

EDITOR'S CHOICE

MEMORY: A role for prions in long-term memory storage

Prions are proteins that are able to adopt two functionally distinct conformations, one of which is self-perpetuating. They are usually associated with a family of mammalian neurodegenerative diseases called transmissible spongiform encephalopathies, which include CJD. In yeast, prions are non-pathogenic and are thought to explain the non-nuclear inheritance of a new phenotype. This paper reports the possession of prion-like properties in the neuronal CPEB (cytoplasmic polyadenylation element binding) protein from the sea slug, *Aplysia californica*. This protein facilitates messenger RNA (mRNA) translation by polyadenylating the tails of dormant mRNAs. Prion-like properties may allow the protein to produce the localised synaptic strengthening thought to be important in memory storage.

The study demonstrates that, in many respects, CPEB behaves like yeast prions. It possesses an amino terminal domain rich in polar glutamine residues and possesses conformational flexibility that allows it to switch into a self-perpetuating form. Moreover, when the amino terminal domain of CPEB is fused to a reporter protein in yeast, it induces a dominant conformational change that is transmissible along cell lines. Finally, like yeast prion propagation, the switching of CPEB conformation is influenced by heat shock proteins. Unlike normal prions, it was surprising to find that it was the self-perpetuating, aggregated form of CPEB that represents the active state of the protein.

Despite the fact CPEB has yet to be found in different conformational states in *Aplysia* neurons in vivo, the authors propose a model to explain how the prion-like state may contribute to the long-term synapse-specific changes involved in long-term memory formation. Pulses of the neurotransmitter serotonin, which simulate long-term memory training, upregulate CPEB levels at the active synapse in *Aplysia* neurons. It may be the neurotransmitter itself or the elevated level of protein that leads to the switch of CPEB to its active "prion" state. The CPEB in the active synapse triggers local translation of dormant mRNAs, associated with structural and regulatory molecules leading to strengthening of specific synaptic connections. The self-perpetuating nature of CPEB in its "prion" state means it can sustain the altered rate of translation on a long-term basis with minimal energy expenditure, compared to phosphorylation.

CPEB is present in post-synaptic regions of vertebrates and higher mammals, but it is unclear at present whether this prion mechanism contributes to long-term memory storage in such organisms and work is currently underway to investigate this. -LMS, SJT

A Neuronal Isoform of the Aplysia CPEB Has Prion-Like Properties.

Si K, Lindquist S, Kandel ER.

CELL

2003; 115: 879-91

Panel of Reviewers

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NEUROLOGICAL DRUGS**How does intravenous immunoglobulin work?**

There are dozens of suggested answers to this question, possibly different in different diseases. The most robust come from electrophysiological studies of autoimmune peripheral nerve diseases. We reported last year on Klaus Toyka's *Annals* paper showing the neutralisation of blocking antibodies in Guillain-Barré syndrome by IVIG.

Now Hugh Willison's group in Glasgow have produced similar results in Miller Fisher syndrome, that variant of Guillain-Barré syndrome characterised by ophthalmoplegia, ataxia and areflexia associated with anti-GQ1b antibodies. This group has developed a system for assaying the "latrotoxin-like" (a spider toxin) effects of anti-GQ1b antibodies on mice diaphragm muscle strips: application of Miller Fisher serum produces miniature end plate potentials that summate to produce visible twitches and complement is deposited at the neuromuscular junction. IVIG blocked the binding of serum anti-GQ1b antibodies to the GQ1b ganglioside in an ELISA; furthermore IVIG was able to partially displace anti-GQ1b antibodies already bound to GQ1b ganglioside. When applied to muscle strips, IVIG reduced the latrotoxin-like effects of serum containing anti-GQ1b antibodies. However, if serum was applied first and then IVIG later, latrotoxin-like effects were still seen. The conclusion is that IVIG works in this model by preventing, or reversing, the binding of anti-GQ1b antibodies to their target, but does not influence downstream effects.

Whilst such a mechanism nicely explains why IVIG sometimes has such rapid clinical effects, it does not account for its prolonged action, well beyond its half-life in serum, in diseases such as multifocal motor neuropathy. -AJC *Immunoglobulins inhibit pathophysiological effects of anti-GQ1b-positive sera at motor nerve terminals through inhibition of antibody binding.*

Jacobs BC, O'Hanlon GM, Bullens RW, Veitch J, Plomp JJ, Willison HJ.

BRAIN

2003;126:2220-34

☆☆☆ RECOMMENDED

MEMORY: Sleeping on it: solutions from sleep

When our parents told us that "it would all be clearer in the morning", they may just have been right. This fantastic experiment tests our ability to solve problems during sleep. The design was very simple: people were given a problem to solve and then given 8 hours of either night time sleep, night time wakefulness or daytime wakefulness. They were then re-exposed to the problem: those who had slept had more that double the chance of solving it than the other groups. The task was crafty. Subjects had to process a string of numbers by two rather laborious rules to get a final answer. But there was a shortcut, which the subjects had to discover for themselves. The endpoint of the test was the number of people who spotted and used this shortcut in each group.

