

EDITOR'S CHOICE

Friends in high places

The process by which the visual image is built up in the brain has been an area of controversy for many years. Simplistically this consists of two main opposing views. One is serial processing leading to hierarchy of processing areas/units culminating in a grandmother cell versus a parallel processing of information about different attributes of the image leading to object recognition via co-ordinated patterns / rhythms of activity. The former should predict cells/areas of high visual specificity such as 'face' recognition so that damage to it should lead to a selective deficit such as prosopagnosia. Experimentally, in non human primates, 'face specific neurons' have been recorded in the infero temporal cortex. This recording of single units has now been extended to humans in this recent study by Quiroga et al. A group of patients with intractable epilepsy had single unit recordings made from their medial temporal lobe. The recordings were made in response to a series of images of famous people viewed in different contexts. By so doing they were able to demonstrate that a number of units had very high specificity for that image irrespective of the context in which it was seen. So for example one cell could recognise different images of Jennifer Aniston out of nearly 100 different images, whilst others recognised Halle Berry again in the context of several different profiles and image presentations. This seemed to be a relatively consistent response and suggest that these cells recognise that person's face as a whole and not the combination of features that make up any old face. Of course whether these cells were involved in the perception or recognition and naming of that person's face is not clear, as opposed to simply representing a memory trace for that individual. However it does show that the specificity of stimuli stored in individual cells in the human brain is extraordinary. Of course it does make one worry about how much of one's own brain is cluttered up with irrelevant non-significant images. - *RAB*

Quiroga RQ, Reddy L, Kreiman G, Koch C, Fried I.

Invariant visual representation by single neurons in the human brain.

NATURE

2005 Jun 23;435(7045):1102-7.

Panel of Reviewers

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MIGRAINE: a new channelopathy

Clues that help to unravel the pathogenesis of any disease, and present opportunities to discover novel drug therapies, are always interesting. When the disease is as common as migraine, the interest generated is obviously heightened. In this paper, Dichgans et al. report a mutation in the SCN1A sodium channel, which causes familial hemiplegic migraine in three related families. The mutation inherits in an autosomal dominant manner and may cause the voltage-gated sodium channel to recover too quickly from fast inactivation leading to excessive neuronal firing. The authors speculate that this initiates the cortical spreading depression, considered the underlying mechanism behind migraine aura. However some important functional data has yet to be provided, owing to technical difficulties in introducing the mutation into SCN1A cDNA. SCN1A is now the third gene for migraine, joining the calcium channel gene CACNA1A (1996) and a Na⁺/K⁺ pump ATP1A2 gene (2003). The mutations in all three genes affect ion channel function, a fact in itself highly suggestive that more common forms of migraine also share an 'ionopathic' basis. It is worth noting however, that based on data from other linkage studies, further potentially novel migraine genes are expected in the future. At this early stage there are no clinical features that discriminate this gene from other hemiplegic migraineurs and the authors describe the phenotype as 'clear cut familial hemiplegic migraine'. An interesting quirk to the familial hemiplegic migraine story is the excess of co-morbid epilepsy in all three of the migraine genes, including three patients in this study that had infantile seizures. Furthermore, in familial forms of epilepsy, mutations have already been found in the SCN1A gene albeit that the causative mutations may have different functional consequences. These include 'generalised epilepsy and febrile seizures plus' and 'severe myoclonic epilepsy of infancy'. A common pathogenesis between these two paroxysmal disorders is likely, which may explain the efficacy of some anticonvulsants in migraine prophylaxis. Finally, one major dilemma facing medicine is the critical translational step from rare mendelian discoveries to relevance for common disease. This is not specific to migraine and a similar dilemma faces other common disorders like Parkinson's and Alzheimer's disease. Doubtless a plethora of association studies will follow the discovery of this gene; all searching for population-based genetic susceptibility factors. However if previous mendelian genes are to go by, this will be a harder nut to crack. - *DGH*

Dichgans M, Freilinger T, Eckstein G, Babini E, Lorenz-Depiereux B, Biskup S, Ferrari MD, Herzog J, van den Maagdenberg AM, Pusch M, Strom TM.

Mutation in the neuronal voltage-gated sodium channel SCN1A in familial hemiplegic migraine.

LANCET

2005;366:371-7.

PARANEOPLASTIC: what is the anti-amphiphysin syndrome?

