

EDITOR'S CHOICE

Imagine that...

The notion of using cerebral activity to control external electronic devices and movement has always been regarded as belonging in the realm of fantasy. The idea is that people with high spinal cord lesions, but intact supraspinal structures, could use electrical signalling from these intact pathways to bypass the obstruction and activate muscles and devices which in turn may be able to control actions. This interesting area has currently been highlighted in two papers in *Nature* and an excellent 'News and Views' article by Stephen Scott in the same issue. One of these studies involves a single patient and the second is a primate study, the details of which are somewhat harder to extract. In the first study by Hochberg et al, a single patient (MN) with a complete C3-4 spinal cord lesion was studied. He received this traumatic lesion (from a knife) in 2001 and had an array of electrodes implanted into the M1 motor arm area in June 2004, with data collected over a nine month period. The patient was then trained to think about doing an action which then was translated into moving a cursor on a computer screen, a process that was only made possible by previous work looking at motor cortical neuronal firing in non-human primates. As the authors conclude "These results indicate that, even years after spinal cord injury and in the absence of kinaesthetic feedback and limb movement, M1 neurons can still be actively engaged and encode task-related information during the intention to move the limb ordinarily controlled by that M1 region". Whilst of limited clinical and practical value, this is nevertheless a clear demonstration that using neuronal activity to think about movements in the absence of a motor pathway still enables the brain to control actions through electronic interfaces. The second study by Santhanam et al is more technical and seeks to improve the information throughput that such systems will require in order to be more efficient and effective using the primate dorsal premotor cortex as the site of signal collection. Whilst there remain major problems in the widespread adoption of these approaches, these studies are very exciting new developments and build on the established use of cochlea implants as well as functional electrical nerve stimulation for locomotion and standing in paraplegic patients (see the review by Johnston et al in this issue of the ACNR). Indeed as our ability to use electronic technology improves in parallel with our better understanding of motor cortical control of movement, we can expect to see advances such as this which could ultimately radically change the prognosis and outlook of patients with spinal cord lesions. - **RAB**

Scott S H.

Neuroscience: converting thoughts into action.

NATURE

2006;442:141-2.

Hochberg LR, Serruya MD, Friehs GM, Mukand JA, Saleh M, Caplan AH, Branner A, Chen D, Penn RD, Donoghue JP.

Neuronal ensemble control of prosthetic devices by a human with tetraplegia.

NATURE

2006 Jul 13;442(7099):164-71.

Santhanam G, Ryu SI, Yu BM, Afshar A, Shenoy KV.

A high-performance brain-computer interface.

NATURE

2006 Jul 13;442(7099):195-8.

CARPAL TUNNEL SYNDROME: Endoscope or get a better job

Carpal tunnel release is one of the most frequently performed surgical procedures: 350,000 annually in the US. And recently endoscopic methods have been introduced with the claimed benefit over traditional open surgery of less pain and more rapid return to work. This Swedish group puts that claim to the test in a single-centre study of 128 patients. The number of patients reporting pain at three months was 33 (52%) in the endoscopic group and 53 (82%) in the open group, giving a number needed to treat of 3.4 (95% C.I 2.3 to 7.7). Taking into account the operating time (nine minutes for the endoscopic method and 15 minutes for the open technique), and using some dodgy maths, this means endoscopy is 5.6 more times effective at reducing pain per operating session..... Before the accountants get too excited, there was no difference in the number of patients reporting improvement in symptoms (about 70% each group), or in the time off work. In fact, the main mes-

sage for work was that you went back sooner if you had a white collar job (median 21 versus 36 for 'blue collar'). There must be a moral in that ... quite what I am not sure...-**AJC**

Atroshi I, Larsson GU, Ornstein E, Hofer M, Johnsson R, Ranstam J.

Outcomes of endoscopic surgery compared with open surgery for carpal tunnel syndrome among employed patients: randomised controlled trial.

