

## EDITOR'S CHOICE

**Culture and developmental dyslexia**

This elegant study shows that the basis of developmental dyslexia differs across cultures and, in so doing, provides insight into the neural basis of reading. The authors give a brief but fascinating description of the Chinese language. Chinese is a logographic language that differs from alphabetic languages, in which the visual, graphic forms (graphemes) map onto minimal phonological units of speech (phonemes). In Chinese, the graphic forms (characters) map onto meanings, which may then be sounded. Neither characters nor their subdivisions, however, relate consistently to phonology and the letter-sound conversion rules of alphabetical languages do not occur. As such, the left temporo-parietal dysfunction found in developmental dyslexics whose languages use alphabetic scripts, and its association with impaired grapheme-to-phoneme processing, seems an implausible model for explaining reading difficulties in Chinese children of normal general intelligence, i.e. those with developmental dyslexia.

Sixteen children attending school in Beijing were studied, aged between 10 and 12, of whom half were reading-impaired and half unimpaired. All participated in two functional MRI experiments. The first experiment consisted of a homophone judgement task: subjects decided whether or not two simultaneously-presented Chinese characters had an identical pronunciation. The control condition was to decide whether or not two characters had the same physical size. In the second experiment, the children were shown two characters, one real, one meaningless (but graphically 'legal'), and asked to decide which was which. Normal readers performed significantly better than the impaired readers at the experimental tasks but not the control task. In brief, the imaging showed weaker activation in the left middle frontal gyrus in the impaired readers. Furthermore, activation at this location correlated with task performance. The region is proposed to have a role in the integration of graphemes and semantics necessary for reading ideographic script. The paper raises the practical point that the management of developmental dyslexia should take cross-cultural factors into account. More fundamentally, it refutes the idea that neural basis for reading is universal. By contrast language, as in speech, is presumably more primitive and its neural basis less likely to vary across cultures. The authors relate their results to the recent anatomical finding that the left middle frontal gyrus is larger in Chinese-speakers than English-speakers which, in turn, suggests an influence of culture on brain development. - RD

Siok WT, Perfetti CA, Jin Z, Tan LH.

*Biological abnormality of impaired reading is constrained by culture.*

NATURE

2004;431(7004):71-6.

**HUNTINGTON'S DISEASE: real-time microscopy reveals the neuroprotective nature of inclusion bodies**

## ★★★ RECOMMENDED

Huntington's disease (HD), a neurodegenerative disorder caused by abnormal polyglutamine expansion within the protein huntingtin (Htt), is characterised by the aggregation of Htt into intracellular deposits called inclusion bodies (IBs) and by the death of striatal and cortical neurons. The role of these inclusion bodies in the pathogenesis of HD is a hotly debated topic. Over the years, a wealth of conflicting experimental data has been generated. Inclusion bodies have been proposed as the major pathogenic species because they absorb critical cellular proteins. In contrast, they have also been hailed as protective because they sequester mutant protein. Finally to complete the debate, some believe that they are purely incidental. Arrasate et al developed an elegant real-time technique to assess factors influencing the risk of neuronal death in cell culture. They employed an established model of HD, in which striatal neurons are transiently transfected with a pathogenic fragment of mutant Htt (Htt-exon1) with polyglutamine stretches of various lengths. To visualise the deposition of Htt in the cytoplasm and nucleus of living striatal neurons, they used the construct of Htt-exon 1 fused to green fluorescent protein (GFP) and devised an automated microscopic system to track specific neurons over a period of days (at 12-24h intervals). They measured the following factors; neuronal survival, aggregation of Htt into inclusion bodies and the levels of diffuse Htt and made two conclusions. First, cells expressing the control construct (non pathogenic Htt-exon1) were

at low risk of dying, whilst those expressing an expanded polyglutamine tract were at high risk of dying. Moreover, as in HD, the risk of death increased with the size of the polyglutamine tract. Second and most interestingly, it was observed that cells failing to form inclusion bodies had an increased risk of death. Furthermore, cells with equal mutant Htt-exon 1 expression had a reduced risk of dying if they formed inclusion bodies than if they exhibited diffuse Htt distribution. These findings clearly indicated that inclusion bodies were not required for polyglutamine-induced neuronal death. By improving the temporal resolution of conventional techniques, this study provides conclusive evidence that inclusion bodies are not pathogenic. In fact their formation prolonged survival and protected neurons by reducing diffuse levels of Htt. Although inclusion bodies are not pathogenic, it may be that early precursors of the inclusion body, microaggregates, may be the principal toxic species in HD. This technique could illuminate the pathogenicity of protein aggregates in other human neurodegenerative disorders, including Alzheimer's Disease. - LMS & SJT

Arrasate M, Mitra S, Schweltzer ES, Segal MR, Finkbeiner S.