*** RECOMMENDED

Very few laboratories could do this study... with the possible exception of Angela Vincent's laboratory in Oxford, none could beat the through-put of serum samples of the Mayo's Neuroimmunology Laboratory, run by Vanda Lennon (she of the NMO-Ig antibody associated with Devic's disease, reported last year in the Lancet). Over the last 15 years, they have handled samples from approximately 120,000 patients with suspected paraneoplastic neurological syndromes. So, think of an antibody; screen the samples; pull the notes; et voila! The biggest series ever. The Mayo have now done this job for antibodies against amphiphysin, a lowly cytoplasmic molecule whose job it is to retrieve spent synaptic vesicles from the axon terminal's plasma membrane. They found 71 positive samples, of which they could recover clinical information from 63 patients. Most (79%) turned out to have a neoplasm, mainly lung cancer; and the majority (74%) also had positive serology for other autoantibodies associated with neurological disease. After six months of a subacute multifocal neurological syndrome most patients were in a wheelchair. A handful of patients responded either to treatment of the tumour or to immunotherapy (steroids and IVIG, but plasma exchange did not work!). So what is characteristic of the anti-amphiphysin syndrome? Of the 19 patients with only this antibody present in their serum, there were more women, who tended to have breast cancer, and who presented with a progressive myelopathy (53%) or stiff-person syndrome (58%). And in the one patient of these who went to post-mortem, inflammatory cells (CD8+ and macrophages especially) were found in their brainstem and spinal cord. So: anti-amphiphysin antibodies are very uncommon, usually found with other

paraneoplastic antibodies and we have probably overestimated their relationship with stiff-person syndrome. Now to start my collection of 120,000 patient samples... - *AJC*

Pittock SJ, Lucchinetti CF, Parisi JE, Benarroch EE, Mokri B, Stephan CL, Kim KK, Kilimann MW, Lennon VA.

Amphiphysin autoimmunity: Paraneoplastic accompaniments.

ANNALS OF NEUROLOGY

2005;Jul;58(1):96-107.

STROKE: The familial risk of subarachnoid haemorrhage

*** RECOMMENDED

All clinical neurologists, I suspect, have been faced with the situation of an apparently healthy individual attending the clinic because of a family history of a 'cerebral bleed'. Anxiety levels are usually high, and information about the relative's precise clinical diagnosis (was it a subarachnoid haemorrhage [SAH], or an intracerebral or extradural or subdural haemorrhage?) correspondingly scarce. Any study which might assist clinicians in these tricky circumstances would therefore be welcome. This paper reports two samples of relatives of patients with SAH; one covers the whole of Scotland for SAH occurring in the years 1994-5; the other relates to admissions to the West of Scotland neurosurgical unit in Glasgow in 1986-7. Hence, large samples, and long follow-up. The epidemiological contortions required to extract and obtain the data seem to have been formidable, and one must commend the investigators for their fortitude (bloody mindedness?) in pursuing the study to a meaningful conclusion, despite the obstruction of the Data Protection Act. The overall finding, common to both cohorts, was a low absolute risk of SAH among relatives of patients with SAH (2%), although this is about 10 times the risk in the general population. As might have been expected, risk is higher for first-degree relatives compared to second-degree relatives; and is highest with two first-degree relatives affected, and lowest with one second-degree relative affected. Hence, on the thorny issue of screening, this would seem inappropriate except for families in which two or more first-degree relatives are affected. Hence, this may be that oddity, the Brain paper which is of use to the common-or-garden clinical neurologist in the face-to-face outpatient clinic encounter. Whether patients, apprised of this data, will be happy in some cases to be reassured that doing nothing is appropriate, remains to be seen. Most of those I have seen want 'a scan'. - *AJL*

Teasdale GM, Wardlaw JM, White PM, Murray G, Teasdale EM, Easton V; Davie.

Cooper Scottish Aneurysm Study Group.

The familial risk of subarachnoid haemorrhage.

BRAIN

2005;128(7):1677-85.

EPILEPSY: focal lesions cause febrile seizures

It has long been known that there is a clinical association between complex febrile seizures and temporal lobe epilepsy (TLE) due to hippocampal sclerosis, conferring a risk up to 8 times higher than the background risk, whereas the common brief febrile seizures carry virtually no additional risk of later epilepsy. Some (not all) pathological studies of human temporal lobe resections for TLE have shown dysplastic neurons within the neocortex of the temporal lobe, leading to the suggestion that there may be a developmental abnormality predating the febrile seizures. In this experimental study the authors used freezing probes to produce tiny lesions on the fronto-parietal neocortex of neonatal rats. This creates a lesion which has the histological appearance of focal microgyria. The rats were then rendered hyperthermic in a chamber attached to a hairdryer. They were heated until they had a convulsion and then moved to room temperature. Following this they were observed for any clinical evidence of seizure activity and underwent regular EEG monitoring. They were also tested on a water maze task of learning and memory. Control groups included naive controls (9 animals), rats with just lesions (9 animals) and rats with just hyperthermic seizures (17 rats). Four of 11 rats with lesions and hyperthermia were observed to have clinical temporal lobe seizures, sometimes with secondary generalisation, without EEG recording. Seven had EEGs recorded from the amygdala and six of these had spontaneous electrographic seizures – an average of 11 per rat. All EEG recorded seizures were associated with behavioural arrest, typical of TLE. Abnormal EEGs were recorded in 2 of 6 rats with hyperthermic seizures alone but in

