

EDITOR'S CHOICE

Multiple sclerosis: Have we got it all wrong?

A paper in the *Annals of Neurology* has to be pretty special to get reported in *The Economist*, as this was. The findings of this study of one lesion from one case with multiple sclerosis are certainly remarkable. Whether they are extraordinary enough to completely rewrite the textbooks is another matter. But any study of multiple sclerosis pathology from John Prineas has to be taken very seriously.

The patient is an unusual one: a 14 year old girl dying of neurogenic pulmonary oedema 17 hours after the symptomatic onset of a brainstem plaque. The autopsy was 13 hours later. It is very rare for such early stages of the multiple sclerosis lesion to be examined pathologically. Contrary to all expectations, the first abnormality seen was oligodendrocyte death, by a process similar to apoptosis (with nuclear condensation but without activation of caspase 3). There is microglial activation but neither T cell infiltration nor myelin phagocytosis. The authors examine the brains of 11 other patients with multiple sclerosis and find, amongst many plaques, 9 lesions in 6 other cases with similar apoptosis of oligodendrocytes.

The authors conclude that the primary event in multiple sclerosis is the programmed death of oligodendrocytes, of unknown cause, and that demyelination and infiltration of inflammatory cells are all secondary. Dogma has it that apoptosis does not induce inflammation, so that needs explaining.

This is not a completely novel suggestion. The landmark series of papers from Claudia Luchinetti and Hans Lassmann describe a rare subset of multiple sclerosis lesions without much inflammation and a primary oligodendropathy as their key feature: the "Type III" lesion. However Barnett & Prineas are claiming this is the universal mechanism for multiple sclerosis plaque formation.

This is provocative stuff and, of course, seriously bad news for anti-inflammatory treatment strategies. - AJC

Relapsing and remitting multiple sclerosis: pathology of the newly forming lesion.

Barnett M & Prineas J.

ANNALS OF NEUROLOGY

2004; 55: 458-468

REHABILITATION: Training doctors with disabilities

Having recently learnt that a young third year medical student, who lost his hand at wrist level during a summer job, is soon due in our prosthetic clinic, this article caught my eye. Though focused on the North American medical school system and US legislation, it does offer an interesting insight into how we in the medical profession view how people with disabilities can or should be facilitated to qualify and practice as a doctor.

Similar to legislation in the UK, Ireland and most European countries, the Americans with their Disabilities Act outlaw discrimination based solely on disability including admission to educational institutions. It specifies that applicants must be able to perform the "essential functions" of the educational program but in turn the institution must provide "reasonable accommodations". The authors discuss the Association of American Medical Colleges 1979 report and how it tried to define the essentials of an "undifferentiated" medical graduate as one who possesses all of the technical skills required to enter any speciality of medicine. This report identified five categories of abilities and skill deemed necessary for a graduate to possess: observation; communication; motor; conceptual, integrative, and quantitative; and behavioural and social. Thus the questionnaire was based on this construct.

Though 2,930 people associated with the Northwestern University School of Medicine were sent a questionnaire, no firm conclusions can be drawn from this survey given the poor response rate from only 523 (18%). The questionnaire consisted of three multiple choice questions, 27 questions in five-point Likert-scale format, five demographic questions and a space for comments along with a cover letter. The group surveyed included most "levels" of the medical profession: attending physicians, house staff in residency programmes and third year medical students. Perhaps not surprisingly Physical Medicine & Rehabilitation had the highest response rate (26.9%) of the specialities compared to 14.9% for other medical specialities and 11.1% for surgical ones (though the authors didn't offer that this may have been due to their contacts in the department).

The majority of responders (69.8%) disagreed with the above interpretation of "undifferentiated" graduates and this held true regardless of disability status or level of training. Technical skills used in interpretation and observation (such as auscultation and palpation/percussion) were more important to respondents than those skills that are purely procedural (such as suturing

and performing CPR). One comment noted that physicians rarely work in isolation so that they needn't be expected to perform all skills. On the opposite end of the spectrum was "would you fly with a blind pilot, if the pilot's assistant reads the instruments?" In the past couple of years there has been greater awareness of the issue of people with disability entering and working in the medical field (see *BMJ* Oct 18). However, more research like this survey is warranted on this side of the Atlantic. I wonder what lies in store for my third year medical student who (already!) is interested in cardiology?

