

EDITOR'S CHOICE

Specific verb deficit in a familial neurodegenerative disease

There is accumulating evidence that language is an integrated cognitive function, rather than being distinct from other cognitive domains; and that different neural networks underlie specific word categories, such as nouns and verbs. For example, the motor cortex is activated somatotopically upon hearing relevant verbs; selective verb deficits have been observed in motor disorders such as MND and PSP; and motor deficits have been observed in patients with 'specific' language impairments. Thomas Bak and colleagues, from Cambridge, have described two patients (father and son) and presented pathological, genetic, functional imaging and psycholinguistic data to shed light on the relationship between language and motor function. Both father and son developed a movement disorder resembling PSP, but with a prominent and more global dementia than would be expected in PSP. Naming, comprehension and semantic knowledge of verbs (using the kissing and dancing test, a verb-specific equivalent of the pyramids and palm tree test) were selectively impaired in both father and son; and this selective verb impairment persisted despite a global cognitive decline. Left-sided frontal hypometabolism was observed (using FDG-PET) in the son, and in a similar distribution, ubiquitin-positive inclusions were found in the father. The left frontal cortex is believed to be involved in verb processing. Ubiquitin-positive inclusions are unusual in PSP, and are more often associated with motor-related neurodegenerative disease like MND and semantic-related neurodegenerative disease like semantic dementia. PSP is a tauopathy, but there were very few tau-positive inclusions or tangles observed in the post-mortem brain; and no mutations in the tau gene in either patient. This study describes an unusual familial PSP-like disorder and suggests that there may be a genetic influence linking the abstract representation of movements (verbs), and the movements themselves, furthering our understanding of neurodegenerative disease, genetics, linguistics and cognitive science. - WAP

Bak TH, Yancopoulos D, Nestor PJ, Xuereb JH, Spillantini MG, Pulvermuller F, Hodges JR.

Clinical, imaging and pathological correlates of a hereditary deficit in verb and action processing.

BRAIN

2006;129:321-32.

PARKINSON'S DISEASE: Pride and Prejudice and GDNF

*** RECOMMENDED

The discovery of GDNF in 1993 led to great expectations that this trophic factor might have a positive effect in the clinical course of Parkinson's disease by rescuing the dopaminergic neurons and their projection to the striatum. Steve Gill and colleagues in Bristol embarked on a trial some years ago in which they directly delivered GDNF into the putamen of five patients with Parkinson's disease. This followed an unsuccessful trial where the factor was delivered into the ventricular system. The delivery of GDNF directly into the brain by implanted catheters, in a small open label study, clearly showed that it was a safe and efficacious procedure. Indeed in one case that was reported last year dopaminergic fibre sprouting was seen around the site of catheter implantation at post-mortem, which sat well with the previously reported increased dopaminergic signal on PET scanning at the site of GDNF delivery to the posterior putamen. It is on this background that we have to view the recent paper by Lang et al on the Amgen sponsored GDNF study in PD. This study involved 34 patients who were randomised to either receive placebo or GDNF infusion and the primary end point was changes in their UPDRS motor scores at six months. There was no significant effect of the growth factor. There were other concerns. Three patients developed antibodies to GDNF (although remained asymptomatic from this) and there were problems of catheter migration and infection in three other patients. At first glance, this negative study would lead one to believe that GDNF has no place in the future management of Parkinson's disease. This study has been criticised on a number of levels. The first relates to the delivery of the growth factor, in terms of concentration, rate and mode of delivery (size of catheter etc. were different) such that there were real concerns that the growth factor did not diffuse across the striatum but simply refluxed up the catheter tract

thereby, suggesting this study might be a false negative. In addition the patients chosen for treatment were very young and the end point was relatively short. This trial has caused a great deal of controversy not least because many of the patients on active treatment felt they were improving yet the negative outcome of the trial led Amgen to withdraw treatment. Several patients are taking court action to try and obtain further supplies of the medication. Overall this study is disappointing, but I think there are a number of methodological issues which means that it has to be interpreted with a great deal of caution. Furthermore on a broader issue, it would seem that, as with the neural transplantation double blind placebo controlled trials for PD, these trials are being performed before the therapeutic technique has been fully developed. Whilst open label studies will always be criticised because of placebo effects, it is nevertheless the only way to work out the best parameters and the optimal way to deliver that new agent. Only once that has been achieved can double blind placebo controlled trials take place. Therefore my own feeling is that GDNF definitely does have a role to play in Parkinson's disease and that this trial has not shown any efficacy for methodological, rather than scientific reasons. - RAB

Lang AE, Gill S, Patel NK, Lozano A, Nutt JG, Penn R, Brooks DJ, Hotton G, Moro E, Heywood P, Brodsky MA, Burchiel K, Kelly P, Dalvi A, Scott B, Stacy M, Turner D, Wooten VG, Elias WJ, Laws ER, Dhawan V, Stoessl AJ, Matcham J, Coffey RJ, Traub M.

