

## EDITOR'S CHOICE

**Improving the outcome of spinal cord injury**

When the spinal cord is injured, astrocytes form scars that act as physical barriers to axon growth. In addition there is a chemical barrier: the extracellular space of such scars contains molecules that actively inhibit axon extension, including chondroitin sulphate proteoglycans. In this elegant study Stephen McMahon's group, at King's College London, investigate the effects of inhibiting chondroitin sulphate proteoglycans on recovery from a spinal cord injury. Adult rats received a dorsal column crush at C4, as well as an intrathecal injection of chondroitinase ABC, which degrades chondroitin sulphate proteoglycans. The controls were rats with no spinal injury and rats with a spinal lesion who received placebo. Chondroitinase ABC treatment increased the number of fibre bundles approaching and crossing the lesion (by cholera toxin B-subunit labelling of median nerve projections for ascending tracts and biotinylated dextran amine injected into the motor cortex for descending tracts). This increased anatomical connectivity was accompanied by a greater preservation of the dorsal column potentials evoked by electrical stimulation of the motor cortex. Most importantly, chondroitinase ABC treatment was associated with improved function on behavioural tasks such as beam or grid walking, as well as an adhesive tape removal task (!). Lastly, (and it is hard not to smile when this antique test appears after such technological wizardry) the analysis of footprint traces from rats with inky feet shows that chondroitinase ABC preserves normal gait after animals with spinal lesions, unlike controls.

Chondroitinase ABC does not restore full anatomical connectivity across injured cord lesions. But it does so sufficiently to support a very real and useful improvement in function.

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E-Mail [AdvancesinCNR@aol.com](mailto:AdvancesinCNR@aol.com) or Tel. [Rachael Hansford on 0131 477 2335](tel:01314772335).

So it now becomes a candidate for clinical trials of spinal injury treatment, along with blockade of NogoA, neurotrophic factor treatment and cellular grafting.-*AJ*

**Bradbury EJ, Moon LD, Popat RJ, King VR, Bennett GS, Patel PN, Fawcett JW, McMahon SB.**

**Chondroitinase ABC promotes functional recovery after spinal cord injury.**

NATURE

2002;416(6881):636-40

## NERVE REPAIR

## ☆☆☆ RECOMMENDED

**Acute stroke: no Nogo = go?**

Nogo-A, originally known as NI-250, is a myelin-associated glycoprotein, originally characterised by Martin Schwab and colleagues, which inhibits neurite growth and causes growth cone collapse. A monoclonal antibody (mAb) to this protein, IN-1, was produced some years ago, and has been shown to promote CNS functional regeneration following various experimental lesions in neonatal and adult rats, as a consequence of axonal regeneration and/or neuroanatomical plasticity of uninjured pathways. The effects of IN-1 in acute stroke have now been examined.

Adult rats underwent unilateral middle cerebral artery occlusion (MCAO); some received IN-1 given by hybridoma xenograft, others a control mAb, others no treatment (all received cyclosporin immunosuppression, necessary to block rejection of the xenograft). Although stroke volume examined eight weeks postlesion did not differ between the groups, the animals receiving IN-1 showed 80% recovery of prelesion behavioural performance in a forelimb reaching task (grasping sucrose pellets), whereas the recovery in controls reached only 50% of baseline values. Anatomical studies showed that neuroanatomical plasticity paralleled functional recovery, with the development of increased projections from the intact primary motor cortex to the contralateral red nucleus (the corticorubral projection in rats is mostly ipsilateral).

Of course caution is appropriate in interpreting these findings, since there are many claims for treatments that improve outcome from MCAO in experimental animals, some of which have failed to translate to the clinical arena. However this study does suggest that the CNS has regenerative potential which if exploited, by providing a permissive environment for axonal growth by blocking growth inhibitory factors, may lead to meaningful functional recovery.-*AJ*

**Papadopoulos CM, Tsai S-Y, Alsbie T, O'Brien TE, Schwab ME, Kartje GL.**

**Functional recovery and neuroanatomical plasticity following middle cerebral artery occlusion and IN-1 antibody treatment in the adult rat.**