- JJMACF

Technical Standards for the Education of Physicians with Physical Disabilities: Perspectives of medical students, residents, and attending physicians.

VanMatre RM, Nampiaparampil DE, Curry RH, Kirschner KL

AM J PHYS MED REHABIL

2004;83:54-60

EPILEPSY: My memory is awful

Memory disturbances in epilepsy are widely recognised and frequently complained of by patients. There are clearly many potential mechanisms, which may contribute, including the aetiology of the epilepsy; the epilepsy syndrome; seizure frequency; interictal electrical disturbances; medication and social consequences. This study tries to tease out some of the factors implicated. 121 children with epilepsy aged 7-12 years were included if they had moderately frequent interictal EEG changes, no evidence of a malignant epilepsy syndrome but some evidence of cognitive problems or fluctuations in cognitive performance. Activity of epilepsy was assessed in the period before and during a variety of cognitive tests. These included baseline measures of knowledge base such as vocabulary and transient measures of cognition, including short-term memory attentional tests and speed of information processing.

Reading and arithmetic showed no significant delay in children with generalised epilepsy but a mean of over 1 year delay in children with focal epilepsy, both cryptogenic and symptomatic. Generalised seizures were associated with a delay in reading by 10 months and partial seizures by 21 months. This effect was much greater than any effect of frequency of epileptic EEG activity on these measures. Reaction time scores were not affected by type of epilepsy but were adversely affected if patients had frequent epileptic discharges. Memory testing for word recognition, figure recognition or Corsi memory span were worse in patients with epilepsy than in controls. Word recognition was significantly more severely affected in patients with symptomatic epilepsy than in the other groups. Not surprisingly, seizures during testing had an adverse effect on memory tests.

So what does all this mean? Firstly, aspects of cognition affected will depend on the type of epilepsy and the activity of epilepsy. Focal epilepsy associated with structural abnormalities give problems akin to developmental delay, presumably due to the structural damage and not directly related to the epilepsy. Frequent seizures affect processing speed as do frequent "sub-clinical" EEG discharges but the effect of the latter is mild and limited to transient cognitive processes. When assessing patients with epilepsy and memory complaints, we need to clarify the nature of the complaint, ideally with psychometric testing and relate it to the epilepsy and seizure types as well as EEG findings, before deciding on how to change drug treatment. -MM

The relative influence of epileptic EEG discharges, short non-convulsive seizures and type of epilepsy on cognitive function.

Aldenkramp A, Arends J

EPILEPSIA

2004;45:54-63

☆☆☆ RECOMMENDED

DEMENTIA: Driving and dementia

Drivers suffering from dementia are two to five times more likely to be involved in road accidents than age-matched controls (no comparisons with adolescent males available!). Conversely, advising patients not to drive can have serious practical repercussions, can dent self-esteem and undermine doctor-patient relationships. Reger and colleagues contribute a meta-analysis of 27 primary studies that evaluate neuropsychological tests in the prediction of driving ability.

Numerous standard neuropsychological tests are included, subdivided into six domains according to the primary function tested (attention, visuo-spatial skills, memory, executive functions, language and 'general' cognition). The primary studies compare test performance to three more-or-less direct measures of driving ability – on-road tests, non-road tests (e.g. driving simulators) and caregiver reports; official accident records proved too heterogeneous to include. An effort is made to restrict the analysis to subjects diagnosed with Alzheimer-type dementia and to standardise 'effect size' across the myriads of primary studies. Correlations excluding controls are rightly given

prominence: incorporating controls into such analyses would overestimate predictive value.

In the analyses that exclude control subjects, no significant association is found between general tests (mainly MMSE) and on-road assessments. The effect sizes for correlations with driving scores are 'small' in each of the cognitive domains except for visuo-spatial function, where the effect size is 'moderate'. Whilst this might have been expected, it is surprising that tests of attention (also conventionally regarded as crucial to driving) appear to have less predictive value.

The message is that neuropsychological tests do not add greatly to evaluations of driving ability. In difficult cases, specialist driving assessments using simulators and on-road testing seem warranted. -RD

The relationship between neuropsychological functioning and driving ability in dementia: a meta-analysis.

