twelve patients (8 vegetative and 4 minimally conscious) showed no change and one minimally conscious patient showed a one point decrease in the highest ranked behaviour in standing. Although WHIM scores in 3 vegetative patients increased during standing, the behaviours observed did not reach a level suggesting awareness of self and/or environment. WHIM scores in the second supine period were the

same or lower than in the first.

This study demonstrates that simple interventions can enhance behavioural repertoires in some low awareness patients, and that consistent use of the WHIM can help identify changes over short periods of time. Making all nurses, therapists and staff aware of the sorts of behaviours to look out for, using the WHIM definitions, is a simple way of educating people and raising interest in the active management of this group of patients.

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# 23rd Congress of the European Committee for Treatment and Research in Multiple Sclerosis

11-14 October, 2007; Prague, Czech Republic.

More than 5000 neurologists from 75 countries around the world attended the 23rd Congress of the European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS) to hear the latest research in the field, ranging from the basic science of MS to highly sophisticated innovations with targeted new drugs and detailed scanning techniques. The meeting was held in the Czech capital of Prague, a city combining historical buildings and squares with modern transport and facilities to meet the challenges of a 21st European centre.

In the opening lecture of the congress, Christian Confavreux, Hôpital Neurologique Pierre Wertheimer, Lyon, France, underlined the importance of neurologists from around Europe working together with collaborative databases and large cohorts of MS patients to make progress. He suggested that these efforts had resulted in major advances in understanding over the past decade, including the influence of pregnancy on the course of the disease and the risk of relapse following vaccination.

Professor Confavreux considered that there was now good evidence that relapses in MS are the clinical counterpart of acute focal inflammation of the central nervous system while progression is that of chronic diffuse neurodegeneration. He questioned whether MS should be considered as a primary autoimmune disease or as a primary degenerative condition. Late pathological studies have shown the presence of activated microglial-like inflammatory cells disseminated in the CNS. "In other words, diffuse neurodegeneration is likely to be related to inflammation, even if the latter is not autoimmune," he proposed. Assuming this pathogenetic picture was well founded, he told delegates, "Treating the acute focal inflammation is not enough. One must fight against the silent diffuse inflammation nested in the central nervous system beyond the blood-brain barrier. This is the new challenging frontier in MS treatment."

## Study confirms Epstein-Barr virus associated with MS

Patients with MS have higher levels of Epstein-Barr virus (EBV) DNA than healthy controls and viral load fluctuates with disease activity, according to a study reported at the congress.

The study measured levels of EBV DNA in peripheral blood leukocytes from 112 patients with stable, relapsing remitting (RR) MS, 28 at the onset of a clinical relapse of RRMS, and 39 controls, using quantitative PCR for the BamHIW repeat and the LMP2a gene. Results showed a trend to higher viral loads in the MS patients. The median number of copies of BamHIW per million cells was 59 for controls, 91 for patients with stable RRMS and



102 for patients in relapse. The corresponding values for LMP2a were 0, 10.6, and 9.8. Although the range of values in the three groups overlapped, the differences approached statistical significance for the comparison of LMP2a in controls and patients with stable MS ( $p=0.068$ , rank sum test).

Fourteen of the patients had blood collected both during a relapse and while stable. Their levels of EBV DNA were increased during relapse in six of them, unchanged in six and decreased in two.

The researchers, led by J William Lindsey, Associate Professor in Neurology at the University of Texas, Houston, USA, said, "Our assay sensitivity was excellent and detected EBV DNA in the majority of subjects. There is a trend towards increased viral loads in MS patients and a suggestion that viral load may fluctuate with clinical disease activity."

A second, Norwegian Study showed that all 61 patients with RRMS tested were positive for a marker of previous EBV infection, anti-VCA IgG, while 98% were positive for a second marker, anti-EBNA IgG. However, there was no association between disease activity and EBV reactivation. A third study reported at the congress was consistent with EBV acting as a trigger of MS, with a higher level of activation of EBV-specific CD8+ T cells in patients with early MS.

*Multiple Sclerosis 2007;13:P484, P483, P485*

## Study suggests FTY720 may repair MS damage by direct effect on brain

Encouraging findings were reported with several new agents, including a study showing that FTY720 (fingolimod), an oral sphingosine-1-phosphate receptor agonist, acts directly on the central nervous system (CNS) to reduce disease severity in addition to peripheral effects on the immune system.

The study in experimental autoimmune encephalomyelitis showed that administering FTY720 directly into the CNS significantly reduced disease severity. This occurred even though there was no reduction in lymphocytes in the bloodstream, indicating that the agent has a direct effect in the CNS that is

independent of its effects on peripheral lymphocytes. When FTY720 is given orally, it stops lymphocytes leaving peripheral lymph nodes and infiltrating the CNS, which is another important part of its action in MS.

Howard Weiner, Professor of Neurology at Harvard Medical School, Boston, USA, said: "MS is a disease affecting the central nervous system – but most of the drugs we currently have act peripherally. These results suggest that the mechanism of action of FTY720 may involve CNS-mediated effects, in addition to reducing T-cell infiltration into the CNS. This raises the possibility that it might also have protective effects in progressive stages of the disease."



A further study showed that FTY720 increased the number, growth and survival of oligodendrocytes – the cells that make myelin, which insulates nerve fibres and is damaged in MS - in cell culture. This effect could potentially limit destruction of myelin and promote its repair, which could contribute to the effectiveness of FTY720 in MS.

Results from a phase II study in 281 patients with relapsing MS (the commonest type) showed that once-daily, oral FTY720, reduced relapse rates by more than 50% after six months, compared to placebo. It also reduced magnetic resonance imaging (MRI) measures of inflammation, with around 80% of patients free of active brain lesions. In patients continuously treated with FTY720 for up to two years, up to 77% remained relapse-free and more than 80% were free of active brain lesions at two years.

Commenting on the findings, Gavin Giovannoni, Professor of Neurology at Barts and The London, Queen Mary's School of Medicine and Dentistry, London, said, "In the emerging therapies, FTY720 is interesting because of its mode of action – with results showing that it may act centrally to provide neuroprotection, as well as having effects on the immune system. The availability of an oral drug would change the face of MS treatment completely."

Positive results were also reported with rituximab, a monoclonal antibody that selectively depletes CD20+ B cells. A double-blind, controlled trial randomising 104 patients with RRMS to intravenous rituximab (1000mg) or placebo on days 1 and 15 showed a significant reduction in gadolinium (Gd) enhancing lesion counts at weeks 12, 16, 20 and 24 (mean 0.5 vs 5.5 with placebo, equating to a 91% reduction;  $p < 0.0001$ ). There was also a reduction in new Gd-enhancing lesions and in relapses. Infusion-associated adverse events affected more than three-quarters (78.3%) of patients given rituximab.

A study in 45 patients with active RRMS who had failed beta-interferon treatment showed that alemtuzumab, a humanised monoclonal antibody targeting the CD52 antigen expressed predominantly on lymphocytes, achieved a 9.3 fold reduction in relapse

rate in the two years after treatment compared to the two years previously ( $p < 0.0001$ ). Most patients (70%) also had stable or improved Multiple Sclerosis Functional Component scores at two years. Alemtuzumab was generally well tolerated, although four cases of autoimmune thyroid disorder and one case of transient thrombocytopenia occurred. Professor Giovannoni considered the efficacy results were 'remarkable.'