*Inclusion body formation reduces levels of mutant huntingtin and the risk of neuronal death.*

NATURE

2004;431:805-10.

**STROKE: Cerebral lithotripsy**

In 2000, Andrei Alexandrov and colleagues from Houston published an extraordinary finding in *Stroke*: that monitoring of the effects of thrombolysis with transcranial ultrasound actually improved recanalisation rates. This spawned a great deal of experimental work on the possible mechanisms of "ultrasound-enhanced fibrinolysis". And now the same group has got into NEJM with a phase II trial, called CLOTBUST (bless stroke doctors and their acronyms!). 126 patients presenting within 3 hours of a stroke received t-PA with or without two hours of transcranial ultrasonography (using frequencies equivalent to regular diagnostic ultrasonography). Every half hour all patients had a brief diagnostic ultrasound to assess recanalisation. The one clear result is that the ultrasound group had a statistically significant improved recanalisation rate (38% versus 13%). There was a trend, which was not significant, towards an associated improvement in clinical outcome (42% versus 29% reached 0 or 1 on the Rankin scale). There were no adverse effects associated with ultrasonography, including no increased haemorrhage as earlier studies had suggested. Great stuff. Of course, more research need-

**Panel of Reviewers**

<b>Roger Barker</b>	Honorary Consultant in Neurology, Cambridge Centre of Brain Repair
<b>Richard Body</b>	Lecturer, Department of Human Communication Sciences, University of Sheffield
<b>Alasdair Coles</b>	Lecturer, Cambridge University
<b>Rhys Davis</b>	Research Registrar, Addenbrooke's Hospital, Cambridge
<b>Dan Healy</b>	Neurology SPR, National Hospital, Queens Square, London
<b>Lucy Anne Jones</b>	Research Associate (Cognitive Neuroscience)
<b>Mark Manford</b>	Consultant Neurologist, Addenbrooke's Hospital, Cambridge, and Bedford Hospital
<b>Andrew Michell</b>	Neurology Research Registrar, Addenbrooke's Hospital, Cambridge
<b>Wendy Phillips</b>	Research Registrar, Addenbrooke's Hospital, Cambridge
<b>Liza Sutton</b>	UCL PhD Student, Institute of Neurology
<b>Sarah J Tabrizi</b>	DoH Clinician Scientist and Clinical Senior Lecturer, Institute of Neurology
<b>Ailie Turton</b>	Research Fellow, Burden Neurological Institute, Bristol

**Would you like to join ACNR's reviewer's panel?**

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ed... and so on. The main snag is that transcranial Doppler is technically difficult and can be performed by only highly trained operators. It will be a while before hospitals have on-call transcranial clotters! - *AJC*  
See *ACNR Volume 4 Issue 4* for the article by Dr Paul Syme, on *Detection of Small Vessel Knock using Transcranial Doppler Ultrasonography*. This can also be found on *ACNR's* web site with a video clip, see [www.acnr.co.uk/controversies.htm](http://www.acnr.co.uk/controversies.htm)  
**Alexandrov AV, Molina CA, Grotta JC, Garami Z, Ford SR, Alvarez-Sabin J, Montaner J, Saqqur M, Demchuk AM, Moye LA, Hill MD, Wojner AW; CLOTBUST Investigators.**

*Ultrasound-enhanced systemic thrombolysis for acute ischemic stroke.*  
NEW ENGLAND JOURNAL OF MEDICINE  
2004;351(21):2170-8.

