

## EDITOR'S CHOICE

**Is the Lewy body important in the death of neurons?**

The relationship between alpha synuclein, Lewy body formation and neurodegenerative processes has always proven slightly elusive. Indeed the normal function of alpha synuclein has always remained somewhat mysterious but is thought to have something to do with normal synaptic function. In the mid 1990's it was discovered that mutations in alpha synuclein could cause parkinsonism and shortly afterwards it was shown that the Lewy body (the pathological hallmark of Parkinson's disease) contained alpha synuclein. This implied that alpha synuclein could have something to do with Parkinson's disease and by inference Parkinson's disease dementia and dementia with Lewy bodies (DLB). In a recent paper in the Journal of Neuroscience, Michael Kramer and Walter Schulz-Schaeffer have investigated this and suggest that it is not the Lewy body formation that is responsible for the neurodegeneration but the presynaptic aggregation of alpha synuclein. They used a technique called paraffin embedded tissue (PET) blot [not to be confused with PET imaging] and a protein aggregation filtration assay so that they could sensitively and accurately detect alpha synuclein aggregates in various tissue sources. They found that they could detect using this technique large amounts of alpha synuclein aggregates in patients with dementia with Lewy body and that this correlated more with the cognitive impairment than Lewy body formation which was relatively limited and not related to any measures of cognitive decline. This suggests that Lewy body formation may be a protective mechanism and not a direct pathogenic pathway and that the aggregation of alpha synuclein presynaptically may be the critical event in triggering neuronal dysfunction leading to neuronal death. It would therefore be this that causes neuronal death in DLB and also presumably in Parkinson's disease. This raises many interesting questions not least of which is what is the role of the Lewy body and in particular should we be targeting therapies to get rid of such structures or would such an approach prove to be more disastrous than helpful. - *RAB*

Kramer ML, Schulz-Schaeffer WJ (2007).

**Presynaptic alpha-synuclein aggregates, not Lewy bodies, cause neurodegeneration in dementia with Lewy bodies.**

JOURNAL OF NEUROSCIENCE

2007;27:1405-10.

**STROKE: Stenting is not inferior to endarterectomy**

This is, bless its cotton socks, a preliminary positive non-inferiority trial. For all that, I suspect its conclusions may not be correct. In the Stent-Supported Percutaneous Angioplasty of the Carotid Artery versus Endarterectomy (SPACE) trial, 1183 people within 180 days of a TIA or ischaemic stroke, and with severe symptomatic carotid stenosis, were randomised to stenting or surgery. The headline result is that there is no difference in the early outcome at 30 days. Whilst this may be true statistically, endarterectomy outperformed stenting (non-significantly) on nearly every outcome (for instance the primary outcome measure of recurrent stroke was 4.0% in the carotid-artery stenting group and 2.9% in the carotid endarterectomy-group). I am not entirely sure why the Lancet published this... because the conclusion has to be wait and see what the 6-24 month data shows, but my suspicion is that endarterectomy will win the day. - *AJC*

SPACE Collaborative Group.

**30 day results from the SPACE trial of stent-protected angioplasty versus carotid endarterectomy in symptomatic patients: a randomised non-inferiority trial.**

LANCET

2006 Oct 7;368(9543):1239-47.

**MEMORY: working memory dysfunction in subclinical hypothyroidism**

Hypothyroidism is often quoted as a cause of reversible dementia, but how many practitioners have ever seen a case? Nonetheless, the possibility that thyroid dysfunction may influence cognitive function remains, and is added to by this study from China. Patients with subclinical hypothyroidism (SCH; = low TSH with normal T3, T4, free T3 and free T4) performed a digit n-back task, a test of working memory, as well as the Wechsler Memory Scale (WMS) as did euthyroid, hyperthyroid, and hypothyroid patients. The former test was also performed whilst undergoing fMRI. The task load of the digit n-back task may be increased: n = 0 is a straight identification task, whereas n = 1 (recall

the digit before the current one) and n = 2 (recall the second digit before the current one) require more "online manipulation", such that subjects with hypothyroidism may disengage from the task if it becomes too difficult. SCH patients proved less accurate than euthyroid and hyperthyroid patients at the 2-back task, but better than hypothyroid patients, whilst the WMS showed no significant differences across the groups, suggesting that working memory is impaired in SCH and hypothyroidism but not other memory functions. fMRI activation of a common frontoparietal network known to underpin performance of the n-back task was not seen in SCH subjects, in whom frontal activation was abnormal, suggesting impairment of executive function. Interestingly, a subgroup of the SCH subjects who were retested after 6 months treatment with thyroxine showed recovery in both task performance and fMRI parameters. Hence this study shows impairment of working memory in SCH with clues to the neural substrate for this dysfunction, and also provides some tentative evidence for the use of thyroxine in SCH. - *AJL*

Zhu DF, Wang ZX, Zhang DR, Pan ZL, He S, Hu XP, Chen XC, Zhou JN.