*Multiple Sclerosis 2007; 13: P484, P554, P558*

Summing up the new developments at the meeting, Gavin Giovannoni considered studies reported atECTRIMS with some of the newer agents had shown particularly promising results for the future. He suggested that the results seen with FTY720 were interesting, particularly because of the potential for activity in the central nervous system, and for neu-

roprotection. The phase 2 study results with rituximab also looked very interesting, in addition to the data reported with BG-12, laquinimod and cladribine.

Focusing on patients' needs, Professor Giovannoni thought that the development of oral therapies was the most pressing issue. "The introduction of effective oral treatment will change the face of treatment completely," he said. With moves to diagnose MS earlier, he predicted that earlier treatment would become standard. "It is beyond doubt that we should treat earlier, as the damage starts from an early phase of MS – so we need treatments that patients can use earlier easily, effectively and safely." He hoped that the next couple of years would see further positive data.

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## Neurosocieties: The Rise and Impact of the New Brain Sciences

12-13 November, 2007; London, UK.

The launch meeting of the European Neuroscience and Society Network was held in the comfortable and attractive Darwin Building at Regent's College Conference Centre, within the beautiful setting of Regent's Park, London on 12th and 13th November 2007.

Professor Nikolas Rose, sociologist and Director of the BIOS Research Centre (for the study of Biosciences, Biomedicine, Biotechnology and Society) at the London School of Economics, welcomed a broad mix of specialists from the fields of neuroscience (neuroanatomy, clinical neuroscience, neuropharmacology etc) and the social sciences (sociologists, psychologists and anthropologists etc) to this bold venture in interdisciplinary discussion of the political, ethical and social implications of 'the new brain sciences'. Rose spoke of 'setting an agenda for Europe', in terms of discovering 'what's going on', noting major differences between countries, and also 'what's going on in different fields', getting the picture from, say, clinicians, imagers, psychiatrists and neuroscientists.

'Public health and the politics of the neurosciences' was the theme for the opening plenary. 'The challenges of regulating neuropharmacology' were outlined with lively and controversial examples by Simon Gregor (Director of Communications), stepping in for Professor Kent Woods (CEO) to speak about their work at the Medicines and Healthcare Products Regulatory Agency. The UK regulators' view was juxtaposed with the concerns of the clinician, Professor Matilde Leonardi, Consultant Neurologist (adult and paediatric), from the Neurological Institute Carlo Besta, Italy, speaking of 'Neurosciences and neuropolitics: two challenges for brain disorders'. "Maybe neurological patients do not get their voices heard: your GPs do not allow patients to get to neuro-

logists", but, " these disorders are at the top of the patients' agenda". Substantiating her arguments initially with figures from 28 European countries, Leonardi then challenged us to look afresh at statistics and their very conceptualisation towards a count of 'Years lived with disability', which added to length of life, produce the measure: 'Disability Adjusted Life Years' (DALY). On this basis, "neurological conditions count for 50% of all diseases in Europe... therefore, investment is not yet compatible with the impact of neurological disease". (see 'Measuring Health and Disease in Europe' at [www.mhadie.it](http://www.mhadie.it)).

Rose, chairing this first plenary, raised three issues:

- that psychiatric and brain trauma had been brought together in Leonardi's figures;
- that the word 'burden' (used in reference to the amount of disease) is 'a term contested by survivors';
- the terms: 'disability' versus 'disease', how to reconcile this?

Here was an indication of the plunge pool of battles over words that the ENSN will encourage in its bringing together of embodied medical and social thought! Leonardi concisely and robustly defended her use of language before Rose proceeded to gather in questions of a diverse nature from the audience, which Gregor and Leonardi addressed. Ample time was arranged for these discussions within each plenary, and in the breaks for refreshments, delicious lunches and the splendid conference dinner, intensely interesting debates continued.

Each of the four plenaries was planned on a similar model, with two speakers from different disciplinary backgrounds presenting, a stimulus to lively question and answer sessions, for example:

'Sources of the Neurochemical Self: consciousness, personhood and difference' Professor Alexandre Maunon, University of Geneva 'The neurochemical self and social inequality: a new face of neuroethics' Dr Ilna Singh, BIOS Centre, LSE. 'Theories of personhood: self, brain and behaviour in boys with ADHD'.

The third session on 11th November was 'Neuroeconomies: markets, choice and the distribution of neurotechnologies', in which their global development and production was stunningly illustrated by the first speaker, Zack Lynch, Executive Director of the Neurotechnology Industry Organization. A discursive note on 'The birth of neuroeconomy' by Dr Philippe Pignarre, University of Paris, followed as counterpoint. The final plenary, to close the meeting on 12th, was 'Neuroscience and Society: Future Directions in Europe', after a morning spent in selected discussion workshops relating to the four plenary themes.

The interdisciplinary exchanges between life scientists and social scientists, from this and subsequent ENSN conferences and workshops (in Europe and North America), will be published in a series of annual volumes in international journals. Additionally, the network will provide exchange and travel grants to junior scholars in the field. The project is funded by the European Science Foundation to run from June 2007 to June 2012.

Further information:  
[www.esf.org/ensn](http://www.esf.org/ensn)  
[www.neurosocieties.eu](http://www.neurosocieties.eu)

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# Association of British Neurologists' Autumn Conference

14-16 November, 2007; London, UK.

## What's New?

Historically, the ABN meeting comprised single sessions, from Wednesday lunchtime to Friday afternoon, including a mixture of basic science and clinical research presentations, and lectures from invited experts. However, with increasing numbers of attendees representing an ever-wider range of interests a number of innovations premiered this year including parallel sessions and dedicated teaching sessions. Although biased because one of the ABNT posters featured, I thought the expert led poster session was excellent, allowing lots of questions in an informal setting.

## Teaching

In common with other meetings, the teaching role of ABN meetings is increasingly recognised, and the first session this year was a practical session on neuro-ophthalmology, led by Dr Gordon Plant and Prof Chris Kennard. This covered a wide range of practical aspects of ophthalmology as relevant to the neurologist.

## Parallel Sessions

Two sessions were run at once on days one and two of the meeting, allowing for a greater spread of specialist interest. Although all presentations were of extremely high quality, several stood out as excellent.

- Confocal retinal microscopy for idiopathic small fibre sensory neuropathy. It appears sensitive, quick, and does not require a neurophysiologist (Pitceathly).
- The spectrum of neuro myelitis optica includes brain stem dysfunction at presentation. The aquaporin 4 antibody test offered at Oxford appears to be more sensitive than the original NMO IgG antibody. (Viegas). Why?
- Axonal loss in MS may be related to acid sensing ion channel 1. Craner showed results from genetic knock-out models, and small molecule inhibition with amiloride. Amiloride is a partial blocker that was effective even when given after onset of experimental autoimmune encephalomyelitis (EAE). Targeting the acid sensing channel 1 on immune cells had no effect.
- Biomarkers of neurodegeneration continue to be sought. The use of Diffusion Tensor Imaging (DTI) in PD was highlighted by Bajaj and Positron Emission Tomography (PET) using amyloid and microglial markers in AD by Okello.

## Guest Lectures

As usual, the guest lectures (this time all on day 2) were of very high quality.