## ALZHEIMER'S DISEASE: In vitro and in vivo imaging demonstrate neurotoxicity of amyloid plaques in mouse model

★★★ RECOMMENDED

Alongside intracellular neurofibrillary tangles, extracellular  $\beta$ -amyloid (A $\beta$ ) plaques are the key diagnostic neuropathological hallmarks of Alzheimer's disease (AD). Their role in disease pathogenesis remains controversial. On the one hand, the "amyloid cascade hypothesis" claims that amyloid plaques are the triggering factor in AD pathogenesis and therapies aimed at reducing plaque load slow disease progression. On the other hand, it is proposed that amyloid plaques are inert tombstones of the disease process, because plaque load does not correlate with the onset or severity of symptoms. Furthermore, functional deficits and synaptic loss are often evident prior to any A $\beta$  deposition. This elegant study by Julia Tsai and colleagues at New York University aimed to investigate the effect of A $\beta$  deposition on neuronal circuitry, and hence clarify its role in AD pathogenesis. Both in vitro and in vivo imaging techniques were used to study a double transgenic mouse model of AD called PSAPP, which overexpresses mutant human amyloid precursor protein (APP) and presenilin-1 (PS1). Neuronal labelling of fixed brain slices revealed local structural abnormalities in neurites located both within and close to (< 15 $\mu$ m) fibrillar amyloid deposits (labelled with Congo Red). The dendrites exhibited a reduction in spine density and shaft diameter and axons bore swellings that indicated major cytoskeletal disruption. Triple transgenic PSAPP mice, in which cortical pyramidal cells were fluorescently labelled, were used for in vivo transcranial 2-photon imaging to investigate the time-course of these structural neuritic changes near to amyloid plaques. This novel technique allowed specific neurites to be monitored over several weeks. It was noted that there was continuous elimination and formation (to a greater extent) of these structural abnormalities in neurites close to the amyloid plaques whilst those further away remained stable. It also became clear that such changes eventually lead to neuritic breakages. This finding suggested that amyloid plaques are more detrimental to neuronal circuitry than originally thought; not only do local axonal and dendritic abnormalities affect signal integration at the whole cell level but neurite breakage means there is a permanent, global disruption in signal integration. It is possible that secondary regenerative processes further disrupt signalling. Since up to 15% of the cortical area of AD patient brains can be made up of amyloid plaques, Tsai claims that plaques would severely disrupt connectivity and could quite conceivably contribute to disease progression and dementia. Importantly their findings also demonstrate a 'microenvironment' in the vicinity of A $\beta$ -deposits that is permissive to neuronal remodelling, highlighting the possibility of reversing plaque-induced structural abnormalities. This has important therapeutic implications: early plaque prevention or clearance is clearly an important strategy in halting disease progression. - *LMS & SJT*

**Tsai J, Gruntzender J, Duff K, Gan W-B.**

*Fibrillar amyloid deposition leads to local synaptic abnormalities and breakage of neuronal branches.*

NATURE NEUROSCIENCE  
2004;7(11):1181-3.

## PARKINSON'S DISEASE: helpful magnetism

★★★ RECOMMENDED

The components of Parkinson's disease, tremor, bradykinesia and rigidity, reflect a failure of neurophysiological mechanisms. The interference of nigrostriato-thalamic networks may have the effect of generating a deafferented motor cortex with secondary changes in pyramidal cell excitability. By readjusting motor cortex excitability, as measured by transcranial magnetic stimulation (TMS), a benefit in terms of one or more of these clinical disabilities may temporarily result. Applying trains of TMS pulses (rTMS) is known to change primary motor cortex excitability and has been demonstrated by a number of groups. The increase or decrease in excitability depends on the stimulation

parameters applied (frequency and number of pulses) as well as the type of coil used and its location relative to the scalp. This research group from France used a range of 'treatments' including: high frequency, low frequency, sham rTMS (focal coil) and dopamine. They measured pre and post motor performance (gait, UPDRS, peg board and a ballistic task). Patients ('off drug'-single dose missed, n=12) with dominant bradykinesia were chosen and tremor-dominant patients were excluded. Interestingly both high and low frequency stimulation had therapeutic effects on the contralateral arm, whilst sham stimulation had no effect. Low frequency had bilateral effects improving motor scores, bradykinesia and gait time. High frequency had similar unilateral effects but also improved ballistic scores, again unilaterally. Compared to dopamine treatment the benefit with either train of TMS was modest (28-32%). The duration of the effect was not clarified but some patients reported a benefit lasting 24 hrs. Significant changes were also seen in neurophysiological measures of cortical excitability. There were no detrimental effects. This is an exciting study with potential therapeutic implications, which need to be explored in a more heterogeneous patient group to define benefit in the various subcategories of PD along with a better profile of its duration. - *JLR*

**Lefaucheur J, Drouot X, Von Raison F, Ménard-Lefaucheur, I Cesaro Pand Nguyen J.**

*Improvement of motor performance and modulation of cortical excitability by repetitive transcranial magnetic stimulation of the motor cortex in Parkinson's disease.*

CLINICAL NEUROPHYSIOLOGY  
2004;115(11):2530-41.