no control rats or those with just lesions. No seizures were observed in these 3 groups or recorded on EEG. In the experimental animals with seizures there was an associated learning and memory deficit on the maze task. Pathological examination of the brains of these animals demonstrated the freeze lesions of the cortex but showed no evidence of cell loss in the hippocampus. This model shows the interaction of a pre-existing cortical lesion and febrile seizures in the development of TLE. Clinically and electrographically this looks like human epilepsy but the absence of hippocampal damage raises questions about the applicability of the model. It is nevertheless interesting how the same phenotype can be produced without obvious hippocampal damage. The authors argue that this may be related to the age of the animals. It is important to remember the differences in scale between the rat and human brains - the cortical freeze lesions were only about 100µm from the hippocampus but do seem to be histologically distinct. If this represents a valid model of TLE, it may be useful in the development of drugs that are effective in preventing the development of TLE rather than just those for seizure control, which could be applied to high risk febrile seizure patients. - *MRAM*

Scantlebury MH, Gibbs SA, Foadjo B, Lema P, Psarropoulou C, Carmant L.
Febrile seizures in the predisposed brain: a new model of temporal lobe epilepsy.

ANNALS OF NEUROLOGY

2005;58:41-9.

STROKE: and virtual reality games

*** RECOMMENDED

Task specific practice is considered important for recovery of function after stroke. In the best conditions for motor learning, practice should be varied and feedback or knowledge of results should be accurate. In clinical practice time is short for therapists to provide much good quality practice. And speaking from personal experience, practice can also be boring, and therapists are often side tracked by aspects of treatment that may be more interesting to them. Several groups have tried to resolve this problem by interfacing exercises with computer games that can of course be played repeatedly and can be tailored to give accurate performance information. Now also virtual reality is receiving interest in the literature. An article in the June edition of Stroke caught my attention because it assessed both behavioural and functional brain changes resulting from practice using virtual reality (VR) games. Ten stroke patients, aged between 45 and 66 and all over a year post stroke were randomly assigned to control group or to VR training. The control group received no intervention. The VR group practised for 60 minutes a day, five times a week for four weeks. The training included a stepping exercise game, a Sharkbait game in which players have to shift weight, step and squat to avoid sharks and a snow boarding game in which like real snow boarding the weight has to be shifted laterally to control motion. Locomotor function was assessed using the Functional Ambulation Category and the Walking items of the Modified Motor Assessment Scale. And since it's not possible to walk in a fMRI scanner cortical activity during a knee flexion and extension task was captured. Although the training tasks were not exactly like walking, in that they were more static, the VR group showed significantly better gains in walking than the control group. Alongside this improvement the VR group's cortical activity showed a reorganisation from ipsilateral sensorimotor cortex activity before VR to a more normal pattern of activation in contralateral sensorimotor cortex after VR. The technology used in the VR training and in imaging places constraints on training real locomotion and assessing task specific cortical reorganisation. The results of this study can demonstrate only a relationship between brain and lower limb performance in simpler exercises. However it's exciting to see neural changes that are approaching normal that parallel improved function. Therapists will find encouragement for the value of high quality practice from these results. It is just a shame expensive therapeutic tools, such as VR, are unlikely to be seen in many NHS rehabilitation settings in the UK. - *AT*

You SH, Jang SH, Kim Y-H, Hallett M, Ahn SH, Kwon Y-H, Kim JH, Lee MY.
Virtual reality-induced cortical reorganisation and associated locomotor recovery in chronic stroke.

STROKE

2005;36:1166-71.

MULTIPLE SCLEROSIS: Conserving energy and self-help

A 'managing fatigue' programme has recently been investigated within an Occupational Therapy-led randomised controlled trial. Involving people with M.S. in face-to-face community education sessions, the aim of the

programme is to promote energy conservation. Mathiowetz et al (in press) report efficacy in terms of increased use of strategies to conserve energy, and reduced severity and impact of fatigue among participants. The findings are encouraging as fatigue is often a debilitating symptom of the disease. This paper discusses whether there were any differences between the outcomes of people with multiple sclerosis who completed six sessions of the "managing fatigue" programme (n=46) compared to individuals who for one reason or another did not attend all six face-to-face sessions, and received a module to self-study whenever they missed a session (n=49). The authors make a retrospective comparison of how these two naturally occurring groups of patients fared with respect to the same outcome measures. After taking account of multiple comparisons, it was found that there were no significant differences between the two groups in outcome. This suggests that self-study is a useful means of educating patients if they miss part of the community based program. As the authors suggest, further investigations may establish whether self-study alone could provide a suitable alternative to group based study. Self-study through distance learning (sometimes, including elements of group work) has become a popular enabling tool within education. To some individuals, a group situation may fulfil social support needs whereas for others, self-help could be more empowering. Interesting further studies could look at psychological and social factors influencing an individual's choice of health study method. - LAJ

Lamb AL, Finlayson M, Mathiowetz V.