Raymond Tallis talked eloquently on the evolution of man, with relevance to the importance of the hand. An infinite array of movement was made possible by the move to bipedal locomotion in early humans. The hand, freed from locomotor tasks, became a "proto-tool", driving consciousness and ultimately to the evolution of a self-aware homo sapien. Tallis argued that 'man' is now free from the constraints of nature and biology that define the existence of all other life-forms on this planet. Whilst thought provoking, it is hard to cover this topic in 1 hour, with unavoidable gaps in the story. There is evidence of tool use from over 5 million years ago, followed by little evolutionary or societal change, but in the last 100,000 years language, technology and sociology have developed in an exponential fashion. Unanswered questions include:

1. Why did Homo sapiens come on to the scene so late and then become so successful?
2. Why did Neanderthals (and other hominids) fail to survive? Did they have subtly different hands, or were they just unlucky?

Richard Wise reviewed modern tractography and connections between Broca's area, Wernike's area, area 39, and the anterior temporal lobe. He presented evidence from fronto-temporal dementia subjects with seman-



tic and anomic deficits, as well as functional MRI and tractography from different animal models which although unable to produce language have excellent audiological cortexes. Parallels between these two models were discussed, and an over-riding theory of language dysfunction explored.

## Industry sponsored sessions

The success of ABN meetings is in part thanks to the industry sponsors. Without their hard cash, the meetings (in their present form) would be uneconomical. One of the sponsored sessions was especially interesting.

## Novel Therapeutic Agents: The challenges of Adoption in the UK

The decisions (and consequences thereof) made by NICE on both acetylcholinesterase inhibitors (for treatment of dementia) and Natalizumab (Tysabri, for the treatment of inflammatory disorders including Multiple Sclerosis) were reviewed. Data they presented showed that the UK is slower to use novel therapies than other countries, and that neurologists may be particularly slow to use them, compared with other medical specialties. Professor Isaacs reported data from questionnaire-based research (Programme Identifying and Observing Novel Therapy Adoption in Chronic Diseases: PIONEER), which compared neurologists to rheumatologists, in the treatment of Multiple Sclerosis (MS) compared with Rheumatoid

Arthritis (RA). Rheumatologists are more aggressive in their treatment choices, and far more of them support early treatment in RA compared with neurologists treating MS. Are neurologists more cautious? The rheumatologists said the 'tipping point' came when they accepted that RA was fatal, and that early joint damage was irreversible. The parallels to MS are striking. A Norwegian doctor asked whether we just don't have enough neurologists to treat and to act as advocates for our patients. If neurologists looked after patients with late complications of MS (such as urinary tract infection or aspiration pneumonia) then would we be more aware of the long term consequences of chronic neurological disorders? Would having enough neurologists to do all this change the nature of a UK neurologist?

## ABNT forum

I would like to thank those trainees who got up early on Thursday morning to come to our forum. We would also like to thank all trainees that returned our questionnaires, which have allowed us to provide high quality data to support trainees' views on MMC and other issues.

The Tooke review was discussed, and its radical proposals (including an end to run-through training) were generally welcomed by trainees (Table 1). However, the transitional years of 2008-9 will be more competitive than 2007, due to under-provision of training posts, and mishandled transition mechanisms.

**Table 1: Key points from the draft Tooke Report**

<i>Principles of broad-based, flexible training and aspiration to excellence</i>
<i>Criticism of policy development and governance and current mechanisms for workforce planning</i>
<i>Streamlining of regulation – PMETB to become part of the GMC</i>
<i>Changes to structure of post-graduate training</i>
<ul style="list-style-type: none"> <li>• Foundation year 2 to be abolished</li> <li>• 3 year basic specialist training programmes</li> <li>• Competitive entry to higher specialist training programmes</li> </ul>
<i>Possible distinction between post-CCT specialists and consultants with additional selection at this point</i>

Another future threat is a renewed interest in the sub-consultant grade. With a new potential “bulge” of trainees likely to complete training around 2012, our job is to ensure that consultant positions are available for them, and that they are not forced into non-consultant positions.

A Knowledge based assessment is very likely to be introduced for those of us in the new curriculum but increasing costs, and the potential for the exam to be branded and sold to non-specialist trainees has led to disquiet. There is not an easy solution to this problem – summative assessment of knowledge is required by PMETB, although the best format and style of this is unclear.

For the ABNT to be effective and representative, it is essential that trainees remain engaged and involved. Information is available on the

ABN website; and there is now a trainees forum that allows us to disseminate important information and encourages online discussion of contentious issues. The email addresses of all committee members and regional representatives are also available. It is important that the ABN office has a note of your most up-to-date email addresses to allow for rapid and cost-effective communication with you. Registrars will soon be emailed as part of the British Neurological Surveillance Unit (BNSU). Finally, please, encourage FY1& 2 and ST1 and 2 to become members of the ABN.

*Daniel Blackburn, Andrew Kelso and Biba Stanton  
(On behalf of the ABNT)*

## The True Cost of Brain Injury Headway, the Brain Injury Association’s 2007 Conference and Exhibition

October, 2007; Stratford-upon-Avon, UK.

Baroness Susan Greenfield was the big draw for this gathering of professionals concerned with the needs of the brain-injured. Her speech ‘The Future of Neuro-protection: the Benefits of Early Prevention’, highlighted on conference flyers, was the finale to a day filled with passionate discussion.

‘Passion’ was the word used by two personal injury solicitors from different firms in the exhibition. Asked what had drawn them into this specialist area, each cited the impact in their family lives of someone with brain injury.

Dr Andy Eynon’s opening discussion ‘Is Specialist Intensive Care Really Worth It?’ got people exercised about the relative lack of investment in acute specialist care, which would save vast sums of money in the long run. For example, survivors of ‘head and spinal trauma, stroke, intracranial infections’ whose ‘care is time-dependent’, may have reduced chances of appropriate rehabilitation and re-entry into the labour market, if they have not received specialist management in the critical early days. It is possible to focus on numbers of critical care beds available across the 27 specialist neuroscience centres in England and Wales (Feb. 2006, total adult beds 206). A Paediatric Neuroscience Nurse Consultant gave me a much smaller number available for children, and endorsed Eynon’s main argument, ‘It is the logistical reorganisation that is difficult’ within the NHS. This is despite recent governmental attention to neurological conditions (e.g. the National Service Framework for long term conditions, ‘Mending Hearts and Brains’, and the NICE guidelines for head injury management). NICE recommended ‘that all patients with severe head injury are managed at a specialist centre’. Eynon called for ‘rapid access to specialist units, aggressive treatment and early rehabilitation close to the patient’s home.’ It is not just a matter of more money, but careful and well-informed planning. (Eynon is Director of Neurosciences ICU at the Wessex Neurological Centre. Their evidence is in ‘Intensive Care Medicine’ 2007 33 Suppl 2 S 130).