Randomized controlled trial of intraputamenal glial cell line-derived neurotrophic factor infusion in Parkinson disease.

ANNALS OF NEUROLOGY

2006 Jan 20; [Epub ahead of print].

Other relevant references

Nutt JG, Burchiel KJ, Comella CL, Jankovic J, Lang AE, Laws ER Jr, Lozano AM, Penn RD, Simpson RK Jr, Stacy M, Wooten GF; ICV GDNF Study Group. **Implanted intracerebroventricular. Glial cell line-derived neurotrophic factor. Randomized, double-blind trial of glial cell line-derived neurotrophic factor (GDNF) in PD.**

NEUROLOGY

2003;60:69-73.

Love S, Plaha P, Patel NK, Hotton GR, Brooks DJ, Gill SS.

Glial cell line-derived neurotrophic factor induces neuronal sprouting in human brain.

NATURE MEDICINE

2005;11:703-4.

Gill SS, Patel NK, Hotton GR, O'Sullivan K, McCarter R, Bunnage M, Brooks DJ, Svendsen CN, Heywood P.

Direct brain infusion of glial cell line-derived neurotrophic factor in Parkinson disease.

NATURE MEDICINE

2003;9:589-95.

VENTRICULAR DRAINS: Dogma gone to the dogs

*** RECOMMENDED

It feels somewhat awkward to have an established practice not only called into question but actually undermined so that I must confess to having experienced certain unease whilst reading this paper. Like many other clinicians I have maintained, without justification it would now appear, that daily examination of CSF from an external ventricular or lumbar drain is an important measure in predicting the onset of meningitis. Tales of woe have been passed on to a succession of resident staff about the necessity for daily documentation of CSF glucose, protein, and cell count and to all of these doctors I now offer my apologies. In an extensive prospective study of patients undergoing external CSF drainage the authors demonstrated no statistical difference in the CSF concentrations of glucose and protein, or cell count, or interleukin-6 (IL-6) between patients developing external drain-related bacterial meningitis (ED-BM) [22 patients out of 230] and a control group [patients without ED-BM] in any of the 3 days prior to onset of meningitis or in the first three days following its onset, nor any predictive value in these tests, either individually or longitudinally (ie following daily trends for individual patients - another of my obsessions!). ED-BM was defined as "a positive culture on 1 or more consecutive days in combination with one or more clinical signs of bacterial meningitis (fever, headache, nuchal rigidity, and/or altered mental status) and was considered to have commenced on the first day on which a positive culture was obtained. Whilst IL-6 was significantly higher in patients with active meningitis no predictive value for this test could be established. On the other hand evidence was presented to suggest that a gram stain may be useful in suspected ED-BM. Their conclusion was that a diagnosis of ED-

BM could only be made from microbiological culture. Furthermore, in view of the low risk of meningitis in the first few days after establishing external CSF drainage they recommend sampling only twice during the first week and then daily sampling for culture thereafter and requesting gram stain only in those in whom meningitis is suspected clinically. – RR

Schade RP, Schinkel J, Roelandse FWC, Geskus RB, Visser LG, van Dijk MC, Voormolen JHC, van Pelt H, and Kuijper EJ.

Lack of value of routine analysis of cerebrospinal fluid for prediction and diagnosis of external drainage-related meningitis.

JOURNAL OF NEUROSURGERY

2006;104:101-8.

HEADACHE: in teenagers

As a junior doctor working in a renal unit in Australia, I looked after many people with end-stage renal failure due to analgesic nephropathy. Almost all were women with chronic daily headache and compound analgesic use, often dating back to their teens. Fortunately analgesic nephropathy is now very rare. But the findings of Dyb and colleagues suggest analgesia use and daily headaches in teenagers are not. In this Norwegian cross-sectional population based study of 5,471 people aged from 13 to 18 years, the prevalence of daily headache associated with analgesia use was 0.5%. The rate was higher for females (0.8%) than males (0.2%). The study found a linear relationship between analgesia use and headache frequency. This does not allow us to untangle the extent to which medication overuse exacerbated headache, but there is cause for concern at the degree of analgesia use. The extent to which early intervention and treatment of migraine in teenagers could prevent the establishment of daily headache and analgesics is an important area of future work. - HAL

Dyb G, Holman TL, Zwart J-A.

Analgesia overuse among adolescents with headache.