ANNALS OF NEUROLOGY

2002;51(4): 433-441

## ☆☆☆ RECOMMENDED

**Adult neural stem cells are useful**

These two recent papers have demonstrated that adult neural stem cells do form functional neurons. There has been a long standing debate as to whether the cells labelled in the adult mammalian brain with markers of proliferation, such as BrdU, are of any functional significance. Last year it was demonstrated by Shors *et al* that inhibiting dividing cells in the adult brain of rodents could affect trace memory formation (Shors TJ *et al* (2001) Nature

410:314-315). However this was only circumstantial evidence to support the contention that adult neural stem cells (NSCs) can be incorporated into host circuits with functional effects. Now Gage and colleagues have shown that adult rodent NSCs can form functionally active neurons in vitro and Frisén and colleagues have done the same in vivo.

Song *et al* took GFP labeled adult NSCs and studied them in vitro for their intrinsic electrical properties; capacity to respond to synaptic stimuli and the release of neurotransmitter. This is a beautiful, elegant and extensive study as is typical from the Gage laboratory, and is a tour de force of scientific work. In all cases the GFP NSC were shown to be similar to the primary embryonic neurons, although this was contingent on how the cells were grown - for example the nature of the substrate used in culture and the use of BDNF.

The study by Frisén *et al* took a different approach using BrdU to label the endogenous NSC population, and then trace their connections using specific viral vectors linked to GFP. This demonstrated that BrdU positive cells could be incorporated into circuits, both in the olfactory bulb and hippocampus, and that, in the case of the olfactory system, they responded to olfactory odour stimulation.

These two studies are important in highlighting that adult NSCs can differentiate into electrically active neurons and become incorporated into functional circuitry in the adult mammalian brain. The question that now needs answering is what regulates this process physiologically and what is its role - **RAB**

**Song H-J, Stevens CF, Gage FH.**

**Neural stem cells from adult hippocampus develop essential properties of functional CNS neurons.**

**NATURE NEUROSCIENCE**

**2002 5: 438-445**

**Carlen M, Cassidy RM, Brismar H, Smith GA, Enqvist LW, Frisén J.**

**Functional integration of adult-born neurons.**

**CURRENT BIOLOGY**

**2002 12:606-608**

## NEUROPSYCHOLOGICAL REHABILITATION

### ☆☆☆ RECOMMENDED

#### Assessing money management in rehabilitation

The ability to carry out monetary transactions with competence is a crucial aspect of functional independence and therefore an important area for rehabilitation. In severe instances when a person is incapable of managing their own affairs an appointee may take over this role. But how is financial acumen to be assessed? Many people have difficulties handling money on a daily basis after brain injury and yet there have been few attempts to investigate this problem. Following a brief but useful review of previous attempts to incorporate monetary skills into assessment, this paper reports on the development of a specific tool: the Assessment of Functional Monetary Skills (AFMS). This is a structured assessment protocol for investigating various aspects of monetary understanding, and includes: identification of coin/note denomination and ability to carry out written and mental arithmetic in a financial context. In addition, there is a procedure for investigating how effectively people carry out real-life transactions, including paying of bills and writing cheques. The AFMS is presented as a means of identifying problems and measuring change in response to intervention, not a basis for any specific treatment. A case study is provided but there is little by way of useful clinical information to correlate with monetary performance. However, the issue is important and very common in rehabilitation. For this reason this is a paper that many therapists will want to read, if only to stimulate them to

producing something more structured in their own practice. -**ADW Gaudette M, Anderson A.**

**Evaluating money management skills following brain injury using the assessment of functional monetary skills.**

**BRAIN INJURY**

**2002: 16: 2: 133-148**

#### Disorders of everyday action may be caused by multiple impairments

Action in everyday contexts or 'naturalistic action' is belatedly attracting the attention of cognitive scientists. This paper is one of a number of contributions to a journal special issue on Everyday Action and has interesting implications for clinicians who are regularly confronted with similar problems. Forde and Humphreys contrast the performance of two patients, HG and FK, who have difficulties carrying out basic tasks such as making a cup of tea, preparing a sandwich, and wrapping up a gift. Both patients were disorganised and made many perseverative errors. In an earlier paper the authors suggested that HG's difficulties arose from a failure of inhibition of a specific action once it had already been performed (rebound inhibition). In contrast, FK was thought to show a deficit in the activation of components of action over the duration of a task (impairment in an activation gradient). Whereas HG improved when given one action to complete at a time, FK's performance did not improve with written and visual prompts, but deteriorated when interrupted. Through a series of experimental manipulations the authors argue that FK shows damage to a store of action sequences and to an executive system for monitoring performance. This paper is useful to therapists on three accounts. First, the method of investigating deficiencies in everyday tasks can be adapted for routine clinical use. Second, the detailed analysis of actions illustrates the complexity of routine behaviours and thus militates against oversimplifications in interpretation. Third, it suggests that at least some forms of the disorder are amenable to intervention and this may be dependent on the nature of the underlying deficit. -**ADW**