Ron Payne provided a stark illustration of the individual and social costs incurred by the lack of targeted critical care and the uneven distribution of facilities for longer-term management. Heather, his wife, a brain injury survivor, sent apologies for not being well enough to speak that day. Slides of their lives before and after Heather’s brain injury enhanced Ron’s narrative. Both had worked in local government, enjoying healthy active lives and travelling. Seventy-two hours after a trip abroad Heather had an extensive DVT and intervention was difficult. She was deemed unlikely to survive. However, within a few days, Ron noticed some signs of response (flickering eyes, smiling), but not until Heather squeezed his hand, Ron said, was the care plan altered to support her accordingly. Several months later, Heather came home, and life became even more difficult through the lack of joined-up services. Few facilities were available in their area of Staffordshire, such as hydrotherapy, something Heather had benefited from in the early days. Ron described the strain of living with someone doubly incontinent, whose bedding he changed in the night, living in a downstairs room with insufficient space



Baroness Susan Greenfield at Headway conference 2007, by Richenda Power.

for two single beds and the necessary hoist. He felt unsupported and dealt with his stress by drinking. However, Heather’s sister discovered a specialist centre in Northumbria where ‘they have absolutely everything you could wish for: physio-, OT and neuropsychology for both of us’. They relocated. When asked about his own health, Ron replied, ‘My health has deteriorated to the same degree as Heather’s has improved, but the cost is worth it, to get my Heather back’.

Each personal story surrounding brain injury is unique. But the aims of helping, whether it be through rehabilitation of physiological function or the capacity to rejoin the labour market, as well as

the long term financial management, need to be considered in the round and across the whole of society. Alister Berry, Clinical Neuropsychologist, reported from Rehab UK on an evaluated project in South Tyneside; District Judge Gordon Ashton, Deputy Master, the Court of Protection, gave a compassionate and erudite outline of the implications of the Mental Capacity Act, including recent changes in the Court of Protection procedures and aims. His emphasis on consulting the protected person about the broadest aspects of their personal welfare, beyond basic financial management, was very welcome. Other speakers discussed ‘the Money Minefield’ of state benefits (Gillian Solly, of Davies and Partners) as well as the question of whether those should replace damages (Elizabeth-Anne Gumble QC and Henry Whitcomb QC).

This combination of speakers gave a kaleidoscopic view of the many and various costs of brain injury, to individuals, their families, work places, and society in general, over the decades that many survive.

After all this intensely concerned applied discussion it was a treat to be entertained and educated by Susan Greenfield, using a battery of engaging slides together with a very clear description of her research at the molecular level with possible neuroprotective agents (apoptosis inhibitors, anti excitotoxic agents; neurotrophic factors; ion channel moderators). She proposed to talk ‘controversially about the brain stem area’: ‘if there is damage in this vulnerable hub’, citing as examples, PD and Alzheimer’s, ‘although they arise from different areas embryologically they ‘retain the ability to grow again’ and what is necessary in early brain development may be damaging in later life. Sharing her question-raising approach to experimentation, she demonstrated her renowned skills as communicator of scientific ideas.

For further information on the 2008 Headway Conference and Exhibition, please contact Rachel Broughton on 0115240800 or email [eventsandconferences@headway.org.uk](mailto:eventsandconferences@headway.org.uk). For further information on Headway, please visit [www.headway.org.uk](http://www.headway.org.uk)

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WELLCOME TRUST ADVANCED COURSES

**Molecular Neurology and Neuropathology**

20-27 June 2008 (application deadline: 7 March 2008)

This intensive, discussion-based course offers a unique opportunity to learn the latest concepts and methodologies associated with the study of human neurological disorders, such as Alzheimer's, Parkinson's and epilepsy. Senior investigators will lead participants in detailed discussions on the strengths and weaknesses of the evidence underlying our current understanding of these diseases.

For full details of this and all Wellcome Trust Advanced Courses, bursary and application information plus details of our overseas courses, please visit:

[www.wellcome.ac.uk/advancedcourses](http://www.wellcome.ac.uk/advancedcourses)

All courses are subsidised by the Wellcome Trust and held at the Wellcome Trust Genome Campus near Cambridge – home to one of the world's largest concentrations of expertise in genomics and bioinformatics.

The Wellcome Trust is a charity registered in England, no. 210183.



**National Brain Science Writing Prize 2008**

Launching 10 March 2008 in Brain Awareness Week

Do you have a passion for brains?  
Could you write a newspaper-style article celebrating the amazing world of brain science?

At-Bristol, the European Dana Alliance for the Brain and the British Neuroscience Association have joined forces with Focus magazine to find the best brain communicators in the country!

Visit the website for details of prizes and how to enter.

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



**Brain Awareness Week**  
**10 – 16 March 2008**

Every March the European Dana Alliance for the Brain (EDAB) coordinates Brain Awareness Week, a major collaboration celebrating the wonders of the brain and brain research through hundreds of public events worldwide.



Dr Fabio Carmelito

EDAB is an organisation that is committed to enhancing the public's understanding of why brain research is so important.

THE EUROPEAN  
DANA ALLIANCE  
FOR THE BRAIN



To find out more, visit our website [www.edab.net](http://www.edab.net) or contact EDAB by phone on +44 20 7019 4914, or by email [enquiries@edab.net](mailto:enquiries@edab.net)



**International Symposium On Learning, Memory and Cognitive Function Mechanisms, Pathology and Therapeutics**  
February 10-12, 2008 - Valencia, Spain

**Call for abstracts**

Participants are invited to submit abstracts for oral or poster presentation, the majority being presented as poster. Acceptance will be based upon the quality and relevance of the submissions. Deadline expires on December 31st, 2007.

**Speakers**

Richard G. Morris, Agnes Gruart, Graham L. Collingridge, Denise Manahan-Vaughan, Ángel L. Barco, John O'Keefe, Susan J. Sara, Robert McDonald, Bruno Poucet, Francisco Olucha, Andrea Mele, Chris I De Zeeuw, José M. Delgado-García, John Freeman, Jan Born, Joseph L. LeDoux, Frank Schneider, Paula C. Bickford, Paola Bossù, Jenny Morton, Giulio Pasinetti, Vicente Felipo, Gerhard Winneke, John F. Disterhoft, Carol Greenwood.

**Registration fee**

Up to December 31st: 100 €  
After December 31st: 200 €  
Students: 50 €  
Registration fee for participants includes scientific sessions, coffee breaks and the symposium material.

**Symposium secretariat**

Cátedra Santiago Grisolia  
Fundación Ciudad de las Artes y las Ciencias  
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[www.fundacioncac.es/catedrasg](http://www.fundacioncac.es/catedrasg)

Eighteenth Meeting of the  
European Neurological Society








June 7–11, 2008

*Nice, France*

**20<sup>th</sup> Anniversary of the first ENS Meeting in Nice**  
*Neurology: Learning, knowledge, progress and the future*

**Key symposia:**

-  Coma and locked-in syndrome
-  Behavioural disorders and dementia
-  Autoimmune disorders of the nervous system
-  Multiple sclerosis: when to start a treatment and which treatment
-  Transient ischemic attacks: diagnosis and management

The congress programme includes interactive case presentations, 23 teaching courses, workshops organised by the ENS subcommittees and selected scientific sessions in the form of oral sessions, poster sessions (guided poster walks) and satellite symposia.