The outcomes of using self-study modules in energy conservation education for people with multiple sclerosis.

CLINICAL REHABILITATION
2005;19:475-81.

PARKINSON'S DISEASE: A shot in the arm

The treatment of chronic neurodegenerative disorders of the CNS has always been a subject of much research and many different strategies. This could involve reducing pathology by either targeting the pathogenic pathway or the pathogenic product. Alternatively one can try to restore function by enhancing plasticity or replacing the lost cells. In PD all these approaches have been undertaken with the exception of trying to get rid of the pathogenic proteinaceous mediator of the disease, in part because we are not quite sure what this is. However over recent years a central role for alpha synuclein and the Lewy body in this process seems probable (Harrower et al, *Experimental Neurology* 2005; July 13th epub), and thus one strategy is to get rid of the abnormal alpha synuclein. Obviously this is easier said than done, given that alpha synuclein in its normal state must fulfil an important role in the CNS. Ways to achieve this might be using interfering RNAs or immunising against alpha synuclein as has been tried for amyloid in Alzheimer's disease. It is this later approach that Masliah et al have tried in a recent paper in *Neuron*. In this study they immunised a transgenic synuclein mouse model of Parkinson's disease and demonstrated that this immunisation induced variable antibody responses. In those mice that produced high levels of antibodies there was less alpha synuclein present, presumably because of its increased clearance via a lysosomal pathway. There was no behavioural aspect to the study and it was not clear what this means in terms of disease progression and expression, nor is it clear how the antibody could actually get inside cells to remove the alpha synuclein. What it does do however is suggest that immunisation strategies may have a role to play in the treatment of neurodegenerative conditions and where there is widespread pathology coupled to a core pathogenic protein. - RAB

Masliah E, Rockenstein E, Adame A, Alford M, Crews L, Hashimoto M, Seubert P, Lee M, Goldstein J, Chilcote T, Games D, Schenk D.

Effects of alpha-synuclein immunization in a mouse model of Parkinson's disease.

NEURON

Jun16;46(6):857-68.

APHASIA: measuring outcome

Assessment of the outcome of intervention is generally deemed a good thing, in theory at least. The practice in many areas of healthcare is rather less straightforward as a result of what the authors of this article term 'the complexity and multidimensionality of clinical outcomes measurement'. The challenge of outcome measurement in aphasia therapy, where meaningful initial assessment can take several hours, is the focus of this American survey. The authors distributed the survey electronically to mailing lists of therapists working in aphasia, an approach which reached a fairly large number of potential participants (roughly 1000), of whom about 100 responded. The

results, while not entirely surprising, highlight ongoing tensions between well-recognised theory and limitations on full implementation of the theory. Somewhat unexpectedly, only 85% of respondents reported that they undertook outcome measurement in aphasia. One wonders what the other 15% are thinking. Be that as it may, the most frequently reported barrier to measuring outcome in individual clients was time constraints, occasioned particularly by caseload and other administrative issues. Interestingly, in this American context several respondents reported that re-evaluations were not funded. The focus of the majority of outcome assessment was reported to be re-evaluation of abilities in individual clients (as opposed to group/cohort/population outcomes), with none of the respondents interpreting outcome in terms of cost or amount of therapy associated with specific language improvement. A high proportion of therapists used a combination of both formal linguistic reassessment and social participation measures. Having said this, only a small proportion (12%) cited the WHO framework as philosophical background to their approach. The authors' interpretation of the survey results focuses on the continuing need for 'a coherent model of outcome assessment to guide the choice of outcome assessment tools and the management of outcome data'. They argue that the WHO International Classification of Functioning, Disability and Health, while in need of expansion to accommodate issues specific to communication, provides the most logical platform for just such a coherent model. - RB

Simmons-Mackie N, Threats TT, and Kagan A.

Outcome assessment in aphasia: a survey.

JOURNAL OF COMMUNICATION DISORDERS
2005;38:1-27.

EPILEPSY: new drugs safe to OD?