**fMRI revealed neural substrate for reversible working memory dysfunction in subclinical hypothyroidism.**

BRAIN

2006;129(11):2923-30.

**STROKE: Therapy time in stroke units: what are we doing with it?**

\*\*\* RECOMMENDED

Intensive task specific exercise has a significant positive effect on the functional recovery of stroke patients. The evidence for this is very strong. However, stroke rehabilitation units in the UK are not organized to optimise the amount of therapy given to patients. Indeed, a recent investigation of therapy time allocated to therapeutic activities in four stroke units in different European countries showed the UK unit was for the most times poorest. Physiotherapists and occupational therapists spent only 46% and 33% of their time doing therapeutic activity with patients in the UK unit. This compared with 54%, 66% and 62% for physiotherapists in the Swiss, German and Belgian Units and 45%, 63% and 50% for occupational therapists. More time was spent on patient related co-ordination activities (e.g., administration, ward rounds) in the UK unit. The units involved in the study all have a long tradition of stroke rehabilitation. The survey was carried out by asking therapists to document their activities in 15-minute periods for two weeks. Diaries from 95 physiotherapists and 51 occupational therapists were collected and a total of 20,421 periods of 15 minutes encoded. The lack of time spent in therapeutic activity in the British unit was not due to lower staffing levels. The reason is more likely to be due to differences in priorities of the unit managers. This study is part of a larger European project, Collaborative Evaluation of Rehabilitation in Stroke across Europe (CERISE) comparing the outcome after stroke between SRUs and it remains to be seen whether outcome is any worse in the UK unit than the others, or indeed if the increased time spent communicating with the rest of the team in the UK unit leads to better discharge management and patient satisfaction. However, given the evidence for the benefits of task specific training, it would seem wise to explore ways in which we can increase opportunities for patients to practice. Perhaps some therapy could be given in groups. The survey also showed that most treatments were delivered on a one to one basis (91.2% of physiotherapy treatments and 86% Occupational therapy). It's time for a culture change in British stroke rehabilitation. - *AJT*

Putman K, De Wit L, Schupp W, Ilse B, Berman P, Connell L, Dejaeger E, De Meyer A-M, De Weerd W, Feys H, Walter J, Lincoln N, Louckx F, Anneleen M, Birgit S, Bozena Smith B, Leys M.

**Use of time by physiotherapists and occupational therapists in a stroke rehabilitation unit: A comparison between four European rehabilitation centres.**

DISABILITY AND REHABILITATION

2006;28:1417-24.

**MULTIPLE SCLEROSIS: Treated by carbon monoxide poisoning?**

In this paper, Soares' group in Portugal examine the role of hemeoxygenase-1 and carbon monoxide as treatments of EAE. This all arises from the finding of raised levels of hemeoxygenase-1 (HMOX1/HO-1) in the CNS during the course of MS and EAE, where it is the rate-limiting enzyme in the catabolism of heme. They showed first that HO-1 knock-outs get much worse disease than normal animals, and induction of HO-1, by cobalt protoporphyrin IX, reduced the severity of EAE -both when given prophylactically and therapeutically- in healthy animals. Based on their experience in other

inflammatory conditions, where exogenous CO mimics the effect of HO-1 induction, they then gave animals CO (250 ppm in air) before attempting to induce EAE and fewer animals succumbed. Nice pathology showed that HO-1 induction reduced the amount of inflammatory cells and foci in the brains of EAE animals. And there were fewer infiltrating T cells expressing IFN-gamma, but no change to those expressing IL-10, so all good anti-inflammatory stuff. On the other hand, there was no change in the number of regulatory T cells [see ACNR this issue - page 10] in the animal's brains. It turns out that HO-1 exerts its effects on T cells by reducing the reactivation of T cells that are already primed (as they would be in someone with multiple sclerosis) by reducing the expression of the key Class II molecule on CNS antigen-presenting cells. One of the first experiments that now needs to be done is to type, in multiple sclerosis patients, the (GT)<sub>n</sub> micro satellite polymorphism in the human HMOX1 promoter, which is already associated with susceptibility to a variety of other inflammatory disease. But, of course, the authors' main suggestion is that we should administer CO to patients with multiple sclerosis..... which would be a brave thing to do for after 3 hours of CO at 250ppm, most people will experience nausea, chest tightness and memory loss; at 800ppm people can develop seizures and become comatose within 45 minutes; and at 1600 ppm, death can occur within the hour. - *AJC*

Chora AA, Fontoura P, Cunha A, Pais TF, Cardoso S, Ho PP, Lee LY, Sobel RA, Steinman L, Soares MP.