BRITISH MEDICAL JOURNAL

2006;332:1473.

EPILEPSY: A reassuring lack of progress

Unverricht-Lundborg disease is classed as one of the progressive myoclonus epilepsies (PME), characterised by epilepsy, ataxia and myoclonus with less cognitive decline than is seen in some PME. Twenty patients from Southern France and Northern Italy were identified with this condition and followed for a mean of 25.7 years. Mean age of onset was 12 years (range 6 to 17). They were last assessed in 2002. Fourteen walked independently and seven of these were in full time employment. Three walked with support, two were wheelchair-bound and one was bed-ridden. Eighteen patients had normal intellectual function, two had mild impairment. One patient had never had a major seizure and three had only ever had one seizure each. After ten years, median seizure frequency was less than one per year. Treatments were generally valproate, clonazepam, levetiracetam or piracetam. The main disabling symptom for most patients was myoclonus, which was classed as moderate to severe for most patients, on a criterion based on interference with ambulation. This study highlights exactly how good the prognosis is of this condition compared to other causes of PME. - **MRAM**

Magaudda A, Ferlazzo E, Nguyen V-H, Genton P.

Unverricht-Lundborg disease, a condition with self-limited progression: long-term follow-up of 20 patients.

EPILEPSIA

2006;47:860-66.

HEADACHE: Glutamate and trigeminal activation

Much headache research has focused on electrophysiological and other studies of the neuronal pathways activated in cranial nociception, in attempts to understand the pathology of migraine and other head pains. This article focused on the neurotransmitters involved in activation of pathways relevant to nociceptive processing in headache. The paper summarised data from microdialysis experiments in the rat trigeminal nucleus caudalis (TNC) during dural stimulation. Microdialysis allowed the direct measurement of changes in extracellular concentrations of neurotransmitters in vivo. Extracellular amino acids in the deep lamina of the trigeminal nucleus caudalis were quantified during stimulation of the dura with an inflammatory 'soup' compared to saline. After inflammatory application there was a transient decrease in glutamate levels at 30 minutes, followed by a three-fold increase at three hours. The latter correlated with changes in sensory thresholds on the face of the rat from electrophysiological recordings of secondary sensory neurons in the TNC. There were no changes in levels of another excitatory amino acid, aspartate, or the inhibitory amino-acids gamma-aminobutyric acid or glutamine. This work suggests that glutamate plays a role in central sensitisation of neurons in the trigeminal nucleus caudalis, and suggests an important role of glutamate in allodynia and hyperalgesia seen in headache. The authors postulate that increased extracellular glutamate may induce sensitisation of neurons with receptive fields outside the initial area of activation, and that this mechanism may be relevant to the increase in size of sensitive areas of the face that occurs during a migraine. It provides an experimental example of the neurochemical changes that may underlie an acute migraine episode. - **HAL**

Oshinsky ML, Luo J.

Neurochemistry of trigeminal activation in an animal model of migraine.

HEADACHE

2006;46(s1):S39-S44.

REPAIR: A cocktail for spinal cord injury

This John Hopkins group has been working for a while on transplanting motor neurones, derived from embryonic stem cells, to repair spinal cord damage, specifically in their case due to the 'neuradapted Sindbis virus' which selectively depletes motor neurons of adult rats. Their usual experience is that only 2% of the transplanted neurons get into the ventral roots and none connect with muscles, and – unsurprisingly – there was no functional recovery. This paper reports the effects of three strategies to promote the efficacy of the transplants... to good effect. In one group of animals, before transplantation, the ES cells were dipped in dibutyl cyclic adenosine monophosphate, which is believed to promote motor neuron survival and axonal growth.