M.A. Reger, R.K. Welsh, G.S. Watson, B. Chorleton, L.D. Baker and S. Craft.
NEUROPSYCHOLOGY
2004, 18: 85-93.

COGNITION: Emotions in Urbach-Wiethe disease

No, not the garbled name of an unusual myoclonic epilepsy syndrome but another autosomal recessive condition, extremely rare and associated with bilateral calcification of the amygdala. Urbach-Wiethe disease is associated with deposition of hyaline-like material in the skin, mucous membrane and other organs; it has been associated with learning difficulties and with seizures, although neither point is emphasised here.

The main contribution of the paper is in drawing attention to a disease, which despite its rarity, may prove to be a very instructive natural experiment. The authors have found cases, mainly in South Africa, that compare favourably to matched controls in most areas of cognition but have deficits in emotional processing. There are particular difficulties with recognising 'complex' emotions (surprise and disgust, as compared to fear) and some impairment on an association task involving olfaction. Very much as expected, memory for emotionally arousing material was severely impaired.

It is to be hoped that the rather limited imaging data-set (CT, SPECT and one PET) is an indication of more to come. -RD

Amygdala, affect and cognition; evidence from 10 patients with Urbach-Wiethe disease.

M. Siebert, H.J. Markowitsch and P. Bartel
BRAIN
2003, 126: 2627-2637.

MEMORY: Caudate contributions to working memory: an fMRI study.

Common cognitive problems displayed in neuro-rehabilitation settings are deficits in executive function and patients often display specific difficulties on tests of planning and working memory. Converging neuroscience sources show frontal regions of the brain like the frontal cortex being important to working memory. Recent clinical evidence from close analysis of Parkinson's patients however suggests that subcortical brain structures also have an important role.

This fMRI study targeted subcortical structures such as the caudate nucleus to see how activation here relates to specific aspects of working memory. Crucially attempts have been made to isolate component cognitive contributors to working memory by designing the experimental paradigm to assess "maintenance, retrieval and manipulation" independently. During an originally designed verbal memory test, ten healthy participants were scanned using event related functional Magnetic Resonance Imaging. Alongside the neuroimaging process parallel behavioural measures relating to performance were recorded. By combining design with techniques different aspects of the task could be correlated with activation in specific regions of interest. This was in order to illuminate brain function during particular aspects of working memory.

Signal increases were evident in the "frontostriatal network" during the task. Bilateral caudate nuclei activation seemed to be relatively increased when manipulating information over and above maintaining and retrieving it. This interesting finding is consistent with other recent research suggesting that Parkinson's disease patients (who characteristically show neurodegenerative signs of dopaminergic loss in the caudate nuclei) display difficulties in executive function and in manipulation aspects of working memory. Perhaps this research will lead to tests for cognitively relevant pharmacological/ therapeutic interventions targeting subcortical function. -LAJ

Striatal contributions to working memory: a functional magnetic resonance imaging study in humans.

Lewis S.J.G, Dove A, Robbins T.W., Barker R.A. and Owen A.M.
EUROPEAN JOURNAL OF NEUROSCIENCE
2004; 19: 755-760

NEUROINFLAMMATION and degeneration

The role of inflammation (including activated microglia) in neurodegenerative disease and regeneration following acute lesions is complex. Whether or not activated microglia are beneficial or detrimental to regeneration, repair and neurogenesis, is unresolved. Lindvall *et al* found that activated microglia, as induced by lipopolysaccharide (LPS) infusion, reduced survival of new born neurones and postulated this as a mechanism for poor regeneration post injury despite robust initial neurogenesis.

In the first experiment, infusion cannulae were implanted into the right cortex of rats, and LPS from *E. Coli* was infused. The numbers of activated microglia (as determined by immunohistochemical staining for ED1) were quantified 6 and 28 days later, and were very much higher in LPS treated rats compared to vehicle. The numbers of ED1 positive cells were significantly negatively correlated with BrdU/ NeuN double-labelled cells. BrdU is a nucleoside analogue, which incorporates into dividing cells, and when colabelled with neuronal markers indicate new neuronal formation. That is, the more activated microglia, the less neurogenesis (in the subgranular layer, an area of basal neurogenesis).