One interpretation of this result might be that the refreshment of sleep improves cognitive performance. But the authors, from Germany, tested different subjects on this task after sleep, without previous exposure. This group performed at the same levels as the "wake" groups in the first experiment. This suggests that there was processing of the task's rules during sleep following exposure to the task. Another important confound was excluded by studying the subject's reaction time. Normally, the reaction times to stimuli in the second test were shorter than those in the first. But amongst those subjects in the sleep group who solved the problem, reaction times actually slowed between trials. This might suggest some competition for the mechanism underlying sleep-time learning between motor planning and problem solving! -AJC

Sleep inspires insight.

Wagner U, Gais S, Haider H, Verleger R, Born J.

NATURE

2004 Jan 22;427(6972):352-5

PARKINSON'S: Improved understanding of alpha-synuclein biology and pathobiology

Alpha-synuclein is a protein abundantly expressed throughout the brain at nerve terminals. It is implicated in a number of neurodegenerative diseases, particularly Parkinson's disease, where it accumulates in ubiquitinated cytoplasmic inclusions called Lewy bodies. Its normal function remains unclear. In vitro data have suggested a role for alpha-synuclein in cellular lipid metabolism and synaptic vesicle trafficking. It is also thought to be important in development, learning and plasticity.

This paper employs a yeast model, which has a highly-conserved protein quality control and membrane trafficking mechanism, to investigate normal and abnormal alpha-synuclein biology in vivo. Wild-type alpha-synuclein and two mutant forms (A53T and A30P), both associated with early onset

familial Parkinson's disease, were expressed in yeast.

In an attempt to mimic aging neurons, in which misfolded proteins accumulate due to a compromised protein quality control system, the three constructs were over-expressed by two-fold. This doubling in expression levels had severe consequences at the cellular level. First, it severely inhibited yeast cell growth. Second, the wild-type and A53T mutant proteins, which are normally localised specifically to the plasma membrane, had been recruited into large cytoplasmic inclusions. The A30P mutant exhibited impaired membrane-binding capacity. Thirdly, over-expression of all three forms of alpha-synuclein lead to their ubiquitylation, which indicated they were misfolded and were destined for degradation by the proteasome. Finally, these misfolded proteins were demonstrated to directly impair proteasome function.

Alpha-synuclein has also been reported to share biophysical properties with fatty acid binding proteins. The study proceeded to investigate the proposed role of alpha-synuclein in lipid metabolism and synaptic vesicle trafficking. Alpha-synuclein was shown to inhibit phospholipase D (PLD) in vivo, promote lipid accumulation and to disrupt synaptic vesicle membranes causing the release of neurotransmitter into the cytoplasm.

This paper clearly demonstrates how minimal disruption in protein quality control mechanisms and subsequent accumulation of alpha-synuclein can have devastating effects on cellular function. The confirmation of the involvement of alpha-synuclein in lipid metabolism and vesicle trafficking is important, and such findings suggest these may be primary pathogenic pathways in Parkinson's disease. This data is also supported by clinico-genetic observations. It has recently been reported by John Hardy's group that a triplication at the alpha-synuclein locus, causing a doubling of wild-type gene expression, causes premature onset of PD in humans. This supports the notion that a small change in the expression of alpha-synuclein relative to the cell's quality control systems causes disease-related toxicity. -LMS, SJT

Yeast Cells Provide Insight into Alpha-Synuclein Biology and Pathobiology.

Outeiro TF and Lindquist S.

SCIENCE

2003;302:5651:1772-1775

HUNTINGTON'S: The sweet taste of success in treating Huntington's disease

This is yet another paper suggesting a possible treatment for Huntington's disease, but unlike some other compounds this agent is simple, non-toxic and easy to administer orally. In this study Tanaka and colleagues began by using an in vitro screening strategy involving a mutant sperm whale myoglobin! This assay involved screening for inhibitors of polyglutamine-mediated protein aggregation and showed that a disaccharide TREHALOSE caused a significant and dose dependent reduction in this aggregation. This is a property of a number of disaccharides and it appears to work through stabilisation of the proteins containing the expanded polyglutamine. They then demonstrated that trehalose decreased aggregate formation in a transfected neuroblastoma cell line and increased cell viability in a dose dependent fashion. Finally the group tried their compound in the R6/2 transgenic mouse model of HD and showed that it was effective in terms of reducing weight loss but not the development of diabetes (common features of this mouse model of HD), improved motor performance and decreased pathology - both the degree of atrophy and number of inclusions. Finally in this model the compound increased the average life span of the mice from ~97 to 108 days.