NEUROLOGY

2006;66:198-201.

DYSTONIA: Left or right hand? Motor planning decisions in Writer's Cramp

*** RECOMMENDED

Have you ever put a shoe on the wrong foot or a glove on the wrong hand? These everyday tasks require mental rotation, or the ability to match orientation of garment with body part in your mind's eye. Mental rotation of body parts has been used experimentally as an ingenious cognitive analogue for motor planning. Imaging studies have shown that mental rotation involves the posterior parietal and visual cortex, motor cortical areas and basal ganglia. These are the same areas that are involved in the performance of real perceptual motor tasks. This suggests that planning movements might involve a speedy cognitive run through involving an image of the body part that will be used in the action; most typically the hand. Fiorio et al have used a task involving mental rotation of hands and feet to explore the breakdown in motor control in people with Writer's Cramp. Using images of hands and feet presented at six different angles and in four different planes on a computer screen, they tested the ability of 15 patients and 15 age-matched unimpaired subjects, to identify whether the images were of right or left hands and feet. Reaction times from the presentation of the image to the onset of the verbal response were measured. Both groups had more difficulty determining their responses when the hand or foot was presented at an angle that was physically difficult to achieve. This finding supports the idea that to decide, "left or right?" subjects imagined the position by mentally simulating from the perspective of their own hands and feet. In keeping with their focal condition, the patients were slower than the normal subjects in mentally rotating hands but not feet; however their reaction times were slower than normal irrespective of whether the image corresponded to the hand affected by Writer's Cramp or to the unaffected hand. This last finding is puzzling but is in keeping with neuroimaging and electrophysiological studies showing that sensorimotor structures may be affected bilaterally in the brain despite unilateral clinical manifestations. The authors surmise that central processing abnormalities could be present before the manifestation of the condition, rather than be caused by it. Could these motor planning impairments be predictive of a susceptibility to dystonia or other peripheral sensorimotor deficits? – AJT

Fiorio M, Tinazzi M, Aglioti SM.

Selective impairment of hand mental rotation in patients with focal hand dystonia.

BRAIN

2006; 129: 47-54.

VARIANT CRETZFELD JACOB DISEASE: Beef and chicken, but not tonsillectomy

Bob Will's group in Edinburgh identified the first case of new variant CJD in the UK in 1996 and has followed the emergence of the 135 other cases since then. It is widely accepted that the disease was caught by eating beef from cows infected with BSE. Particular suspects have been neural contaminants of head meat and meat mechanically recovered from vertebral columns (a practice that ceased in 1995), which end up in low-cost meat products. This paper summarises the low-tech end of the group's enterprise: the results of interviews of the patients and their families and 922 controls (and their relatives as well!). Cases were more likely to have consumed beef, pies and burgers than controls. This seems to support the dogma. However there was evidence that these results might reflect recall bias; similar eating behaviour was reported in the 33 cases who had been labelled as having vCJD, yet turned out to have other illnesses. And eating chicken also associated with vCJD! Sausage, haggis, pork, lamb and venison consumption was no more likely amongst cases and brain itself was eaten by slightly more controls! There was no evidence that being a farmer, butcher or abattoir worker predisposed to vCJD. And, thank goodness, no association was found with surgical operations or blood transfusions (despite the one proven case of transfusion-associated vCJD which occurred in 2003). Interestingly a tonsillectomy after 1980 seemed to protect somewhat against vCJD, perhaps reflecting the role of an intact lymphoreticular system in the pathogenesis of the illness. This paper is the product of laborious, and probably rather tedious, work and has produced no real surprises. But what it lacks in charisma, it easily makes up in importance.... We are surely beholden to study closely the consequences of a terrible mistake in our food processing industry. - AJC

Ward HJ, Everington D, Cousens SN, Smith-Bathgate B, Leitch M, Cooper S, Heath C, Knight RS, Smith PG, Will RG.

Risk factors for variant Creutzfeldt-Jakob disease: A case-control study.