Rats were implanted with a stimulating/recording electrode (right hippocampus) and status epilepticus was induced, interrupted by intraperitoneal phenobarbitone. The numbers of activated microglia were much greater in generalised status. As expected, partial status induced a robust neurogenic response (measured by double labelled BrdU/NeuN cells), but this was attenuated in generalised status (although still higher than the basal rate of neurogenesis). This was seen at 28 days (double labelled cells then indicating those which had survived from the initial labelling injections on day 1). Markers for proliferation (Ki67) were not different between partial and generalised status, indicating that there is an effect on cell survival as opposed to formation. The degree of new neuronal survival in partial status was reduced to levels seen in generalised status by infusion of LPS into animals that had undergone partial status. Infusion of LPS increases levels of activated microglia without inducing further tissue damage. Thus this effect seems to be specific to microglial activation rather than tissue damage. Finally, the authors showed that the attenuation of new neuronal survival seen in generalised status could be ameliorated by intraperitoneal injections of minocycline. Minocycline is a specific inhibitor of activated microglia, and readily crosses the blood-brain barrier.

So microglial activation in this model inhibits neurogenesis; it is not yet known whether this effect is reproducible in other acute lesions, or in neurodegeneration. The role of activated microglia is likely to be complex and involve different effects (supportive versus toxic) depending on timing and location of injury, morphological state of the microglia, surrounding environment, and so on. -WP

Inflammation is detrimental for neurogenesis in adult brain.

Ekdahl CT, Claassen JH, Bonde S, Kokaia Z, Lindvall O.
Proc Natl Acad Sci U S A. 2003 Nov 11;100(23):13632-7.
Epub 2003 Oct 27.

TECHNIQUES: A new agent to measure neurogenesis

The concept of adult neurogenesis is an exciting one, having profound implications for our understanding of memory and learning, plasticity and repair. Unfortunately, it has been difficult to measure and the most widely accepted method is beset with difficulties and inaccuracies. Bromodeoxyuridine (BrdU) is a thymidine analogue, which incorporates into DNA during the S phase of replication and thus labels dividing (proliferating) cells. Neurogenesis has been measured by counting cells, which label for both neuronal markers and BrdU (thus indicating that the neurones have recently proliferated). This method has problems, which will be described below.

Doublecortin (DCX) is a microtubule associated phosphoprotein required for neuronal migration and differentiation, and is expressed in immature neurones. Doublecortin immunoreactivity has sometimes been used as a marker for neurogenesis but it has not been systematically validated until now. Rao and Shetty compared immunoreactivity for BrdU, DCX and both in the adult rat dentate gyrus. Proliferating cells were labelled with a 100 mg/kg intraperitoneal injection of BrdU per day for 12 consecutive days. They showed that 90% of all DCX positive cells in the dentate gyrus are also BrdU positive. The remaining 10% may not be labelled because either they were generated before the 12 day injection regime, after injection but before sacrifice or in between the daily injections. 76% of all BrdU positive cells were also DCX positive therefore most differentiate to neurones. 95% of DCX positive cells expressed TuJ1 (an immature neuronal marker), none expressed nestin (which indicates an undifferentiated state) or glial markers, demonstrating its sensitivity and specificity. No DCX cells were positive for TUNEL staining (a measure of apoptosis) despite many reports that around 50% newly generated neurones die by 4 weeks. Neurones could lose their DCX immunoreactivity as they become apoptotic; they could be dying via another mechanism other than DNA fragmentation (which is what TUNEL mea-

tures); or simply, apoptosis may be occurring in temporal clusters, missed when the rats are sacrificed. In addition to measuring neurogenesis, in thicker brain slices DCX accurately demonstrates dendrites and can be used to quantify dendritic outgrowth.

The validation of DCX to measure neurogenesis is a very exciting development because it overcomes many of the problems encountered when using BrdU:

- No injections are required with DCX
- It is less stressful for the animal
- There are no problems with under- or overestimating labelled cells
- There are no concerns about killing cells as with high dose BrdU regimes
- Some neuronal markers are not very specific, and one must rely on neuronal markers when using BrdU
- Importantly, DCX can be used in human PM tissue where BrdU clearly cannot.

More work needs to be done, however, to validate DCX in different species, different brain regions and in lesioned or diseased brains. -WAT

Efficacy of doublecortin as a marker to analyse the absolute number and dendritic growth of newly generated neurones in the adult dentate gyrus.