Another group of animals were given rolipram subcutaneously; this inhibits phosphodiesterase type 4 and neutralises the inhibitory effects of myelin on axonal outgrowth. Finally, and cleverly, they transplanted other cells into the sciatic nerves of another groups of rats that were induced to secrete glial cell-line derived neurotrophic factor to attract growing axons out of the cord from the transplanted neurons. There were a few controls, and a few lucky rats got all the goodies. The outcome measures were comprehensive. By deriving their embryonic stem cells from animals knocked-in for green fluorescent protein under a motor neuron promoter, they were able to follow the fate of transplanted cells with ease. Only in the rats receiving all three treatments did GFP positive cells find muscle targets. They looked as though they had made anatomical connections, first noticeable at three months after transplantation, and had induced clustering of ACh receptors. Electrophysiological measurement of motor unit number (not straightforward in a rat, I would imagine) showed an improvement in the combination group only, first observed at four months. And this was the only group that showed any functional recovery, albeit incomplete. In a rather nice side-experiment, some animals had received motor neuron transplants into both sides of the spinal cord, but a GDNF-secreting transplant into only one sciatic nerve: there was only motor recovery on the GDNF side....Which goes to show three things. Firstly, that embryonic stem cells may yet live up to their promise as repair agents, despite initial disappointments. Secondly, as in so many other situations, that efficacy comes with complex combination treatments. And finally, that this very promising treatment would not have emerged without understanding the basic science of neuronal development. - *AJC*

Deshpande DM, Kim YS, Martinez T, Carmen J, Dike S, Shats I, Rubin LL, Drummond J, Krishnan C, Hoke A, Maragakis N, Shefner J, Rothstein JD, Kerr DA.

Recovery from paralysis in adult rats using embryonic stem cells.

ANNALS OF NEUROLOGY

2006 Jul;60(1):32-44.

STROKE: Releasing the potential for recovery

Recovery from stroke is hampered by the activity of the so-called 'unaffected' side. Just as the preferred and prevalent use of the unaffected hand can rob the impaired hand of its chance to practice and regain function, so too can the contralesional hemisphere of the brain dampen down activity in the lesioned hemisphere. But there is a way to foil the good hemisphere's controlling influence to give the poor damaged hemisphere more chance to marshal its remaining connections and improve the function of the impaired hand. A group in Boston have shown that inhibitory repetitive transcranial magnetic stimulation applied over the contralesional cortex results in better and long lasting performance of hand function, and in shorter simple and choice reaction times, in those with clumsy hands after stroke. The rTMS was delivered for 20 minutes a day over a course of five days, at a rate which has previously been shown to cause inhibition. Ten patients received this treatment and five others were randomly allocated to receive sham treatment. The performance of the rTMS patients' affected hands improved substantially more than the performance of their unaffected hands or the hands of the sham treated control patients. What is more, these differences were still evident at a follow up assessment two weeks later. Some people may be worried about the safety of rTMS as a treatment for stroke; after all these are people with damaged brains who are at greater risk of seizures than normal subjects. Cognitive function and EEG analysis showed no signs of deterioration with time or treatment group. These are very promising results from this phase II study. We'll wait now for the results of a larger RCT, but maybe in the future we'll be pepping up recovery in rTMS clinics. - *AJT*

Fregni F, Boggio PS, Valle AC, Rocha RR, Duarte J, Ferreira MJL, Wagner T, Fecteau S, Rigonatti SP, Riberto M, Freedman SD, Pascual-Leone A.

A sham controlled trial of a 5-day course of repetitive transcranial magnetic stimulation of the unaffected hemisphere in stroke patients.

STROKE

2006;37:2115-22.