**Abstract Submission Deadline: January 31, 2008**

**Early Registration Deadline: April 8, 2008**

**For further information please contact:**

Administrative Secretariat:

18<sup>th</sup> ENS 2008, c/o AKM Congress Service

P.O. Box, CH-4005 Basel / Switzerland

Phone +41 61 686 77 11 Fax +41 61 686 77 88 E-mail [info@akm.ch](mailto:info@akm.ch)

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

## EDITOR'S CHOICE

**MULTIPLE SCLEROSIS: A few bad lymphocytes spread all over the brain in multiple sclerosis**

Open any neurology textbook and you will find multiple sclerosis described as a condition where CD4+ T lymphocytes invade the brain where they encounter a brain protein (perhaps "MBP", myelin basic protein) and so they set up pockets of inflammation ("plaques"). If it is an up-to-date textbook, it may go on to say that "antigen-specific therapy" is the holy grail of multiple sclerosis therapeutics; that is to say, those techniques which identify and eliminate, say, MBP-reactive CD4+ T cells are the answer. This German-Austria study has upset all that. It is a study of the lymphocytes found in 19 plaques and in normal appearing brain from the post-mortem brains of just four people with multiple sclerosis. In particular, the group analysed the T-cell receptor gene rearrangements, using "TCR spectratyping". This is a clever way of asking: what antigen do these lymphocytes recognise? (For the techno-nerds, 325 semi-nested PCR reactions were performed to sequence 800 Vbeta-NDN-Jbeta combinations at the single-cell level). There were four key findings:

1. In the brains of each patient, the lymphocyte population mainly consisted of just one or two clones which had considerably expanded. In other words, only a few antigens drive the abnormal immune response in each person with multiple sclerosis.
2. These distinct T-cell clones were present throughout the brain, both in plaques and in normal appearing white matter. So, the immune attack of multiple sclerosis is far less focal than we thought.
3. The lymphocyte clones from one patient's brain were completely different to those of another brain. So, the antigens driving multiple sclerosis are "private" and specific for each individual. (However, a little caveat here is that a study of just four brains is hardly epidemiology!)
4. At least some of the T cell clones are CD8+ cells. So we need to pay attention to this cell group as well in multiple sclerosis therapies.....

Unfortunately, Junker's technology does not actually tell us the identity of the antigens recognised by the T cell clones. Nonetheless, this is all seriously bad news for those academics and companies who are busy devising "antigen-specific therapies" on the assumption that one antigen (MBP, PLP and a host of other candidates) drives multiple sclerosis in all individuals. It turns out to be all rather more complicated..... Ah well.... – *AJC*

**Junker A, Ivanidze J, Malotka J, Eiglmeier I, Lassmann H, Wekerle H, Meinel E, Hohlfeld R, Dornmair K.**

*Multiple sclerosis: T-cell receptor expression in distinct brain regions.*

**BRAIN**

2007;130(Pt 11):2789-99. Epub 2007 Sep 21.

**EPILEPSY: and osteoporosis**

Anyone who has been to the Chalfont Centre for Epilepsy knows that it is a special place. A rural idyll fulfilling the 19th century dream of care for the severe epileptic. A cluster of houses and a workshop for simple work for the residents was a progressive development and the brainchild of the great neurologists of the late nineteenth century. That the residents are said to have built one nearby neurologist's house for nothing was simply part of their occupational therapy. Now with the addition of a 21st century assessment centre and the most up-to-date neuroimaging, it is a curious juxtaposition of cutting edge and faintly anachronistic – but a great place to work; all the clinical and support staff are devoted to the centre, its residents and its mission. I am not sure that the patients who end up there for a mixture of social and clinical reasons necessarily are representative of epilepsy sufferers in the community, but they nevertheless have some lessons to teach us. Of 208 patients, 31% were osteopaenic and 37% osteoporotic. All but one had started AED's before reaching maximum bone mass and the younger the patient at onset of epilepsy, the worse the problem. A small number of patients had never received enzyme-inducing drugs and these seemed to fare no better with regard to bone density. Interestingly, men were more affected than women. These patients tended to have low levels of physical activity; my recollection

is that sport does not figure largely on the timetable at Chalfont. By contrast, from memory, tobacco consumption is high and alcohol consumption is not and of course all these are confounding factors when assessing causation. The key lesson that bad epilepsy is likely to mean bad bones, reinforces recent research and we all need to take this more seriously. Did you know that NICE recommends densitometry every five years for patient on AED? Do you tell the GP this when you discharge the patient to their care? I feel an audit coming on, but I am going to bed and hopefully the feeling will have passed by the morning. Good night! – *MRM*

**Swanton J, Simister R, Altmann D, Watts H, Keen R, Duncan JS, Koeppe MJ.** *Bone mineral density in institutionalised patients with refractory epilepsy. SEIZURE*

2007;16:538-41.

**HUNTINGTON'S DISEASE: potential quantitative biomarker in peripheral blood or not?**

Up to now, no single therapy has been shown to delay disease onset or slow the progression of Huntington's disease, in part because it is hard to know how one can easily measure such an effect. One solution could be quantitative biomarkers in peripheral blood. In this recent study, Runne et al have measured mRNAs in peripheral blood cells and evaluated their utility as a potential transcriptomic biomarker. The authors have performed microarray gene expression profiling analysis on lymphocyte samples collected from 12 moderate stage HD patients and 10 controls using Affymetrix U133 Human Genome 1.0 Plus array for gene expression. Surprisingly, despite the authors initial hypothesis that neuroinflammation is an established and progressive facet of HD pathology and their expectation that related transcriptional change would be identified in HD blood, no HD-related statistical changes were detected on a single gene testing basis. This is in contrast to a previous study which had shown that transcriptomic changes in blood were a robust biomarker in tracking HD progression. The authors suggest that this difference may be due to varied subpopulations within HD. If this is the case, then there are real concerns as to whether any biomarkers may be useful in HD, until there is a better understanding of disease heterogeneity. – *CA*

**Runne H, Kuhn A, Wild EJ, Pratyaksha W, Isaacs JD, Regulier E, Delorenzi M, Tabrizi SJ, Luthi-Carter R.**

*Analysis of potential transcriptomic biomarkers for Huntington's disease in peripheral blood.*

**PNAS**

2007;104(36).

**HEADACHE: Brainstem dysfunction in chronic migraine**

The term "transformed migraine" used for chronic migraine accurately reflects the mystery surrounding its aetiology. In attempting to unravel central mechanisms in pathogenesis, this study investigated cortical excitability in chronic migraineurs and controls. Magnetic suppression of visual perceptual accuracy was measured. Positron emission tomography (PET) was used to see if there were correlated areas of excitation or inhibition. In patients with chronic migraine the study found reduced visual suppression and therefore a lack of inhibition in these patients. This correlated with PET studies in the same patients showing increased metabolism in the pons and right temporal cortex but reduced metabolism in the medial frontal cortex. The authors suggest that cortical excitability is raised in chronic migraine patients and point to evidence that patients with episodic migraine have similar but less marked changes. This correlates with the clinical observation of heightened sensitivity in migraine patients to external, particularly visual, stimuli. The findings must be treated with caution as the numbers studied are small, but they are intriguing. It seems likely that modulation of central excitatory and inhibitory pathways are one component of the intricate complex of peripheral and central changes in migraine. – *HAL*

**Aurora SK, Barrodale PM, Tipton RL, Khodavirdi A**

*Brainstem dysfunction in chronic migraine as evidenced by neurophysiological and Positron Emission Tomography studies.*

**CEPHALALGIA**

2007;47:996-1003.

**NEURAL TRANSPLANTATION: Taking neural crest stem cells to new heights**

Adult neurogenesis has been a hot topic for some time, but really in the context of the brain. A recent publication from a group in Spain led by Lopez-Barneo and colleagues has now taken the topic to the carotid body. In this structure they have shown:

- a. expansion or shrinkage of the carotid body as it experiences hypoxia and

normal oxygen tensions.