**Forde E M E, Humphreys G W.**

**Dissociations in routine behaviour across patients and everyday tasks.**

**NEUROCASE**

**2002: 8: 151-167**

#### Picture this - I must remember to E.T (phone home)

Evidence for effectiveness of intervention for cognitive deficits is often limited to single case experiments. The need for individualisation of treatment and the length of time that training takes limits the number of cases that can be studied in any one centre. A newly published memory training study has pooled resources from 7 centres in Europe so that the effect of using imagery as a strategy for improving memory in 21 brain-damaged patients was assessed. Imagery proved to be an effective and useful strategy for patients with mild to moderate memory impairment.

Patients with mild memory impairment such that it might prevent effectiveness and functioning at work were included in the study. Patients with severe memory loss or other cognitive deficits such as neglect, apraxia, agnosia and aphasia were excluded. The patients were randomly allocated to the imagery-training group or to a control group. The imagery group were taught to generate images of objects and actions rapidly until they could recall 8/10 items. They were also helped to apply imaging to their own daily living needs. The control group received the kind of memory training they would normally have received in their respective centre. This included various internal and external strategies such as face-name associations, keeping notebooks and calendars.

The design was ABA, with 4 weeks of baseline, ten weeks of training (3 times a week) and a three month follow-up period in which no training was given. A variety of memory assessments were used, imagery training was expected to lead to improved

performance on some of them. The results were in keeping with the researchers predictions. Imagery training significantly improved recall of everyday verbal materials, e.g. stories, appointments and the frequency of memory problems observed by relatives was reduced. What's more these effects lasted over the follow up period.

There is strength in numbers. This study will carry more weight than 20 reports of n=1 studies that might be produced over years. Rehabilitation research into cognitive deficits must benefit from collaborative studies such as this one. -AJT

**Kaschel R, Della Sala S, Cantagallo A, Fahlböck A, Laaksonen R, Kazen M.**

**Imagery mnemonics for the rehabilitation of memory: a randomised group controlled trial.**

NEUROPSYCHOLOGICAL REHABILITATION

2002; 12: 127-153

## EPILEPSY

### ☆☆☆ RECOMMENDED

#### Do seizures damage the brain?

This longstanding debate remains without a clear answer but the current study does move it forward. It has long been known that the hippocampus is damaged by seizures in animals and that severe acute insults can damage the hippocampus in humans. Studies are compounded by complicating factors such as head injury from seizures and bouts of status epilepticus. What is not known is whether recurring seizures themselves cause a progressive deficit.

In this study 24 patients with well-lateralised TLE were followed from diagnosis and subjected to repeat MRI scans with hippocampal volume measurements after 3.5 years. The diagnosis of TLE was made on the basis of EEG and clinical criteria and all patients had a normal initial MRI. They were 30 +/- 14 years of age, so not in the usual age group for hippocampal sclerosis (HS) to be the cause of their seizures.

Epilepsy was generally mild and 15 patients had 0-1 generalised tonic clonic seizures (GTCS) and 9 had 2-8 GTCS during the follow-up period. One patient developed clear signs of hippocampal sclerosis on MRI and the others developed signs of hippocampal volume loss, of the order of 10-25%, which correlated strongly with the number of GTCS during follow-up.