## WRITING ACNR REVIEWS: Alcohol and the harmonious brain

Alcohol at persistently high levels of intake is neurotoxic. Damage occurs at the cortical cellular level and white matter connections are thought to be particularly vulnerable, the corpus callosum can reduce in volume. It would therefore be expected that a measure of inter-cortical connectivity would show a lack of synchronicity between cortical regions in those at risk of alcohol related damage compared to controls. Surprisingly this group in the Netherlands demonstrated the reverse effect. Students were divided into heavy or light drinkers (<30 units per week, n=11 in each group) and underwent high density EEG array. Off line analysis of coherence of each EEG frequency across all electrodes was performed. In the high alcohol group there was increased synchronicity at low frequency (theta) and at a particular high frequency (gamma, thought to be involved in higher cortical processing such as memory formation), in both a passive eye closure state and also during a mental task. I don't know what this means, but the researchers suggest this is due to functional changes within neocortical hippocampal circuits. I think it is a little worrying that such changes can be detected in relatively young drinkers and clearly moderation is the way to go. I'm not put off from the odd glass and perhaps it's the associated brief periods of increased connectivity that help me put my thoughts together when writing these reviews! - *JLR*

**Bruin EA, Bijl S, Stam CJ, Böcker KB, Kenemans JL and Verbaten MN.**

*Abnormal EEG synchronisation in heavily drinking students.*

CLINICAL NEUROPHYSIOLOGY  
2004;115(9):2045-55.

## REHABILITATION: Are the Americans more efficient than us?

How many of us think our rehabilitation service could be more efficient? Do we worry about the impact a reduced length of stay might have on patient outcomes? Most of us feel the pressure for change especially in this era of increasing calls for improved efficiency within a finite budget. This paper from the US looked at the change in rehabilitation outcomes over the years 1994-2001 during which there was a dramatic reduction in length of stay (LOS) in rehabilitation institutions. They used data from the large (over 1/4 million patients) national Uniform Data System for Medical Rehabilitation which uses the Functional Independence Measure as the main outcome. They sub-divided into 5 specific groups, including stroke, brain dysfunction, other neurological disorders and spinal cord injury. In summary, the end result remained unchanged despite the reduced LOS and thus there was an increased efficiency across all groups. Unexpectedly there was an increased mortality across most groups but possible confounding factors to explain this are discussed in the accompanying editorial. Above all, for me this paper highlights the dearth of extensive rehabilitation outcomes data available in most European countries. We need better routine data collection systems on which to base our decisions to change (and monitor) our rehabilitation services. Who is going to take up this responsibility? - *JMcF*

**Ottensmeyer FJ, Smith PM, Illig SB, Linn RT, Ostir GV, Granger CV.**  
*Trends in Length of Stay, Living Setting, Functional Outcome and Mortality Following Medical Rehabilitation.*

JAMA  
2004;292(14):1687-95.

**NEOPLASIA: finding the occult tumour – my pet subject**

★★★ RECOMMENDED

It is not uncommon in neurological practice to have a patient with a paraneoplastic syndrome but without an obvious tumour. In recent years the identification of increasing numbers of different antibodies associated with these syndromes has meant that the diagnosis can be made with more confidence and relies less on clinical recognition and a list of negative findings. However these patients still pose a problem as often the antibody response holds the primary tumour in check, so that it is small and hard to find with conventional investigations. A recent hope has been that whole body [18F] fluorodeoxyglucose (FDG) PET could be used to find these hidden, metabolically active, tumours. In order to try and help sort out some of these issues of sensitivity and specificity, Younes-Mhenni et al have prospectively studied 20 patients with paraneoplastic antibodies and associated syndromes but with negative conventional imaging investigations. Of these 20 patients, 18 (90%) had abnormal PET uptake and 14 of these went on to have a histological diagnosis of a tumour. Of the 18 original abnormal PET scans, two returned to normal and in the two negative PET scans one patient was found to have peritoneal carcinomatosis and in the other no tumour was seen. Thus this technique seems to be very helpful in patients with paraneoplastic syndromes with a high sensitivity although rather a low specificity. Nevertheless this paper has confirmed that when stuck with a patient with such a syndrome, especially when the antibodies are positive and conventional imaging is negative, a whole body FDG PET scan may be very helpful...although whether it ultimately makes any difference in prognosis is not clear. – *RAB*

Younes-Mhenni S, Janier MF, Cinotti L, Antoine JC, Tronc F, Cottin V, Ternamian PJ, Trouillas P, Honnorat J.