Heme oxygenase-1 and carbon monoxide suppress autoimmune neuroinflammation.

JOURNAL OF CLINICAL INVESTIGATION

2007 Feb 1;117(2):438-47.

### REHABILITATION: Hand splints, a stretch of the imagination?

Recovery of arm and hand movement after stroke can take many weeks. While the arm is immobile muscle stiffness and contractures frequently develop which can lead to pain and discomfort and inevitably compromises emergent recovery of movement. In severe cases the stiffness can make every day activities such as dressing, washing and hand care difficult. The most common occupational therapy intervention to address this problem is to provide splints to prevent or correct contractures in the wrist and long finger flexors. Until a few years ago, there were no high quality trials to support or refute the effectiveness of wearing hand splints in stroke patients. Then a group of therapists in Sydney reported a randomized controlled trial comparing the effect of splinting plus stretch exercises, versus stretch exercises alone, in which no effect of splinting was apparent. They used splints that held the wrist in slight extension with the fingers with the metacarpophalangeal joints in flexion and interphalangeal joints extended. This 'neutral position' is most often used since it is comfortable but keeps length in the extensor tendons. However because the aim of splinting is to influence muscle extensibility, some therapists believe that sustained positioning of muscles close to the end of range is more likely to provide a greater effect on contracture. So now the same Australian group have reported another excellent trial but this time they compared three conditions. One group of 21 patients wore 'extension' splints, that held the wrist and finger in a comfortable end-of-range position >45° wrist extension and with the metacarpophalangeal and interphalangeal joints all extended. The second group of 20 patients wore neutral position splints and a third group of 21 patients did not wear splints at all. The splints were worn at night for between 9 and 12 hours on average for four weeks and none of the patients received stretching exercises over the period of study. An assessor who was blinded to the treatment group measured wrist extension range with the metacarpophalangeal and interphalangeal joints in the extended position with a standardised torque applied. There was no significant difference between the three groups; neither splint was effective in increasing the extensibility of the wrist and long finger flexor muscles. These results are contrary to current thinking, based on animal studies, that muscle length adapts to sustained stretch. The splints were worn all night and that is as long as a stretch as most therapists would advise, therefore the dose is as long a stretch as the maximum that would usually be considered practical. In the light of these new results it is time for occupational therapists to consider whether the time-consuming practice of making and fitting hand splints to prevent muscle contracture during acute rehabilitation after stroke should be discontinued and instead more effective solutions should be sought - *AJT*

Lannin NA, Cusick A, McCluskey A, Herbert RD.

Effects of Splinting on Wrist Contracture After Stroke: A Randomized Controlled Trial.

STROKE

2007; 38:111-6.



## A Day in the Life...

...is a simple and fun way for European neuroscientists to get involved in communicating what you do to the public. Using a disposable camera to document your day, we want to show the public and young people in particular what the everyday lives of neuroscientists entail: highlighting the important research work as well as showing the human side to a career in neuroscience.

The project is run by The Manchester Science Group [www.manchesterscience.blogspot.com](http://www.manchesterscience.blogspot.com) and sponsored by the European Dana Alliance for the Brain.

To take part, email your postal address to: [mansci@googlemail.com](mailto:mansci@googlemail.com) with **A DAY IN THE LIFE** in the subject line and you will receive a disposable camera pack and instructions.

PARKINSON'S DISEASE SOCIETY



Parkinson's  
Disease Society

The PARKINSON'S DISEASE SOCIETY (PDS) helps people with Parkinson's and their families by providing advice and support, information, and funds for research into the condition.

## Project Grant Applications

Research is one of the Parkinson's Disease Society's (PDS) key aims, and has been a major focus of our work for the last 30 years. The Society is looking to make a major step forward in funding quality research into all aspects of Parkinson's disease research. As part of our continuing commitment to build research capacity related to Parkinson's, we wish to invite applications for our highly successful and established project grant scheme.

Applications are invited for project grants of up to three years. Grants are tenable only at a United Kingdom University, an NHS Trust, a statutory Social Care organisation, or other research institution.

The Parkinson's Disease Society supports Biomedical, Health and Social Care and Social Policy research and wishes to particularly encourage research related to the improvement of the quality of life for people with Parkinson's.

Application forms may be obtained from our website, [www.parkinsons.org.uk](http://www.parkinsons.org.uk) or Research Office, Parkinson's Disease Society, 215 Vauxhall Bridge Road, London SW1V 1EJ or email [research@parkinsons.org.uk](mailto:research@parkinsons.org.uk)

Closing date: Thursday 5 April 2007. Please ensure that you use the current guidelines and application form, both on the Society's website.

Parkinson's Disease Society of the United Kingdom. Registered Charity No. 258197.