ANNALS OF NEUROLOGY

2006 Jan;59(1):111-20.

MENINGITIS: Cognitive outcome of bacterial and viral meningitis

In this study from Göttingen, Germany, survivors of bacterial and viral meningitis aged between 16-70 years admitted to one centre over a 12-year period were given an extensive (3 hour) neuropsychological test battery focusing particularly on the domains of attention, memory and executive function rather than general intelligence measures. Prior history of alcoholism or substance abuse, recognised predisposing factors for bacterial meningitis, were amongst the exclusion criteria. 59 cases each of bacterial and viral meningitis were tested; of the former group, the commonest organisms identified were *S. pneumoniae* and *N. meningitidis* (16 each), in 18 cases no organism was identified. 30 healthy controls were also tested. With the exception of attention, patients were worse than controls in all domains. Bacterial meningitis patients were generally worse in their cognitive performance than viral meningitis patients, with short-term and working memory and executive tasks being the most frequently and severely affected domains, but with additional difficulties with language and visuoconstructive function. There was no obvious difference in outcome between infections with *S. pneumoniae* and *N. meningitidis*, contrary to a previous study which did not control for comorbidity such as alcoholism. Neuroradiologically, bacterial meningitis survivors had reduced brain volume and greater ventricular volume compared to viral meningitis patients, and white matter lesions correlated negatively with short-term and working memory performance. The findings largely conform to what one might expect on the basis of clinical practice. They demonstrate that complaints of memory disturbance in meningitis survivors should be taken seriously and highlight the fact that viral meningitis is not necessarily benign or self-limiting. These cognitive sequelae may therefore become outcome measures in studies of the treatment of meningitis. Whether they are remediable once established, however, must be doubtful. - AJL

Schmidt H, Heimann B, Djukic M et al.

Neuropsychological sequelae of bacterial and viral meningitis.

BRAIN

2006;129(2):333-345.

EPILEPSY: the scientific basis of paternalism

Don't stay out too late or drink too much. It certainly gets us on the right side of the parents of kids with juvenile myoclonic epilepsy, although perhaps is not appreciated so much by the patients themselves. This study used TMS to measure cortical excitability in 10 patients with JME and 10 controls in the morn-

ing, the day before and the morning after sleep deprivation. In JME, sleep deprivation caused a loss of short latency intracortical inhibition and an increase in short latency intracortical facilitation, which was not seen in controls. This was seen without any change in EEG spike activity. It is thought that these changes relate to alteration of GABAergic activity. So now in true TV commercial-speak we can say it's scientifically proven that late nights affect JME brains. - **MRAM Montagnotti P, Bongiovanni LG, Fugetta G, Zanette G, Fiaschi A.** Effects of sleep deprivation on cortical excitability in patients affected by juvenile myoclonic epilepsy: a combined transcranial magnetic stimulation and EEG study.

JOURNAL OF NEUROLOGY, NEUROSURGERY AND PSYCHIATRY
2006;77:56-60.

HEADACHE: Migraine and analgesia-overuse headache

*** RECOMMENDED

There have been several clinical studies this year on the prevalence of analgesia overuse headache. The clinical scenario is familiar – episodic migraine changing to chronic daily headache associated with analgesia overuse. But there is little understanding of the mechanisms underlying this. In this study, Schoenen and colleagues studied metabolic changes using 18-FDG PET in 16 chronic migraineurs with analgesia overuse before and 3 weeks after medication withdrawal compared with a control population of 68 people. While analgesics were taken, there was reduced metabolism in several areas (thalamus, anterior cingulate gyrus, insula/ventral striatum, right inferior parietal lobule and orbitofrontal cortex). There was increased metabolism in the cerebellar vermis. After cessation of medication, all changes were reversed except for persistent orbitofrontal hypofunctioning. This same area shows persistent hypometabolism in drug dependence. The authors suggest this could predispose migraineurs to recurrent analgesic overuse, but there are a number of alternative explanations. This study begins to address the pathophysiology of an important clinical problem, and raises interesting possibilities. - **HAL Fumal A, Laureys S, Di Clemente L, Boly M, Bohotin V, Vandenheede M, Coppola G, Salmon E, Kupers R, Schoenen J.** Orbitofrontal cortex involvement in chronic analgesic-overuse headache evolving from episodic migraine.

BRAIN
2006;129: 543-50.

EPILEPSY: It's not just the fits!

Canada has two systems of validated door-to-door health surveys which gives valuable information on medical issues at a general population level. Some areas were excluded, especially military bases and Indian reserves but also some more remote areas in Quebec and Ontario were not reached. Overall ascertainment was just under 90%. Interviewers sought 20 chronic conditions including epilepsy. All 20 conditions were commoner in those with epilepsy but the following diseases were more than twice as common amongst patients with epilepsy compared to the rest of the population: peptic ulcer; stroke; urinary incontinence; chronic fatigue; migraine; chronic bronchitis; emphysema and heart disease. Confidence intervals for all these conditions did not cross unity and cancer was also significantly commoner in one of the two studies. The findings were similar in both men and women. Some of these data – stroke and migraine for example – hardly come as a surprise. It is also not clear whether the study includes data regarding smoking rates, generally higher in those with epilepsy or social class. Unemployment is common in epilepsy and associated social disadvantage may explain some of the findings but it nevertheless remains very clear that the consequences of epilepsy extend outside the obvious effects of fits and the immediate pathophysiological associations with psychiatric and other neurological diseases, which are familiar to us. - **MRAM JF Téllez-Zenteno S Matjevic and S Wiebe.** Somatic comorbidity of epilepsy in the General Population in Canada.