*FDG-PT improves tumour detection in patients with paraneoplastic neurological syndromes.*

BRAIN

2004;127:2331-8.

**STROKE: The effects of botulinum toxin treatment on arm function**

Botulinum toxin is commonly used to reduce spasticity in stroke patients. Although a number of studies have reported reduced impairment, there has been little evidence of improvements in function. One reason put forward is that spasticity is not responsible for limiting function and that weakness is the only significant cause. Another is that the studies done have not had the power to detect functional gain or that inadequate measures were used. The latter reason has been addressed in an exploratory meta-analysis carried out on pooled data (n=142) from two double blind randomised controlled trials of Botulinum toxin for arm spasticity after stroke. The designs of the two studies matched sufficiently to allow pooling of the data and had the additional benefit of repeated measures post treatment to allow the temporal relationship between spasticity and function to be explored. Modified Ashworth Scale scores for the elbow, wrist and finger flexors were used to produce a composite spasticity index. Likewise a composite functional index was constructed from subjective assessments of the ability to clean the palm, cut fingernails and put an arm through a sleeve and three arm relevant items from the Barthel index. The statistical analysis demonstrated a clear relationship between changes in spasticity and changes in arm function in patients treated with Botulinum Toxin (Dysport) at 500 or 1000 units but not in those treated with placebo or 1500 units. Only a small number of patients were treated with this high dose and while spasticity was reduced it is not known whether the high dose added to the disability by over weakening injected muscles or whether their results are simply lacking in power to detect functional improvement. Many rehabilitation studies are small and meta-analysis is increasingly being recognised as the way to get answers to important questions. However the success of this method is going to depend on using common trial designs and outcome measures. In this unusual case the two studies assessed had the same first author. However in most cases in future it will be important for members of the rehabilitation research community across the world to talk to one another. – *AJT*

Francis HP, Wade DT, Turner-Stokes L, Kingswell RS, Dott CS, Coxon EA. *Does reducing spasticity translate into functional benefit? An exploratory meta-analysis.*

J NEUROL NEUROSURG PSYCHIATRY

2004;75:1547-51.

**PARKINSON'S DISEASE: Another gene, PARK8!**

Two independent groups have recently reported mutations in the LRRK2 gene for PARK8-inherited parkinsonism. This brings to five the number of genes to unequivocally cause the Parkinson's disease phenotype. So far, eight

different mutations in the LRRK2 gene have been discovered in unrelated autosomal dominant families, some of whom had previously been linked to the PARK8 region. It is too soon to speculate on the function of LRRK2, however it is of interest that part of the gene encodes a protein kinase, especially as the recently identified PARK6 gene appears to have a similar functional domain. One of the LRRK2 mutations was identified in four Basque families and in 8% of a cohort of 137 apparently unrelated Parkinson's disease patients, some with a positive family history. A detailed phenotype characterisation of PARK8 has not yet been reported, however, between these two studies there are preliminary descriptions for approximately 50 affected individuals. Based on these, PARK8 appears similar to sporadic "idiopathic PD," with disease onset primarily in the 6th or 7th decades (range 35-78-years) and an asymmetric presentation of bradykinesia, rigidity, tremor, and levodopa responsiveness. Interestingly there is a marked variation in the pathological findings, even within individuals carrying the same disease mutation. This included some patients with Lewy-body pathology, others without (pure nigral degeneration) and one individual with tau pathology similar to progressive supranuclear palsy. It will be intriguing to know what the eventual substrates of LRRK2 will be, and in particular whether this gene phosphorylates alpha synuclein, tau protein or both. – *DH*

Zimprich A, Biskup S, Leitner P, Lichtner P, Farrer M, Lincoln S, Kachergus J, Hulihan M, Uitti RJ, Calne DB, Stoessl AJ, Pfeiffer RF, Patenge N, Carbajal IC, Vieregge P, Asmus F, Muller-Miyhok B, Dickson DW, Meitinger T, Strom TM, Wszolek ZK, Gasser T.

*Mutations in LRRK2 cause autosomal dominant parkinsonism with with pleomorphic pathology.*

NEURON

2004;44:601-7.