EPILEPSY: Convulsive status in London's children – epidemiological data

Reliable epidemiological data is always helpful in guiding management and giving prognoses; so this study is to be welcomed. Over two years, from 2002-2004, all children aged 29 days to 15 years, living within a specific region of London, who were admitted with convulsive status epilepticus, were notified to the study. The catchment population was 605,230 and 226 children suffered status, for 176 of whom it was a first episode and 50 had suffered status previously. For 16% of patients the condition recurred in the first year. Using

an alternative ascertainment method, it was felt that case ascertainment in this study was 86%. This gave a crude incidence of first status of 17-23/10⁵ children per year. The highest incidence was in children under one year at 51/10⁵ compared with 29/10⁵ in those aged 1-4, 9/10⁵ in those aged 5-9 and 2/10⁵ in those aged 10-15. One third was febrile status and 17% were due either to acute metabolic derangement or CNS infection. Of those who also had a fever, 11% had bacterial meningitis. Children with a pre-existing neurological abnormality were 2.9 times as likely to have a recurrence in their first year. Seven children died. - *MRAM*

Chin RFM, Neville BGR, Peckham C, Bedford H, Wade A, Scott RC for the NLSTEPSS Collaborative Group.

Incidence, cause and short-term outcome of convulsive status epilepticus in childhood: prospective population-based study.

LANCET

2006;368:222-9.

DEMENTIA: Killing two birds with one stone

Frontotemporal dementia (FTD) is second only to Alzheimer's disease amongst the causes of dementia in mid-life. The FTD concept emerged in the last quarter of the twentieth century, applying to a heterogeneous group of conditions originally described by Arnold Pick some one hundred years earlier. All cases have in common clinical presentation with progressive impairment in behaviour and/or language function and severe focal atrophy of the frontal and/or temporal lobes. Within the spectrum of FTD is a range of clinical syndromes and a plethora of pathological, molecular and genetic abnormalities, which have become ever more complex with the passage of time. One FTD curiosity in particular concerns its genetic linkage to the chromosome 17q21 locus. The link to chromosome 17 was made as far back as the 1980s and the first mutations in the tau gene at 17q21 were reported in 1998, with many more tau mutations following. This resonated not only with the frequent occurrence of abnormal deposits of tau in the brains of FTD patients but also with tau deposition being a pathological hallmark of Alzheimer's disease (i.e. neurofibrillary tangles). The curiosity, however, rests in an increasing number of FTD families linked to chromosome 17q21 despite normal tau sequencing. The finding of Baker, Cruts and their respective colleagues, of null mutations in the progranulin gene at 17q 21 in familial FTD (12 different mutations in 20 families) is, therefore, not only highly significant but is unique among recent advances in FTD for making the field less rather than more perplexing. There is, of course, neurology 'trivia' value in the coincidence (unique?) of a single syndrome linked to one locus through two separate genes (2Mb apart). But the implications for our understanding of neurodegenerative disease, given that progranulin is a growth factor involved in inflammation, tissue repair and tumorigenesis are far from trivial. - *RD*

Baker M, Mackenzie IR, Pickering-Brown SM, Gass J, Rademakers R, Lindholm C, Snowden J, Adamson J, Sadovnick AD, Rollinson S, Cannon A, Dwosh E, Neary D, Melquist S, Richardson A, Dickson D, Berger Z, Eriksen J, Robinson T, Zehr C, Dickey CA, Crook R, McGowan E, Mann D, Boeve B, Feldman H, Hutton M.

Mutations in progranulin cause tau-negative frontotemporal dementia linked to chromosome 17.

Cruts M, Gijselink I, van der Zee J, Engelborghs S, Wils H, Pirici D, Rademakers R, Vandenbergh R, Dermaut B, Martin JJ, van Duijn C, Peeters K, Sciot R, Santens P, De Pooter T, Mattheijssens M, Van den Broeck M, Cuij I, Vennekens K, De Deyn PP, Kumar-Singh S, Van Broeckhoven C.

Null mutations in progranulin cause ubiquitinpositive frontotemporal dementia linked to chromosome 17q21.

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Journal reviewers

Heather Angus-Leppan, Royal Free & Barnet Hospitals;

Roger Barker, Cambridge Centre for Brain Repair;

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, Morrilton Hospital, Swansea;

Ailie Turton, Burden Neurological Institute, Bristol.