- b. that it contains BrdU positive cells that can be grown in vitro to produce neurospheres.
- c. that these cells can express tyrosine hydroxylase and release dopamine, and
- d. the source of these neuroprogenitors is a GFAP positive sustentacular cell derived from the neural crest.

Thus we have evidence for a neural crest derived precursor cell that is capable of dividing into dopaminergic releasing progeny and so could be considered for use in Parkinson's disease. Indeed this group have recently experimented with using carotid body transplants in patients with Parkinson's disease. There was variable clinical benefit with little evidence of dopamine cellular survival in the grafted striatum at least on PET scanning. Nevertheless these studies do suggest that more ethically neutral and practically accessible tissue sources may be available for patients with this common neurodegenerative disorder. – **RAB**

**Pardal R, Ortega-Saenz P, Duran R, Lopez-Barneo J.**

*Glia-like stem cells sustain physiologic neurogenesis in the adult mammalian carotid body.*

CELL

2007 131:364-377.

**Mínguez-Castellanos A, Escamilla-Sevilla F, Hotton GR, Toledo-Aral JJ, Ortega-Moreno A, Méndez-Ferrer S, Martín-Linares JM, Katati MJ, Mir P, Villadiego J, Meersmans M, Pérez-García M, Brooks DJ, Arjona V, López-Barneo J.**

*Carotid body autotransplantation in Parkinson disease: a clinical and positron emission tomography study.*

J NEUROL NEUROSURG PSYCHIATRY

2007;78(8):825-31. Epub 2007 Jan 12

## **PARKINSON'S DISEASE: smoking, coffee and NSAIDs**

The effects of smoking, coffee drinking and use of nonsteroidal anti-inflammatory drugs (NSAIDs) on developing PD have been examined individually but their joint possibly synergistic effects have not. In this recent study, Payami et al have studied 1,186 Parkinson's patients and 928

controls to quantify any associations of these factors in different combinations. Standardised questionnaires were used throughout the study where detailed questions on smoking, drinking and over the counter (OTC) and prescription (Rx) NSAIDs habits were recorded. Results show that smoking at any time was associated with 23% reduction in risk of Parkinson's disease and current smoking with a 55% reduction in risk. Risk seemed to decrease with increasing smoking pack-years ( $P < 0.001$ ), where the lowest risk (56%) was reported for patients with a > 40 pack-year history, regardless of age, sex or family history. High coffee consumption was associated with a 25% risk reduction with a significant dose-response gradient ( $P < 0.001$ ). The coffee effect was more pronounced in men than in women with the coffee dose response relationship being highly significant in men but not in women. For NSAIDs the results revealed a 19% reduction but no obvious dose-response effect. When family history was taken into account, it revealed that the risk reduction for PD was only evident in nonfamilial PD cases. The effects of smoking, amount of coffee intake and use of NSAIDs appeared to be independent and cumulative. This collection of data on such a large number of patients is clearly a major achievement and represents a powerful data set though the fact that individuals were asked to reflect on their habits covering a lifetime of customs such as smoking, coffee drinking and consumption of NSAIDs is problematic. Nevertheless when interactions are further probed, it can be seen that the combined risks of any two factors is lower than the risks associated with the individual factors with the combination of all three factors giving the lowest risk profile. The additive effects of all three factors give a highly significant reduction of developing PD by as much as 87% although whether they are due to direct protective effects remains to be explored by further studies. Till then we might want to start consuming more coffee! – **CA**

**Powers KM, Kay DM, Factor SA, Zabetian CP, Higgins DS, Samii A, Nutt JG, Griffith A, Leis B, Roberts JW, Martinez ED, Montimurro JS, Checkoway H, Payami H.**

*Combined effects of smoking, coffee and NSAIDs on Parkinson's disease risk.*

MOVEMENT DISORDERS

E Pub6 Nov 2007

## **Journal reviewers**

**Heather Angus-Leppan**, Royal Free & Barnet Hospitals;  
**Chrystalina Antoniadis**, Cambridge Centre for Brain Repair;  
**Roger Barker**, Cambridge Centre for Brain Repair;  
**Lloyd Bradley**, Colman Centre for Specialist Neurological Rehabilitation Services in Norwich;

**Alasdair Coles**, Cambridge University;  
**Andrew Larner**, Walton Centre, Liverpool;  
**Mark Manford**, Addenbrooke's Hospital, Cambridge and Bedford Hospitals;  
**Wendy Phillips**, Addenbrooke's Hospital, Cambridge;  
**Robert Redfern**, Morrison Hospital, Swansea;  
**Ailie Turton**, University of Bristol.

## **Episenta: Controlled release sodium valproate that's easy to swallow**

The issue of compliance of AEDs has been raised by a number of studies indicating that poor compliance in patients with epilepsy can relate to increased seizure frequency. However, some tablets, particularly controlled release ones, can be rather large and many patients experience swallowing difficulties. The use of syrup presentations may help, but they are not very palatable and are more expensive.

Whereas some formulations may be difficult to swallow, Episenta capsules or sachets can be opened and the minitablets sprinkled onto soft foods such as yoghurt or taken with drinks. Episenta aims to be the patient friendly option. The capsules and sachets contain many minitablets each of which is a prolonged delivery unit to reliably deliver sodium valproate as a once-a-day treatment to help



enhance acceptability to patients and improve compliance.

Episenta can be taken either before, during or after meals without any affect on absorption as the minitablets pass through the pylorus independent of food and do not get retained in the stomach to cause gastric irritation. This makes it easier for the patient to fit the medication to their lifestyle.

There are good pharmaceutical reasons why Episenta should be the presentation of choice when requiring a prolonged release sodium valproate, but there are also sound financial reasons. Episenta is bioequivalent to Epilim Chrono and yet the NHS price is about 25% less. Episenta even costs less than standard Epilim tablets. Using Episenta ensures significant savings to the drug budget.

For more information T. 01892-600930.

EPISENTA (Prolonged-Release Sodium Valproate) - ABBREVIATED PRESCRIBING INFORMATION See Full SmPC For Details. Episenta 150 mg & 300mg capsules and Episenta 500 mg & 1000mg sachets contain prolonged release sodium valproate minitablets. Indication: The treatment of all forms of epilepsy. Dose: Give in 1 - 2 single doses. Monotherapy: Adults: Start at 600mg daily increasing by 150-300mg at three day intervals to a max of 2500mg/day until control is achieved. Children over 20kg: Initial dosage - 300mg/day increasing to max. of 35 mg/kg bw/day until control is achieved. Children under 20kg: 20mg/kg bw/day; max. 40mg/kg/day. Patients with renal insufficiency: May require decreased dose. Combined Therapy: It may be necessary to raise dose when used in combination with liver enzyme inducing drugs. The dose of concomitant barbiturate should be reduced. Administration: Oral. Swallow capsule or sachet contents without chewing the prolonged-release minitablets. Contraindications: Liver disease. Hypersensitivity to valproate. Precautions: The onset of an acute illness e.g. vomiting, lethargy, anorexia, jaundice or loss of seizure control is an indication of the early stages of hepatic failure and requires immediate with-

drawal of the drug. Routinely measure liver function in those at risk before and during the first six months of therapy. Discontinue if signs of liver damage occur or if serum amylase levels are elevated or if spontaneous bruising or bleeding occurs. Withdrawal of sodium valproate should be gradual to avoid increased in seizure frequency. Interactions & Pregnancy and Lactation: See full SPC. Undesirable Effects: See full SPC but most frequently, gastrointestinal disturbances. Less commonly, increased appetite and weight gain, tremor, drowsiness, ataxia, confusion, headache, reversible prolongation of bleeding time, thrombocytopenia, leucopenia, bone marrow depression and congenital malformations have been reported. Further information & MA Holder: Beacon Pharmaceuticals Ltd. 85 High St., TN1 1YG UK. Tel: 01892-600930. Presentations & Price: POM. Episenta 150 mg capsule x 100 PL 18157/0021, Episenta 300 mg capsule x 100 PL 18157/0022, Episenta 500 mg sachet x 100 PL 18157/0023 and Episenta 1000 mg sachet x 100 PL 18157/0024 have the following NHS prices: £5.70, £10.90, £18.00 & £35.50 respectively. Date of text: March 2007.