Depression is common in epilepsy and attempted suicide flows from this accounting for 13% of epilepsy-related deaths over several studies. From 1979-1985 one study reported that 18% of antiepileptic drug (AED) overdoses had a fatal outcome (however this was done before the new AEDs appeared). Now we have data on non-accidental overdoses of the newer AEDs from Ireland from 1996-2000. Nearly all patients took more than one drug (these are often prescribed as add-on therapy). The number of cases for each drug was Gabapentin 33; Lamotrigine 97; Levetiracetam 1; Tiagabine 5; Topiramate 7; and Vigabatrin 21. None of these overdoses had a fatal outcome. It is probably easier to kill a rat by suffocating it in a vat of gabapentin pills than by trying to give it an overdose and one human has taken 100g of topiramate and survived. Fatalities have been reported with lamotrigine but overall this group of drugs seems safer than older ones and might influence choice of drug in patients with a significant suicide risk. By contrast, as little as 6g of Phenobarbital can be fatal. - MRAM

Sukumaran S, Herbert J, Tracey J, Delanty N.

Safety of newer generation anti-epileptic drugs in non-accidental overdose: an Irish population study.

SEIZURE

2005;14:151-6.

HUNTINGTON'S DISEASE p53 is linked pathogenesis

*** RECOMMENDED

A recent study in *Neuron* reveals a specific role for p53 in Huntington's disease (HD) pathogenesis. The work carried out by Bae et al. provides compelling evidence that p53 is the molecular link between the nuclear pathology and mitochondrial abnormalities associated with Huntington's disease. The tumour suppressor function of p53 is well established but Bae et al. hypothesised its involvement in HD pathogenesis for several reasons. First, it is a nuclear transcription factor that plays a central role in cellular stress response. HD is an autosomal dominantly inherited disease, which is characterised by nuclear pathology. The disease-causing mutation results in an expansion of the polyglutamine repeat region of the Huntingtin protein (Htt), which causes the mutant protein to misfold and aggregate as intranuclear inclusion bodies. Second, p53 regulates mitochondrial genes; the net result of its actions is to alter the permeability of the outer mitochondrial membrane. Multiple lines of evidence have implicated mitochondrial dysfunction in HD pathogenesis. Third, elevated levels of p53 have been detected in brain tissue of several neurodegenerative diseases, including Alzheimer's disease, and p53 overexpression elicits cell death in primary cortical cultures. This study demonstrated an upregulation of nuclear p53 protein levels in mutant Htt-expressing cells, a transgenic HD model and also in cerebral cortical and striatal tissue of HD patients. The increase in

p53 was proposed to be due mainly to post-translational stabilisation of p53 by mutant Htt, rather than transcriptional upregulation. This increase in p53 levels resulted in more p53 transcriptional activity, so that downstream targets of p53 including the apoptotic effector, Bax, were also detected at elevated levels. Functionally, augmented p53 was demonstrated to mediate mitochondrial dysfunction in HD cells and HD transgenic animals. Enhanced mitochondrial membrane depolarisation in HD lymphoblasts and mutant Htt-expressing cells was reversed by a specific p53 inhibitor (pifithrin), RNA interference targeted against p53 and p53 gene deletion. In the HD transgenic mice, impaired mitochondrial complex IV activity was also partially rescued by inhibiting p53 pharmacologically and genetically. Interestingly, p53 was shown not to be involved in nuclear aggregation of mutant Htt. It was also shown that p53 mediates mutant Htt-induced neurotoxicity in vivo. By crossing HD animal models onto a p53 null genetic background the neurodegenerative phenotype was improved. For example, in HD transgenic mice, neurobehavioural deficits characteristic of this HD model, including hind limb dyskinesia, were normalised by genetic deletion of p53. These findings suggest that p53 mediates mitochondrial dysfunction, cell death and behavioural abnormalities associated with HD in vivo. In contrast to its anti-cancer function, this work also identifies p53 as a molecular mechanism that links nuclear transcriptional dysregulation and mitochondrial abnormalities specific to HD. This study demonstrated a direct interaction between mutant Huntingtin and p53 in vitro, which suggests that identification of protein domains that mediate binding between these two proteins may provide important targets for HD therapeutics. - *LMS & SJT*

Bae B, Xu H, Igarashi S, Fujimuro M, Agrawal N, Taya Y, Hayward SD, Moran T, Montell C, Ross CA, Snyder SH, Sawa A.

p53 mediates cellular dysfunction and behavioural abnormalities in Huntington's Disease.

NEURON

2005;47:29-41.