This study provides evidence that even quite mild epilepsy can be damaging to the hippocampus and supports the century old view of the imperative to treat early. The hippocampus is however, a uniquely sensitive structure and whether this can be extrapolated to extratemporal epilepsy or whether the generalised epilepsies carry the same kinds of risks is even less clear. -MRAM

**Briellmann RS, Berkovic SF, Syngeniotis A, King MA, Jackson GD.**

**Seizure-associated hippocampal volume loss: A longitudinal magnetic resonance study of temporal lobe epilepsy.**

ANNALS OF NEUROLOGY

2002;51:641-4

#### To stop frowning on EEGs.....

Presurgical localisation of epilepsy hinges on accurate recording of electrographic seizure onset. A number of factors may hinder recordings and commonly artefact arising from scalp muscles from ictal motor activity is responsible. Traditionally the way to overcome this is to insert electrodes intracranially. The authors reduced scalp muscle activity by injecting botulinum-A (BTX) 100 units between temporalis and frontalis muscles. A week later patients underwent EEG and were asked to perform various facial contortions. If there was still significant artefact on EEG, a further 50-100 units were injected into muscles responsible.

Twenty-four seizures were recorded in 3 patients, 12 before and 12 after BTX injection.

They were reported blind. Prior to BTX only one seizure was localisable (3 lateralisable) whereas afterwards 8 were localisable. There were no adverse effects and muscle activity returned to normal after 8, 11 and 15 weeks.

The authors should be congratulated on lateral thinking to try and solve a problem with a benign, readily available procedure, potentially avoiding highly invasive intracranial EEG. How widely applicable this will be remains to be seen. -MRAM

**Eisenschenk R, Uthman B, Valenstein E, Gonzalez R.**

**Botulinum toxin-induced paralysis of frontotemporal muscles improves seizure focus localisation.**

NEUROLOGY

2002;58:246-249

#### Stopping heart stop

The central nervous system has well-established effects on the heart. A hierarchy of autonomic control is recognised involving cortical levels of modulation. It is therefore perhaps not surprising that epilepsy can result in changes of cardiovascular physiology. However, the precise dynamics are not well understood and need to be elucidated in view of their potential role in sudden unexpected death in epileptic patients (SUDEP). Surges of sympathetic outflow have been postulated to occur during seizures, which may then contribute, to the pathophysiology of SUDEP. Temporal lobe epilepsy is particularly troublesome in causing changes in autonomic activity and case reports of ictal associated tachycardia or bradycardias are frequently documented. Interestingly interictal changes of sympathetic cardiovascular tone have also been demonstrated.

To address this relationship further, Hilz and colleagues have studied autonomic parameters before and after surgery in 18 TLE patients. Variability of heart rate and blood pressure were determined (power spectral analysis) incorporating changes attributable to respiration.

Each signal had a combination of high and low frequency analysis. Calculation of baroreceptor sensitivity was also performed derived from the relationship between these parameters. The standard measures of cardiovascular function did not change. Low frequency components of HR and BP showed an average reduction of over 40% following surgery. Baroreceptor sensitivity also changed. This supports the conclusion that sympathetic tone is augmented in TLE patients. This is a reassuring study and implies that surgery should be accompanied by a reduced risk of cardiovascular emergencies in epilepsy patients. -JLR

**Hilz A, Devinsky O, Mauerer A and Dutsch M.**

**Decrease of sympathetic cardiovascular modulation after temporal lobe epilepsy surgery.**

BRAIN

2002; 125:985-995

## MULTIPLE SCLEROSIS

### ☆☆☆ RECOMMENDED

#### Independent COMparisons of INterferons - INCOMIN: Alternate day Interferon beta-1b versus weekly Interferon beta-1a

In a world where evidence based medicine requires very large randomised double blind placebo controlled studies, direct comparisons between two similar drugs from different manufacturers are rare. Even more so if such a study is completely independent of any sponsorship or links in some form or other to one of the firms concerned. It is therefore pleasing to see that the INCOMIN trial study group has been able to undertake a direct comparison study of two of the three available interferons for relapsing remit-

ting multiple sclerosis as they are currently licensed, guiding our prescription habits in an evidence based manner, albeit with relatively small numbers. The basic protocol employed in this independent study was a 2-year prospective randomised multi-centre study with 96 patients in the beta-1b, alternate day administration, (Betaferon) limb and 92 patients in the beta-1a, weekly (Avonex) limb of the study. Outcome measures were proportion of patients remaining relapse free, clinically and radiologically (no new proton density/T2 lesions). In those receiving alternate day therapy 51% remained relapse free compared to 36% receiving weekly treatment (relative risk 0.76,  $p=0.03$ ) and similarly 55% developed no new radiological lesions compared to 26% (relative risk 0.6,  $p<0.0003$ ). On these grounds alternate day therapy is superior in effect. However, unsurprisingly injection site reactions were significantly more common in the alternate day group but this did not impact on compliance and could be minimised by improved injection technique, the authors suggest. Significantly more patients in the alternate day group generated neutralising antibodies, which adds to the controversy of the role of these antibodies. The observed increased effectiveness in the presence of increased antibody formation would support the argument that these antibodies do not have any effect on the treatment response.