Rao MS, Shetty AK

EUROPEAN JOURNAL OF NEUROSCIENCE

2004 (19) 234-246

☆☆☆ RECOMMENDED

CELL THERAPY: Regenerative capacity of the human brain called into question

Cell therapy is a potential neuroreparative strategy to combat neurodegenerative disease. One approach is to transplant cells directly into the diseased brain, but the two well publicised randomised controlled trials in Parkinson's disease have produced mixed results despite promising preclinical rodent and primate data. Alternatively, it might be possible to stimulate stem cells in the adult human to repair the brain from within, much like the regeneration seen in some non-mammalian vertebrates. It is known, for example, that precursor cells exist in the adult human brain in the subventricular (subependymal) zone around the lateral ventricles and the dentate gyrus of the hippocampus.

A recent study by Sanai *et al* has cast new light on these issues. They studied 65 neurosurgical brain specimens and 45 from autopsy, and revealed two key findings. Firstly, stem cells were found in a subventricular band around the lateral ventricles. Staining with Ki-67 (a nuclear protein associated with DNA synthesis and cell division) revealed that $0.77 \pm 0.29\%$ of these cells were in division, but none expressed markers of immature neurons, suggesting a lack of endogenous neurogenesis in this area. When removed and grown in culture these cells differentiated to neurons, astrocytes and oligodendrocytes, suggesting that the stem cells retained potency but were restrained by their environment *in vivo*.

Secondly they failed to demonstrate the rostral migratory stream - a band of neuroblasts seen migrating from their origin in the subventricular zone towards the olfactory bulb in adult rodents. Thus there are fundamental differences between the human brain and the brains of other mammals commonly used to model neurodegenerative disease. This would suggest that we exercise caution in interpreting data from animal models of disease, and restrain from rushing prematurely into clinical trials. -AWM

Unique astrocyte ribbon in adult human brain contains neural stem cells but lacks chain migration.

Sanai N, Tramontin AD, Quinones-Hinojosa A, Barbaro NM, Gupta N, Kunwar S, Lawton MT, McDermott MW, Parsa AT, Manuel-Garcia Verdugo J, Berger MS, Alvarez-Buylla A.

NATURE

2004; 427 740-744

NEUROPSYCHOLOGY: Out of body experiences

This fascinating article reviews the literature pertaining to out of body experiences (OBE) and related phenomena, and reports extensive data from 6 patients. The authors point out that while related perceptual disturbances such as phantom limb have a neuroscientific correlate, this is not the case for OBE, which has remained partially in the domain of mythology and mysticism.

Three autoscopic phenomena (AP) are described according to visuospatial perspectives: autoscopia (AS), he-autoscopia and OBE. Patients who experience AS see a parasomatic body from their own visuospatial perspective, while patients with OBE see themselves from the perspective of their parasomatic body, and he-autoscopia is between these two states (with alternating, but not simultaneous perspectives). Whereas all AP are characterised by a disintegration of personal space, OBE also represents disintegration between personal and extrapersonal space. AP have been reported in psychiatric, neurological and 'normal' cases (prevalence of around 10%, 1-2 per lifetime).

6 patients were employed for this study and underwent detailed questioning pertaining to the phenomenology of the experience, clinical examination, surface EEG, MRI (T1, T2, FLAIR), PET, and SPECT. Results of neuroimaging were superimposed onto 3D MRI to visualise the exact lesion location. 5 of 6 patients had frequent complex partial epilepsy without generalisation, and the other had presumptive TIA from complicated migraine. One epileptic patient had OBE while undergoing cortical stimulation (as part of the epilepsy surgical workup). One patient experienced AS; three he-autoscopia; and three OBE.

A variety of emotions were reported during AP: three experienced fear; two felt the experience was surprising and intriguing and one felt joy. AP (particularly OBE) tended to be very vivid - indeed there have been reports of patients jostling with and talking to their parasomatic bodies. The parasomatic bodies are recognised as 'self' despite some patients seeing only parts, from behind, wearing different clothes/ being of a different age etc., suggesting that self-recognition is only partially visual.