EPILEPSIA
2005;46:1955-62.

MULTIPLE SCLEROSIS: the diagnostic criteria shift again

Diagnosing multiple sclerosis has never been easy, but in recent years has come the added incentive to diagnose the condition earlier on the unproven basis that early treatment reduces future disability later. So, in 2000, a committee of the great and good met to redefine the illness and the “McDonald criteria” were defined. The novelty of these criteria was that they allowed defined MRI changes to take the place of clinical relapses, and so “multiple” sclerosis could be diagnosed after only one clinical attack, provided there was MRI evidence of disease activity greater than three months later. I suspect that the average jobbing UK neurologist rarely diagnoses multiple sclerosis in this way, and most neuroradi-

ologists I know look pretty blank when asked if the MRI McDonald criteria are met in this or that case. So it is likely that only the MS research community are going to be interested in a proposed revision to these criteria, which appear in the Annals. The most important change is a proposal to shorten still the time to diagnose multiple sclerosis.... by using two MRI scans. If the first scan is done at least 30 days after the onset of a clinical event, then it can be used as a “reference scan”. The second scan can be done at any point after that (even the following day!) and if it shows a new T2 lesion, multiple sclerosis can be diagnosed. Hoorah!?! Other changes are increased weight given to spinal cord MRI lesions and downgrading the role of CSF oligoclonal bands in the diagnosis of primary progressive multiple sclerosis. Diagnosing multiple sclerosis as rapidly as a month after a single demyelinating clinical event may sound good, but it also increases the burden of the illness on the patient and doctor. Conversations in clinic about treatment can be awkward as the role of disease-modifying drugs in such a situation is very unclear. And also the traumatic experience of being diagnosed with multiple sclerosis is compressed into an uncomfortably short time span. I doubt these criteria will make an impact on routine care of people with multiple sclerosis for some time yet, at least in the UK. - **AJC**

Polman CH, Reingold SC, Edan G, Filippi M, Hartung HP, Kappos L, Lublin FD, Metz LM, McFarland HF, O'Connor PW, Sandberg-Wollheim M, Thompson AJ, Weinshenker BG, Wolinsky JS.

Diagnostic criteria for multiple sclerosis: 2005 revisions to the “McDonald Criteria”.

ANNALS OF NEUROLOGY
2005 Dec;58(6):840-6.

McDonald WI, Compston A, Edan G, Goodkin D, Hartung HP, Lublin FD, McFarland HF, Paty DW, Polman CH, Reingold SC, Sandberg-Wollheim M, Sibley W, Thompson A, van den Noort S, Weinshenker BY, Wolinsky JS.

Recommended diagnostic criteria for multiple sclerosis: guidelines from the International Panel on the diagnosis of multiple sclerosis.

ANNALS OF NEUROLOGY
2001 Jul;50(1):121-7.

EPILEPSY: Biting the bullet in non-epileptic seizures

No matter how often you stop the drugs, they come back on them – why? Part of the problem is that the literature contains a confusing statistic that 20% of patients have both epilepsy and non-epileptic seizures and doctors lose their nerve. The trouble is that the literature asks the wrong question. To quote John Cleese: “in my opinion, which I admit is only spot on” there are three main groups. Firstly, patient A who has new onset epileptic seizures, secondly patient B who has new onset non-epileptic seizures and thirdly patient C who has a longstanding and intractable problem. I would argue that patients A and B almost always have a single diagnosis and patient C is responsible for all the confusion. This study gives support to taking confident steps for those patients who have non-epileptic seizures. The authors had the luxury of defining their cases with video-EEG-telemetry and ensuring that their patients historically had no other seizure types. Of 99 patients, one refused to withdraw medication, and another 20 were not followed up completely for various reasons. Amongst the 78 completing withdrawal, the seizure frequency fell from 22 to 9 per month by one year and admissions for pseudostatus fell from 23 to 4. There were no major complications. This study shows us that it is safe to act decisively early in the course of their illness and withdraw the medication, which reinforces the illness behaviour, before the social consequences of their illness become intractable. - **MRAM**

Oto M, Espie C, Selkirk M, Duncan R.

The safety of drug-withdrawal in patients with non-epileptic seizures.

JOURNAL OF NEUROLOGY, NEUROSURGERY AND PSYCHIATRY
2005;76:1682-5.

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