## Guernsey invests in onsite scanning facilities from Siemens

Princess Elizabeth Hospital, Guernsey, has installed the SOMATOM Sensation 64 and MAGNETOM Avanto 1.5 scanner from Siemens Medical Solutions in its newly built scanning department. The installations will add permanent MR and CT capabilities to its in-house services and enhance its imaging, clinical and diagnostic capabilities.

To date patients have had to travel to Jersey or Southampton for their scans; in 2006 approximately 882 people were referred to off-island hospitals. With demand increasing, Princess Elizabeth Hospital needed to provide on-site scanning, imaging, clinical and diagnostic capabilities. The new unit gives permanent access to state-of-the-art MRI and CT scanning equipment.

The combined products have the advantage of providing better imaging and staging processes. The high end MAGNETOM Avanto uses Total image matrix (TIM) technology, providing significant advantages in imaging, allowing a greater range in examinations. The scanner will be used to look at detailed images and the high resolution technology



Pictured beside the new MAGNETOM Avanto with the wall backdrop created by Karl Taylor are: (L to R) Laura Slimm, MRI Deputy Superintendent, Roy McGregor, CEO for Credit Suisse and Deputy Peter Roffey, Health Minister for Guernsey.

offers a new level of clarity. This allows early detection of abnormalities and decreases time to treatment.

It improves patient comfort and care, with the AudioComfort technology reducing noise encountered by patients by 97%. The high speed technology shortens the time to complete the scan and its innovative design gives the patient more room to relax.

For more information  
E. medmarketing.med.gb@siemens.com

## New Ti series – a central resource for live cell imaging

Nikon launched the Ti Series recently. Available in three distinct models, the Ti range combines rapid system speed with a flexible design incorporating capabilities including: confocal, TIRF, fluorescence and Nikon's patented Perfect Focus System (PFS) into one powerful integrated unit set to expand and advance current live cell imaging research.

Offering faster acquisition times and unparalleled levels of accuracy, the Ti platform has been designed in close collaboration with the industry's leading cell biologists and presents the field with a versatile new tool. The Ti-E is now the first microscope system to incorporate optimised syn-



chronised switching improving total system performance. All component parts are integrated within a central hub and intelligently controlled through Nikon's NIS elements software. This enhances speed of operation, minimises component movement and improves experimental accuracy.

Complementing the range, the Ti-S and Ti-U derivatives are ideal for researchers requiring

less advanced systems with a lower level of integration, and are specifically indicated for use in more routine laboratory work.

For more information see  
[www.nikoninstruments.eu](http://www.nikoninstruments.eu)

## Zeiss sets new standard for zoom, magnification and resolution in stereomicroscopy

Carl Zeiss has added a flagship stereomicroscope to its range with the launch of the SteREO Discovery.V20. The 20x zoom is the highest zoom factor and final magnification of any stereomicroscope available on the market. Thanks to the newly computed PlanApo S 2.3x objective, the SteREO Discovery.V20 also delivers the highest resolution in stereomicroscopy with 1000 LP/mm, with a maximum magnification of 345x (eyepieces 10x).

"The new microscope owes much of its exceptional optical performance to the CMO (common main objective) imaging system pioneered by Zeiss", says Aubrey Lambert, Marketing Manager at Carl Zeiss UK. "The 20x zoom range enables users to move seamlessly from a panoramic overview of an object to examining extremely small details without any time-consuming change of objectives. This is a significant benefit in automated workflow environments. Furthermore, the high



final magnification of the SteREO Discovery.V20 permits three-dimensional observation of objects that, until now, could only be examined two-dimensionally with a traditional light microscope."

The advanced design guarantees safe object manipulation, combining high magnification with generous working distances. Ergonomically, every microscope function can be controlled through SyCoP, which integrates the entire System Control Panel into a mouse-like controller. This allows intuitive control of the motorised zoom and focus, the illumination, and the real-time display of total magnification, object field, resolution, depth of field and Z position. A range of high-performance CMO lenses enables fine details to be visualised with outstanding contrast and in three dimensions.

For more information T. 01707 871 200, E. [micro@zeiss.co.uk](mailto:micro@zeiss.co.uk)

## Study shows Topamax® provides sustained reduction in monthly migraine days for up to one year

A new long-term study into migraine prevention published in *The Lancet Neurology* shows that patients who continued with Topamax® (topiramate) for migraine prophylaxis for up to a year experienced a sustained reduction in the number of migraine days per month, with significant associated benefits on quality of life measures.<sup>1</sup> The study also found that there was a significant increase in the number of monthly migraine days following discontinuation of topiramate, however, the number did not return to pre-treatment levels.<sup>1</sup>

The PROMPT (PROlonged Migraine Prevention with Topiramate) study was a 12-month, multicentre, double-blind, randomised, placebo-controlled study conducted to investigate the continued effectiveness of topiramate in reducing the number of migraine days beyond six months, compared with the impact of stopping treatment at six months. All patients received open-label Topamax for the first 6 months, and then were randomised to either continue Topamax or take placebo for the second 6 months in a double-blind design.

After 6 months of open-label topiramate treatment, the mean number of monthly migraine days fell significantly from 8.93 to 5.83, a reduction of 3<sup>1</sup> migraine days per month ( $p < 0.0001$ ). After 12 months, the reduction in the mean number of monthly migraine days seen during the first six months was maintained and remained almost unchanged in the group that continued on topiramate.

For more information T. 01494 567567.

### Reference

1 Diener HC, Agosti R, Allais G. et al. Cessation versus continuation of 6-month migraine preventive therapy with topiramate (PROMPT): a randomised, double-blind, placebo-controlled trial. *The Lancet Neurology*, 2007;6:1054-62.

## SonoSite system excels in rheumatology and musculoskeletal imaging

Dr Philip Platt, Consultant Rheumatologist at the Freeman Hospital, Newcastle, relies on a SonoSite MicroMaxx® hand-carried ultrasound system to help diagnose patients, to assess treatment efficacy and to improve the accuracy of local injection treatments in both his rheumatology and sports injuries clinics.

Dr Platt explained, "Ultrasound gives good diagnostic accuracy for musculoskeletal problems and I believe the patients get better care as a result. Being able to scan while moving a joint around is a unique advantage of ultrasound particularly useful for soft tissue and tendon injuries and gives a whole new aspect that other imaging modalities just don't provide." For rheumatology, Dr Platt described a very significant application of ultrasound in monitoring the effective but expensive anti-TNF drug. "This relatively new drug works for many rheumatoid arthritis patients but not all. It is very important to identify which patients do or don't benefit from treatment so they are not taking drugs inappropriately. One of the best ways to monitor the response is to use ultrasound to see



whether inflammation has reduced."