REHABILITATION: Sing, sing a song...to improve expression of emotion after TBI

Impaired intonation (defined here as the rise and fall in pitch over time within a spoken phrase) in voice production can be one residual impairment affecting quality of life after traumatic brain injury (TBI). Individuals with reduced intonation can be at risk of being misunderstood, being unable to engage and maintain conversations and thus at risk of social isolation. There is some research to support the benefit of music therapy for a range of neurological disorders but studies in this area are limited. This small study of four individuals after severe TBI looked at short and long-term change in characteristics of intonation, which can be recorded and analysed digitally (the pitch control, F0, F0 variability and F0 range), as well as influences of change of mood on these characteristics. Each subject received 15 sessions of 40-50 minutes over 5-8 weeks with a music therapist who sang along and accompanied on guitar – though it is not clear if with the same therapist. Individuals could pick their own three songs that were used for all sessions. The study did show some long-term benefit in intonation and reduced feeling of tension but there was considerable variability between individuals. However in the short term, there was an unexpected drop in post-session mood and intonation scores compared to pre-session scores. They attribute the mood changes to the themes of the lyrics and advise of the need for emotional support for individuals after their sessions. There was no comment on whether individuals practiced singing on their own or with family/carers outside of the sessions or the possibility of using these resources in practice. It is an interesting theme that needs some more development and research evidence before considering it as a valid part of a rehabilitation programme. - *JMCF*

Baker F, Wigram T, Gold C.

The effects of song-singing programme on the affective speaking intonation of people with traumatic brain injury.

BRAIN INJURY

2005;19(7):519-28.

PARKINSON'S DISEASE: Post-mortem study of successful fetal grafts

Clinical trials for neural transplantation in Parkinson's disease (PD) began in 1987, with some positive results, and this led to two double-blind clinical trials (Freed et al, 2001; Olanow et al, 2003). In these studies, minimal benefit was reported, although younger patients did better and there were significant side effects such as off-state dyskinesias. There were, however, many method-

ological differences between these two trials and several open label trials including: amount of tissue used, storage time of tissue prior to grafting, use of solid grafts as opposed to cell suspension, little or no immuno-suppression and short follow-up. Post mortem examination has been performed on some of these patients (Olanow et al, 2003) and shown prominent inflammatory reactions around the graft. It has been proposed that the high levels of class I human leukocyte antigens present in the capillaries of the donor solid graft contribute to this immune reaction, which may in turn account for the poor clinical outcome. This study describes, for the first time, post mortem results of two patients grafted with a cell suspension, who died from a myocardial infarction (patient 1) and acute renal failure possibly due to renal cell carcinoma (patient 2), 3-4 years after surgery. Tissue from two to four donor 6-9 week old fetuses (2.6-3.2 million cells in patient 1 and 4.8 million cells in patient 2) was transplanted into the postcommisural putamen (patient 1) and striatum (two deposits from the caudate to putamen and four into the postcommisural putamen as for patient 1) and dorsostratal SN (patient 2) with a dopaminergic cell survival rate of around 15-30%. Grafts were stored for 6 days, in glial cell derived neurotrophic factor (GDNF) prior to transplantation. These patients (aged 69 and 59) had a good clinical response to grafting, supported by 18F-DOPA PET. The patients received 6 months of immunosuppression (the same time course as the Tampa/Mount Sinai trial - Olanow et al, 2003). There was no inflammatory reaction around the graft (except for a small glial scar in patient 2), as measured by the microglial antigens CD45 and CD68 and astrocytic markers. The grafts were found to densely re-innervate the striatum. The authors found that substantia nigra pars compacta (SNpc) neurons (from region A9), which express the potassium channel protein, Girk2, made up 40-50% of the surviving tyrosine hydroxylase positive (TH+) neurons, and ventral tegmental area (VTA) neurons (region A10), expressing calbindin, comprised 10-20% of the total. Calbindin positive dopaminergic neurons project to the limbic nucleus accumbens and are relatively spared in PD, and animal studies have shown that only the SNpc subtype can re-innervate the striatum. SNpc neurons were expressed around the circumference of the graft, where they could make connections with the host striatum. Interestingly, the midbrain graft contained 4-8% surviving dopaminergic neurons and a lower ratio of SNpc/VTA neurons. The favourable clinical outcome post grafting, and 18F-DOPA PET appearance, was attributed to the good survival of the graft, and dense re-innervation of the target striatum by the higher proportion of area A9 SNpc neurones from the edge of the graft. This favourable outcome may have been due to the use of cell suspension, rather than solid grafts, and the handling of the tissue, such as incubation in GDNF. This post mortem study demonstrates that grafts can survive and appear to appropriately re-innervate the host striatum, and that specific methodological considerations can lead to favourable outcomes. - *WP*

Freed CR et al (2001) *N Engl J Med*, 344: 710-719.

Olanow CW (2003) *Ann Neurol*, 54: 403-414.

Mendez I, Sanchez-Pernaute R, Cooper O, Vinuela A, Ferrari D, Bjorklund L, Dagher A, Isacson O.