Paisan-Ruiz C, Jain S, Evans EW, Gilks WP, Simon J, van der Brug M, de Munain AL, Aparicio S, Gil AM, Khan N, Johnson J, Martinez JR, Nicholl D, Carrera IM, Pena AS, de Silva R, Lees A, Marti-Masso JF, Perez-Tur J, Wood NW, Singleton AB.

*Cloning of the gene containing mutations that cause PARK8-Linked parkinsonism.*

NEURON

2004;44:595-600.

**DEMENTIA: The nosology of Hippocampal Sclerosis Dementia**

These two papers and associated editorial represent an important contribution to the evolving nosology of neurodegeneration. In recent years, progress in the fields of molecular genetics, immunohistochemistry and neuropathology has resulted in a move away from such bland expressions as senile and pre-senile dementia. In their place a bewildering array of terms derived from the various scientific disciplines which overlap one another to varying degrees. The concept of frontotemporal dementia (FTD) encompasses a particularly challenging area of nosology. As a minimum, all cases of FTD have the signature of focal cortical atrophy with neuronal loss, and all have characteristic higher function deficits in the domains of behaviour and/or language, in keeping with a frontal and/or temporal distribution to the atrophy. Hippocampal sclerosis dementia (HSD) is a recently described disease of unknown aetiology and pathogenesis. Cases show neuronal loss in the hippocampus, similar in appearance to mesial temporal sclerosis but in an older age-group and without a history of seizures. Nearby isocortical areas may also show neuronal loss. Parallel studies reported in Neurology last month examined 18 cases of HSD. Various comparisons were also made to groups with other neurodegenerative diseases, namely motor neuron disease (MND) inclusion dementia, Alzheimer's disease (AD) and conventionally-diagnosed FTD. The first is a detailed pathological study. The key finding is that immunohistochemical preparations show 11 of the 18 cases to have cytoplasmic ubiquitin positive inclusions located in the granule cells of the hippocampal dentate gyrus. Such inclusions are well described in motor neuron disease (MND) and FTD with clinical MND; they also occur in the absence of clinical MND in, so-called, MND-inclusion dementia. Comparison of the HSD cases with a further series of MND-inclusion dementia cases also showed similar patterns of atrophy in the two groups. The remaining 7 cases are compared with the entity of dementia lacking distinctive histopathology (DLHD). DLHD, like MND, falls within the pathological spectrum of FTD. No tau-containing lesions are identified on immunohistochemistry in the 18 cases; HSD is therefore differentiated from AD, as well as from the FTD-tauopathies (cases with Pick bodies or with the astrocytic tau pathology of the parkinsonian FTD syndromes). Furthermore, whilst a group of DLHD cases was recently shown to have abnormally low levels of soluble brain tau, tau levels in HSD were no different from controls. The second paper is a clin-

ical study with blinded, retrospective survey of records for the cases diagnosed with HSD, AD or one of the recognised FTD-spectrum pathologies. The key finding here is that the behavioural profile of HSD cases far more closely resembles that of FTD than AD. Unfortunately, limited information is available on language difficulties, which might also produce a contrast between FTD-type cases and AD. Such limitations are, of course, inherent in retrospective studies. Interestingly, memory symptoms are present in almost all cases of HSD, AD and FTD, casting doubt on the usefulness of memory symptoms to differentiate these diseases. Much remains to be clarified in the nosology of FTD. These studies strongly suggest that the majority of cases labelled as HSD may usefully be considered under the rubric of FTD as cases of MND-inclusion dementia. Some cases of HSD, however, seem to defy further labelling at present. These may provisionally be grouped alongside DLDH, on the assumption that DLDH is a heterogeneous grouping that awaits further subcategorisation. - *RD*

Hatanpaa KJ, Blass DM, Pletnikova O, Crain BJ, Bigio EH, Hedreen JC, White CL 3rd, Troncoso JC.

*Most cases of dementia with hippocampal sclerosis may represent frontotemporal dementia.*

NEUROLOGY

2004;63(3):538-42.

Blass DM, Hatanpaa KJ, Brandt J, Rao V, Steinberg M, Troncoso JC, Rabins PV. *Dementia in hippocampal sclerosis resembles frontotemporal dementia more than Alzheimer disease.*

NEUROLOGY

2004;63(3):492-7.