The study design does not allow comparisons to be drawn about which agent is more potent (and clearly does not involve the third commercially available interferon-beta, Rebif) but does suggest that the frequency of administration maybe crucial. -TH

**Durelli L, Verdun E, Barbero P, Bergui M, Versino E, Ghezi A, Montanari E, Zaffaroni M, and the Independent Comparison of Interferon (INCOMIN) Trial Study Group.**

**Every-Other-Day Interferon Beta-1b Versus Once Weekly Interferon Beta-1a For Multiple Sclerosis: Results Of A 2-Year Prospective Randomised Multicentre Study (Incomin)**

LANCET

2002; 359: 1453-60

## Type 1 diabetes mellitus (DM) and multiple sclerosis (MS) in Sardinia

This relatively simple cohort epidemiological study undertaken in Sardinian families with MS reveals a surprising finding when compared to studies on other populations but does raise some interesting observations about the genetics of MS in this population. Sardinians are at high risk of developing MS and DM. This study demonstrates that epidemiologically there is a link in this population between these two autoimmune diseases, with DM being three-fold more prevalent in patients with MS compared with their healthy siblings but importantly DM was found to be five-fold more prevalent than the general population. At first sight this observation may be at odds with most Northern European studies with respect to MS and DM where no such link has been observed. But on closer examination of HLA haplotypes in Sardinian and other Northern European populations, some sense can be made of this apparent contradiction. Coraddu *et al* found that the most preva-

lent HLA haplotype profile of the Sardinian population with MS was DRB1\*0301-DQA1\*0501-B1\*0201 which is different from other MS populations where the haplotype (DRB1\*1501-DQA1\*0102-B1\*0602) is more common. This latter haplotype in fact bestows protection against DM and susceptibility to MS, whereas the Sardinian haplotype is a known risk factor for DM and other autoimmune diseases such as coeliac disease, autoimmune thyroiditis, Addison's disease and atrophic gastritis. So, together with the HLA haplotype profile and epidemiological evidence from this study, common genes are implicated in the susceptibility to both diseases in this population and the genes may be located in or around the HLA region. -TH

**Marrosu MG, Cocco E, Spinicci G, Pischedda Contu P.**

**Patients With Multiple Sclerosis And Risk Of Type 1 Diabetes Mellitus In Sardinia, Italy: A Cohort Study.**

LANCET

2002; 359: 1461-65

## T cells attack MOG

We have yet to identify the antigen targeted by the immune system in multiple sclerosis (MS). Myelin basic protein (MBP) and proteolipid protein (PLP) are both major constituents of myelin in the peripheral and central nervous system. They are therefore not ideal candidate antigens for a condition confined to the CNS. Myelin oligodendrocyte glycoprotein (MOG) is a quantitatively minor constituent of myelin present exclusively within the central nervous system, and therefore an interesting protein to investigate in the context of MS.

Koehler *et al* recruited four sibling pairs discordant for MS, One of the MS affected sibs had been treated with Interferon-beta. All sibs within a given family were haplo-identical. MOG reactive T cell clones (TCC) were generated by culturing the cells in the presence of MOG proteins. TCCs were then incubated with antigen presenting cells and 11 synthetic MOG peptides (all representing portions of the extracellular domain of the MOG peptide) or recombinant MOG protein. The cytokines produced were quantified by the use of ELISAs and cell phenotype was established using flow cytometry.