Cell type analysis of functional fetal dopamine cell suspension transplants in the striatum and substantia nigra of patients with Parkinson's disease.

BRAIN

2005;128:1498-1510.

DEMENTIA: tau deposition irrelevant?

Transgenic mice expressing the P301L variant of human tau have previously been described: they develop progressive age-related neurofibrillary tangles (aggregates of tau phosphoprotein), neuronal loss and behavioural impairment. This paper reports a new mouse model characterised by a suppressible transgene with a doxycycline-responsive element placed upstream of P301L tau. The authors observe that suppression of the transgenic tau (by doxycycline) results in improved memory function (water maze performance) and in stabilisation of neuronal numbers. Their key finding is that histopathological examination of brains from mice that show memory recovery following tau suppression revealed as much abnormal tau deposition as in the unsuppressed tau animals. The latter, by contrast, showed severe memory impairment and had marked brain atrophy. Neurofibrillary tangles are among the commonest pathological lesions found in the brains of patients with neurodegenerative disease. They have been implicated in neuronal death and cognitive dysfunction. This elegant study by Santacruz and colleagues shows, however, that tangles in themselves may be insufficient to cause cognitive decline or neuronal death. A criticism of the paper is that, perhaps because of limited space, the clinical background is focused on Alzheimer's disease (AD). Human kindreds with the P301L tau mutation, however, do not show clinical features of AD

but rather frontotemporal dementia (FTD) with parkinsonism. Neither is there mention of beta amyloid plaques, which are as much a feature of AD pathology as neurofibrillary tangles (or of the continuing challenge of producing a mouse model manifesting both plaque and tangle pathology). The point is that tau involvement in the pathogenesis of FTD, the disease most closely resembled by the new mouse, may differ from that in AD. Tangle 'load' correlates with cognitive impairment in AD but familial AD is caused by genes in the amyloid-beta system. Thus, abnormalities of soluble tau are likely to be important early in the pathogenesis of FTD while tau aggregates may be relevant later in the pathogenesis of AD. Though much can be learnt from transgenic animals, care must always be taken when extrapolating to human diseases. - RD

Santacruz K, Lewis J, Spire T, Paulson J, Kotilinek L, Ingelsson M, Guimaraes A, DeTure M, Ramsden M, McGowan E, Forster C, Yue M, Orne J, Janus C, Mariash A, Kuskowski M, Hyman B, Hutton M, Ashe KH.

Tau suppression in a neurodegenerative mouse model improves memory function.

SCIENCE

2005;309(5733):476-81.

TREMOR: Alcohol for ataxia in Essential Tremor?

The beneficial effects of alcohol on upper limb tremor in essential tremor (ET) are already well recognized by patients and clinicians. Klebe and colleagues, from Germany, looked at the effects of alcohol on tremor and ataxia of 16 patients with ET and 11 matched controls. Clinical measures of tremor and ataxia, as well as instrumental measures (using gait analysis) were taken before and 30 mins after ingestion of 0.25mL of 10% alcohol (a typo? – presumably 0.25L, a large glass of table wine). In the patient group, the ataxia score during tandem gait declined significantly ($p < 0.05$), from a mean of 24.7 to 18.2 while worsening slightly but not significantly in the controls (12.6 to 15.1). The rate of missteps during tandem gait was significantly reduced from 8.8 per minute to 5.6 per minute among patients and increased (non-significantly) from 0.4 to 0.7 among controls. They also note the lack of correlation between the clinical and instrumental measures of ataxia, and the severity of leg tremor. In addition to this, they claim the lack of effect of alcohol on leg tremor (at variance with their data), supports the argument that ataxia is independent of tremor severity and alcohol does not improve ataxia through its effect on tremor. More credibly, they conclude their study does not support the 'neurodegeneration hypothesis' of ET. This paper is helpful in elucidating the pathogenesis of ET and the effects of alcohol, however we don't know if alcohol has any functional day-to-day benefit on ataxia as opposed to tremor symptoms for patients with ET. [And as the authors caution, higher doses of alcohol impairs cerebellar function and a dose-response study "was not practical". I don't think one would have too much difficulty recruiting subjects for such a study!] - JMCF

Klebe S, Stolze H, Gensing K, Volkman J, Wenzelburger R, Deuschl G.

Influence of alcohol on gait in patients with essential tremor.

NEUROLOGY

2005;Jul 12;65(1):96-101.