He added, "The great advantage of these hand-carried systems is the time they save. They are easy to carry to different wards and hospital sites, and are ready to use in under 15 seconds. In contrast, pushing heavy cart-based systems around the hospital, waiting for lifts, trying to find space beside a patient's bed, and then waiting for the machines to boot up is a real waste of time."

For more information T. 01462 444 800, E. [europa@sonosite.com](mailto:europa@sonosite.com), [www.sonosite.com](http://www.sonosite.com)

## New Website and Member Benefits Package for CRT Network

The Community Therapists Network, the new name for the Community Rehabilitation Team Network has a new home [www.communitytherapy.org.uk](http://www.communitytherapy.org.uk). To celebrate the new name and website the organisation are delighted to offer new member benefits including access to a range of free multimedia CD programmes and 20% discount on the forthcoming workshop on 13th March, Building your Business Case in Rehabilitation.

To find out more about the new benefits and how to join for as little as £10 per member, see [www.communitytherapy.org.uk](http://www.communitytherapy.org.uk)

For a full report on the CRT Network Conference held in September 2007 in Sheffield, see <http://www.acnr.co.uk/conferences.htm>

## Awards and Appointments



Professor Richard Langton-Hewer (right) and Professor Graham Venables.

### ABN Medal 2007

The ABN Medal is awarded annually to recognise outstanding contributions by British neurologists to the science or practice of neurology, or for contributions to the Association of British Neurologists. The 2007 award was made to Professor Richard Langton-Hewer at the recent ABN meeting, by ABN President Professor Graham Venables.

In his citation, Derick Wade notes that Professor Langton-Hewer was ahead of his time, practicing through his clinical activities principles that were at the time unusual, but that are now becoming mainstream. He was patient-centred when much of medical practice

was still professionally driven and centred, and was ahead of his time in the collection and use of routine patient data. This was part of his insistence on generating and using evidence to support service development. He was concerned with the development and provision of clinical services. At the time this was not a popular view within the medical profession in general and within the ABN in particular. He was also ahead of his time in that he collaborated with other professions on an equal footing. He was truly committed to multi-disciplinary teams at a time when doctors still expected to lead and to be obeyed.

### ABN Case Report winner

ACNR is delighted to sponsor the ABN Case Presentation Competition which is held at each ABN meeting. At the recent ABN in London, Dr John McHugh won the award for his Case Presentation "Startling new antibody in an old Irish jumper." Dr McHugh's case report also won the 2007 Royal Academy of Medicine in Ireland's Registrar's Prize in Neurology, which took place on Friday, November 23rd, at the Four Seasons Hotel, Ballsbridge, Dublin. See [www.iicn.ie/education/rami\\_registrars\\_prize\\_in\\_neurology.501.html](http://www.iicn.ie/education/rami_registrars_prize_in_neurology.501.html) for an abstract of the case report.



### £250,000 research grant awarded

The Oliver Zangwill Centre, based at the Princess of Wales Hospital in Ely, has just been awarded a major research grant of £250,000 by the NHS "Research for Patient Benefit" programme. This grant will help researchers at the Centre find out whether reminders delivered to patients with acquired brain injury via mobile phone text messaging can improve brain injured patients' achievements in their day-to-day lives.

Dr Fergus Gracey, lead applicant for the grant said "We want to find out whether an alert, delivered via mobile phone text messaging, can improve patients' with acquired brain injury achievements of tasks in their day-to-day lives. We also want to know whether such a service would help improve patients' and carers' emotional well being and stress. There is little research that tells us what helps

patients in their day-to-day lives. We have evaluated the provision of a timed electronic alert reminding someone of what they need to do at a specific time, for example, 'take medication' at 6.00 pm, sent to the patient via a pager and shown this to be effective. We now provide this 'Neuropage' service nationally. However, not everything we do can be timed in this way and patients and relatives tell us they like to have space for flexibility and spontaneity in their lives."

The findings from our research will be used to help develop our existing service and community rehabilitation provision in the region. As the intervention is delivered via mobile phone we have the potential to reach a large number of patients and carers more economically. We will share our findings with others to contribute to the development of clinical practice in rehabilitation."

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PRESCRIBING INFORMATION

**Presentation** - Glatiramer acetate 20mg solution for injection in 1ml Pre-filled Syringe.  
**Indication** - Reduction of frequency of relapses in relapsing-remitting multiple sclerosis in ambulatory patients who have had at least two relapses in the preceding two years before initiation of therapy.  
**Dosage and administration** - 20mg of glatiramer acetate (one pre-filled syringe) administered subcutaneously once daily.  
**Children** (<18 years) Not recommended. **Elderly** No specific data.  
**Impaired renal function** No specific studies. Monitor renal function during treatment and consider possibility of deposition of immune complexes.  
**Contra-indications** - Known allergy to glatiramer acetate or mannitol (excipient).  
**Pregnancy. Special warnings and precautions** - Sub-cutaneous use only. Initiation to be supervised by neurologist or experienced physician. Supervise first self-injection and for 30 minutes after. One or more of vasodilatation, chest pain, dyspnoea, palpitations or tachycardia may occur within minutes after injection. These generally resolve spontaneously after a short time. If severe, treat symptomatically. Caution in patients with pre-existing cardiac disorders and review such patients regularly. Rarely convulsions and/or anaphylactic or allergic reactions. Rarely, hypersensitivity (bronchospasm, anaphylaxis or urticaria). If severe, treat appropriately and discontinue Copaxone.  
**Interactions** - No formal evaluation. Increased incidence of injection-site reactions with concurrent corticosteroids. Theoretical potential to affect distribution of protein-bound drugs, therefore concomitant use of these should be monitored.  
**Pregnancy and lactation** - Not to be used in pregnancy. Consider contraceptive cover. No data on excretion in human milk.  
**Undesirable effects** - Injection site reactions (erythema, pain, mass, pruritus, oedema, inflammation, hypersensitivity, lipoatrophy). An immediate post-injection reaction (one or more of vasodilation, chest pain, dyspnoea, palpitation, tachycardia) may occur within minutes, reported at least once by 41% of patients receiving Copaxone compared to 20% of patients receiving placebo. >1%: Nausea, anxiety, rash, sweating, chills, face oedema, syncope, vomiting, lymphadenopathy, oedema, nervousness, tremor, herpes simplex, skin benign neoplasm, eye disorder, vaginal moniliasis. Rarely: Anaphylactoid reactions, convulsions, shifts in white blood cell counts, elevated liver enzymes (with no evidence of clinical significance) and skin necrosis at injection sites. Please refer to the SPC for a full list of adverse events.  
**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.  
**Legal Category** - POM.  
**Package Quantity and Basic NHS Cost** - 28 pre-filled syringes of Copaxone: £545.59.  
**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** - September 2007.

Information about adverse event reporting 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.

Reference: Ford C. et al. Multiple Sclerosis 2006; 12: 309-320.

# Your decision today can make a difference tomorrow



**COPAXONE®**  
(glatiramer acetate)

Long-term active

**TEVA**

  
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Because health matters

Date of preparation: October 2007 Code: C0807/428a