### PARKINSON'S DISEASE: Gaucher's disease mutations and parkinsonism

In this very simple study from Israel, the glucocerebrosidase gene was screened for six common gene mutations in 99 Ashkenazi Jewish patients with Parkinson's disease and 1543 controls. Remarkably the authors discovered that 31% of the Parkinson's disease group carried mutations (almost all were heterozygous) compared to just 6% of controls. The authors concluded that heterozygous mutations in this gene predisposed to Parkinson's disease in the Ashkenazi Jews and that the clinical phenotype in these patients was indistinguishable from idiopathic Parkinson's disease, with the exception of a slightly earlier age of onset. Homozygous mutations in the glucocerebrosidase gene have long been known to cause Gaucher's disease, a glycolipid storage disorder characterised by the cellular accumulation of glucocerebrosidase. Although Gaucher's disease has rarely been associated with atypical parkinsonism, it is currently difficult to provide a plausible biological explanation for this finding. The authors postulate that this may be from aberrant protein degradation resulting from reduced cellular glucocerebrosidase activ-

ity and/or the accumulation of glucocerebrosidase. However, this hypothesis is very preliminary and untested. Clinicians have got used to considering a genetic explanation for young onset Parkinson's disease. This paper, and the recent discovery of PARK8 mutations, provides further evidence that even the late onset "idiopathic" Parkinson's disease phenotype has a major inheritable component. - *DH*

Aharon-Peretz J, Rosenbaum H, Gershoni-Baruch R.

*Mutations in the glucocerebrosidase gene and Parkinson's disease in Ashkenazi Jews.*

NEW ENGLAND JOURNAL OF MEDICINE

2004;351:1972-7.

### PRION DISEASE: EEG periodic complexes in the diagnosis of sporadic CJD

What role do periodic complexes on the EEG play in the diagnosis of sporadic Creutzfeldt-Jakob disease (sCJD)? How are periodic complexes defined? In 1996, the group from the German CJD surveillance study published (Ann Neurol 1996;53:162-166) EEG criteria for typical periodic complexes, viz.: strictly periodic potentials, duration 100-600 ms, intercomplex interval 500-2000 ms and at least 5 repetitive intervals with a duration difference of < 500 ms (to rule out semiperiodic, or pseudoperiodic, complexes). Now the utility of these criteria has been examined in a larger data set. EEGs were examined from 206 patients with autopsy-confirmed diagnoses (sCJD = 150; non CJD = 56). The EEG assessment was performed blind to all clinical and investigation data. 64% (96/150) sCJD cases had typical periodic complexes; false positive rate was 9% (5/56). Of these five, the diagnoses were Alzheimer's disease in 4 and multiple cerebral infarctions in 1. In only one of these 5 did clinical criteria also suggest a diagnosis of sCJD. The sensitivity and specificity of the EEG criteria for the diagnosis of sCJD were 64% and 91% respectively, with positive and negative predictive values of 95% and 49% respectively. (For those who prefer to digest such data in the form of likelihood ratios, these are LR(+) = 7.1, moderate change in pre-test to post-test probability; and LR(-) = 0.39, small change.) Combining both EEG and clinical diagnostic criteria, the sensitivity, specificity, positive and negative predictive values were 63%, 98%, 99%, and 49% respectively. Hence these EEG criteria are very specific and have high diagnostic value. Their widespread adoption should be encouraged. This may avoid the occasional instance of a patient without sCJD requiring post-mortem with full prion precautions when atypical periodic complexes are recorded on an EEG; we have had 2 such instances in patients with dementia with Lewy bodies (Eur J Neurol 2004;11:838-841). - *AJL*

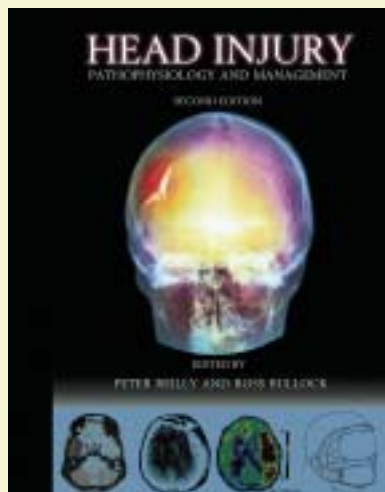
Steinhoff B, Zerr I, Glatting M, Schulz-Shaeffer W, Poser S, Kretzschmar HA. *Diagnostic value of periodic complexes in Creutzfeldt-Jakob disease.*

ANNALS OF NEUROLOGY

2004;56(5):702-8.

## HEAD INJURY

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