COGNITION: A case of vision-touch synaesthesia

Blakemore and colleagues are the first to describe a case of vision-touch synaesthesia, and they compared this subject with 12 controls in a functional MRI study. When the subject, C, observes someone being touched, she perceives the same touch on herself. Astonishingly, C was not aware that this was unusual. C has a cousin who also has vision-touch synaesthesia, and several female relatives with grapheme-colour synaesthesia. C herself had the more common grapheme-colour synaesthesia when she was younger, but no longer experiences this. The tendency for synaesthesia to run in families has been noted previously and it is interesting that different forms of synaesthesia appear in her family and change even in herself, raising the possibility that the tendency to synaesthesia may be general rather than modality specific. The authors aimed to investigate the neural activity to the observation of touch to the face and neck of a human or object and the somatosensory topography of any activation, both in C and in non-synaesthetic controls. Subjects were scanned while being touched on the face or neck by a piece of felt on the end of a stick; while watching images of a human face or neck being stroked by a finger, or watching objects with a 'face' and 'neck' (such as an electric fan) being stroked by a finger. Based on previous studies, the authors made several predictions: the somatosensory cortex would be activated by observing humans more than objects, this activation would be somatotopic, these activations would be higher in C and finally, additional areas would be activated

in C. When subjects were touched, the somatosensory regions SI and SII, the parietal cortex, the premotor cortex and the motor cortex were activated. In controls, the mere observation of touch resulted in activation of the superior temporal sulcus (STS) at the temporoparietal junction especially on the right, the fusiform gyrus, bilateral primary and secondary somatosensory cortices in a somatotopic fashion, and the premotor cortex. Activation was greater when observing humans versus inanimate objects, and in C. The anterior insula was also activated in the synaesthetic subject, C. It is known that the STS and fusiform gyrus are activated in response to faces and might form part of a mirror system (whereby neurons which execute a function are activated during the observation of the same function). The premotor cortex may also form part of a mirror system. It has been suggested previously that mirror systems are particularly sensitive to biological motion, and this study suggests that it is also sensitive to biological targets and as such, biased towards 'social' actions. Three main theories were mooted for C's pattern of activation. First, there could be increased activation in the normal 'mirror system'. Second, there could be direct connections between C's visual and somatosensory areas. Third, there may be hyperactivation of 'bimodal cells' in the STS, which respond to both vision and touch, and could be sufficient to produce the synaesthetic response. The first theory was deemed most likely, primarily due to the activation seen elsewhere, remote from the STS and somatosensory areas. The authors postulated that the normal mirror system allows us to understand the effect of tactile stimulation on others. When a threshold is reached, as in C, this activation results in conscious perception, explained also by activation in the anterior insula, which is associated with self-processing. The cynics among us, and in our journal club, might postulate that she perceives touch in response to observation of touch, along with the neural correlate simply by directing extra attention to the perception of touch. You decide! - WP

Blakemore SJ, Bristow D, Bird G, Frith C, Ward J.

Somatosensory activations during the observation of touch and a case of vision-touch synaesthesia.

BRAIN

2005;128:1571-83.

BRAIN INJURY: Who, when and how to screen and treat for pituitary deficiency after TBI

*** RECOMMENDED

Though figures vary, studies in recent years show that pituitary function is impaired in at least 20-30% of patients following traumatic brain injury (TBI). Yet for physicians (usually rehabilitation) caring for these individuals, there has been great uncertainty on what to do in practice. Limited evidence, the overlap of symptoms of hypopituitarism and TBI (e.g. fatigue, memory and concentration impairment) as highlighted in this paper, and until now, no published guidelines in this area have contributed. This group, comprising recognised neuroendocrinologists and rehabilitation physicians from around the Western World, met in 2003 to develop consensus guidelines and to raise awareness and education amongst professionals and patient groups. They review the evidence published so far in each area of screening, treating and follow-up with many references. Apart from clinical indications, they recommend prospective routine testing of pituitary function at 3 and 12 months in all patients hospitalised after TBI, as well as single retrospective evaluation and testing on those >12 months post (moderate or severe) injury. However they do acknowledge the need for further clarification on who is at most risk and the debate over classification of severity of TBI. Specific basal pituitary hormone tests are recommended but the need for collaboration at local level between endocrinologists and rehabilitation physicians is advocated. They discuss the issue of natural history and the controversies of hormone replacement, yet summarise practice recommendations in helpful flow charts. Although receiving an unrestricted grant from a pharmaceutical company, this paper is balanced in its discussion of the controversies, especially in relation to growth hormone replacement, and on the recommendations made in this area. For all clinicians treating individuals after a TBI, it's a worthwhile read and a challenge to become involved in the development and implementation of suitable outcome measures for efficacy studies. - JMCF

Ghigo E, Masel B, Aimaretti G, Leon-Carrion J, Casaneuva FF, Dominguez-Morales MR, Elovic E, Perrone K, Stalla G, Thompson C, Urban R.

Consensus guidelines on screening for hypopituitarism following traumatic brain injury.

BRAIN INJURY

20 August 2005;19(9):711-24.