While memory was relatively spared (in contrast to medial temporal lobe epilepsy), language and praxic deficits and agnosias predominated, localising dysfunction to the posterior temporal-parietal region. EEG and imaging studies localised dysfunction primarily to the temporoparietal junction (TPJ). During AP, patients underwent brief or partial impairments of consciousness except in the patient who experienced OBE during cortical stimulation.

The authors remind us that continually updated integration of sensory (proprioceptive, tactile, visual) with vestibular information (including discarding of inconsistent information) is required for our central representation and relation to extrapersonal space. They speculate that failure of such integration, by the TPJ, may lead to the experience of seeing one's body in a position which does not concur with where it is felt; thus generating AP. Lesions of the TPJ can lead to visuo-spatial neglect, is activated during egocentric perspective shifts in normal subjects, and physiologically, is important in processing and integrating sensory inputs. The authors hypothesise that vestibular disintegration is also required for AP. Vestibular function is more disturbed in OBE as opposed to AS, and this could give rise to the sensation of the parasomatic body floating upwards from the real one. With AS, other types of sensory information may be dysfunctional e.g. body part illusions were experienced, sometimes only part of the parasomatic body was seen, and the position of the experient's body dictated that of the parasomatic. OBE tended to occur when the patient was supine, and AS when sitting or standing.

In summary, the authors have provided a detailed study of six patients with this rare but intriguing condition and proposed a neurological basis for it; the paper is well worth reading, particularly the patient's descriptions (including pictorial) of their experiences. -WAT

Out-of-body experience and autoscopia of neurological origin.

Blanck O, Landis T, Spinelli L, Seeck M. BRAIN

2004; 127: 243-258

For reasons of space, you can find the following additional reviews on our web site at www.acnr.co.uk/contents.html, under journal reviews

RECOMMENDED - MOTOR NEURON DISEASE: Dysfunctional Glutamate Receptors in Sporadic ALS - LMS, SJT
RNA editing and death of motor neurons: Kawahara Y, Ito K, Sun H, Aizawa H, Kanazawa I, Kwak S. NATURE

RECOMMENDED - EPILEPSY: Buzzing the Pleasure Centre - MM
Ictal pleasant sensations: cerebral localization and lateralization.
Stefan H, Schulze-Bonhage A, Pauli E, Platsch G, Quiske A, Buchfelder M and Romstöck J. EPILEPSIA
Drugs for idiopathic epilepsy. - MRAM

The relationship between treatment with valproate, lamotrigine, and topiramate in the generalised epilepsies: Nicholson A, Appleton RE, Chadwick DW and Smith DF. JOURNAL OF NEUROLOGY NEUROSURGERY AND PSYCHIATRY
Epilepsy and hormones - MRAM

Intercital EEG discharges, reproductive hormones, and menstrual disorders in epilepsy: Herzog AG, Coleman AE, Jacobs AR, Klein P, Friedman MN, Drislane FW, Ransil BJ, Schomer DL. ANNALS OF NEUROLOGY

CREUTZFELDT-JAKOB DISEASE: Diagnosis of sporadic Disease. - AJL

Prion deposition in olfactory biopsy of sporadic Creutzfeldt-Jakob disease: Tabaton M, Monaco S, Cordone MP, Colucci M, Giaccone G, Tagliavini F, Zanusso G. ANNALS OF NEUROLOGY

REHABILITATION: Eyes closed for better balance after stroke - AJT
Reliance on visual information after stroke. Part II: Effectiveness of a balance rehabilitation program with visual cue deprivation after stroke: a randomised controlled trial: Bonan IV, Yelnik AP, Colle FM, Michaud C, Normand E, Panigot B, Roth P, Guichard JP, Vicaut E. ARCHIVES PHYSICAL MEDICINE AND REHABILITATION

PAIN: Integrins are integrally involved in mediating pain states - LMS, SJT
Integrin signalling in inflammatory and neuropathic pain in the rat: Dina OA, Parada CA, Yeh J, Chen X, McCarter GC, Levine JD. EUROPEAN JOURNAL OF NEUROSCIENCE

NEURODEGENERATION: keeping active is good for the brain - RAB
Environmental Enrichment Rescues Protein Deficits in a mouse model of Huntington's disease indicating a possible disease mechanism: Tara Spiess et al. JOURNAL OF NEUROSCIENCE