A total of 235 TCCs reactive to MOG peptide were isolated in the cohort overall, although only four from the patient treated with Interferon-beta. All the TCCs were CD4+. Challenging the TCCs with the 11 MOG epitopes in proliferation assays revealed no single dominant epitope shared between subjects, or even haplo-identical siblings. The cytokines produced by the TCCs on exposure to MOG varied between individuals. TCCs from one MS affected sibling produced a Th1 (cytotoxic- IFN- $\gamma$  and TNF- $\gamma$ ) pattern of cytokines. This was not seen in the unaffected siblings in whom a mixture of profiles was identified - Th2 (predominately IL-4), Th0 (IL-4 and IL-6) and Tr1 (regulatory- IL-10). The pattern of cytokines produced remained consistent despite repeated stimulation.

This paper reports the presence of MOG reactive T cells in nor-

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mal healthy individuals and those with MS (reduced in number in interferon-beta treatment). It identifies no single immunodominant epitope on MOG and demonstrates that TCCs from healthy and MS sibs produce different cytokine profiles on stimulation. The authors speculate that the loss of regulatory control of these MOG reactive T cells could result in demyelination. Unfortunately the cohort studied in this paper was too small to draw conclusions about the pathogenesis of MS, except to identify this as a protein worthy of further investigation. -ALC

Koehler NK, Genain CP, Giesser B, Hauser SL.

**The human T cell response to myelin oligodendrocyte glycoprotein: a multiple sclerosis family-based study.**

JOURNAL OF IMMUNOLOGY

2002, 168:5920-5927

### Chips in Multiple Sclerosis

#### ☆☆☆ RECOMMENDED

Gene chips are the technological cutting edge of gene expression analysis. One chip allows the simultaneous analysis of expression of tens of thousands of genes. They are relatively easy to use, but their results present a considerable bioinformatics headache! Other gene expression techniques (such as SAGE) are harder to use, but have the advantage over chips that they can pick up unknown genes, whereas chips rely on a library of known genes and expressed sequence tags.

Lock *et al.* used Affymetrix chips to compare genes expressed in CNS lesions from 4 patients with MS, and two controls without neuropathology. The four MS samples were classified histologically into acute/active and chronic/silent lesions. Genes demonstrated to be up or down regulated were identified and analysed.

Differences in gene expression between MS and control samples were identified. Of the genes that were up regulated, a number of immune response genes were identified such as MHC class II, IgG and genes suggesting the activation of T cells, B cells, macrophages and complement. Genes reflecting proinflammatory

cytokine activity were also up regulated in all MS lesions. There was an elevation in several stress related genes and genes reflecting astrocyte activity. Of the genes that were down regulated the most significant were those associated with myelin proteins and neuron specific genes such as proteolipid protein and neuronal growth protein.

Differing gene expression was identified between the acute and chronic lesions. Genes elevated in the acute lesions included variable-joining-constant region immunoglobulin (125 fold), a MAP kinase and various growth factors including insulin growth factor-1 and G-CSF. In the chronic lesions, integrin / was elevated. Various gene transcripts associated with Th2 or allergic response were also elevated including the histamine receptor H1, IgE receptor and IgG Fc receptor. In addition a number of matrix metalloproteinases (MMP) were elevated, IL-17 and various neuroendocrine molecules.

One of these proteins was tested therapeutically using an animal model of demyelination - experimental allergic encephalomyelitis (EAE). G-CSF (elevated 13 fold in active compared with chronic lesions) given prior to onset of EAE prolonged time to disease onset and reduced the severity of the acute phase of the disease. Also the role of IgG Fc receptor was tested, as its expression was elevated in chronic lesions; in Fc3 receptor knockout mice the chronic phase of EAE became less severe.

This study demonstrates the power of gene chip analysis to monitor the dynamics of gene expression changes between tissues, and will probably be the best way to investigate the mechanisms of action of the susceptibility alleles identified by genome studies. Also, such studies may identify potential therapeutic targets for disease modification in MS. -ALC

Lock C, Hermans G, Pedotti R, Brendolan A, Schadt E, Garren H, Langer-Gould A, Strober S, Cannella B, Allard J, Klonowski P, Austin A, Lad N, Kaminski N, Galli S J, Oksenberg JR, Raine CS, Heller R, Steinman L.

**Gene-microarray analysis of multiple sclerosis lesions yields new targets validated in autoimmune encephalomyelitis.**

NATURE MEDICINE 2002 May;8(5):500-8

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