This is another interesting study, given its simplicity and thus the obvious translation into the clinical arena. However clearly more work needs to be done before clinical trials can be done, especially given the relative reduced life span of their R6/2 mice. Indeed a better test for the compound may involve the use of the newer better mouse models of HD using full length huntingtin and knock-in strategies. -RAB

Trehalose alleviates polyglutamine-mediated pathology in a mouse model of Huntington Disease.

Tanaka M, Machida Y, Niu S, Ikeda T, Jana NR, Doi H, Kurosawa M, Nekooki M, Nukina N.

NATURE MEDICINE

Published online 18th Jan 2004

☆☆☆ RECOMMENDED

BIH: Venous stenting for idiopathic (benign) intracranial hypertension

Idiopathic intracranial hypertension (IIH) is a syndrome characterised by visual disturbance and headache. Papilloedema is common but not invariable. A variety of terms have been used to describe the syndrome including pseudo-tumour cerebri, benign intracranial hypertension and, as first described by Quincke in 1897, serous meningitis. Ventricular size is not increased but CSF pressure is raised. CSF examination is normal, other than raised pressure. Various causes have been implicated, including middle ear

infection, obesity, various drugs, and venous sinus thrombosis. Management has hitherto been somewhat empirical, relying initially on serial lumbar punctures sometimes combined with the administration of the carbonic anhydrase inhibitor, acetazolamide. For resistant cases CSF diversion strategies, for instance lumboperitoneal shunts, have been employed. When this fails cranial decompression procedures or optic nerve sheath decompression have been used rather as a last resort.

Two recent studies, a report of a single case in Newcastle, and a series of 12 patients reported from Cambridge, emphasise the importance of stenosis of the lateral venous sinus as a possible patho-aetiological mechanism. In both studies treatment was with venous stenting. The background to these studies is recent evidence which suggests that in some patients with IIH the raised intracranial pressure (ICP) may be the result of focal stenotic lesions of the lateral sinus. In Cambridge 12 female patients with IIH, all with raised CSF pressure (> 25cm H2O), intractable headaches and visual disturbance, underwent invasive monitoring of lateral venous sinus pressure and were treated with venous sinus stenting via percutaneous jugular puncture. Follow-up was undertaken at 8-12 weeks. Initially, 5 patients were rendered asymptomatic and 2 showed some improvement but had residual headache. None of these patients showed clinical deterioration over a further follow-up of 9-24 months.

In the case report from Newcastle a diagnosis of benign intracranial hypertension was made on clinical and radiological grounds and phase contrast MR venography (MRV) showed evidence of reduced flow within the left transverse sinus which was felt to be congenitally narrowed or occluded. A significant pressure gradient was recorded across the stenosed segment. At follow-up evaluation, 3 months and 6 months following stenting, symptoms had completely resolved and there was reduction in the severity of pre-treatment papilloedema. Cerebral angiography at 12 months was satisfactory, as were interval repeat MRVs.

The relationship between raised ICP in IIH and possible lateral venous sinus stenotic lesions is not clear-cut. Not only is radiological interpretation complicated by variations in normal anatomy but also raised ICP itself may result in secondary collapse of the lateral sinuses, a reversible phenomenon. Furthermore, removing CSF during venography has been found to reduce or eliminate pressure gradients in the lateral venous sinuses and reduce intracranial venous hypertension. However, with the hypothesis that venous outflow obstruction results from lateral sinus stenosis in mind, venous stenting seems logical and, to the extent that a number of patients thus treated have gained prolonged symptomatic improvement, justified. The question remains as to whether this iterative loop of raised intracranial pressure is the result of a physical, anatomical variant (venous stenosis) or to a physiological phenomenon (venous collapse). Even if selection difficulties can be overcome it remains to be seen whether or not medium-term symptomatic relief in some of these patients is maintained or whether venous obstruction at the site of stenting will recur. - RMR

Endovascular stenting of the transverse sinus in a patient presenting with benign intracranial hypertension.

Ogungbo B, Roy D, Gholkar A, Mendelow AD.

BRITISH JOURNAL OF NEUROSURGERY

2003;17(6):565-8

Idiopathic intracranial hypertension : 12 cases treated by venous sinus stenting.

Higgins JNP, Cousins C, Owler BK, Sarkies N, Pickard JD.

JOURNAL OF NEUROLOGY NEUROSURGERY AND PSYCHIATRY

2003 ;74:1662-6

REHABILITATION: A picture to improve arm recovery after stroke

This winter many England rugby fans were on the edge of their seats while Jonny Wilkinson played a mental movie to himself in preparation for the kick that won the world championship. The power of mental practice is well known in the world of sport. Over the last five years these sports science methods have become of interest for retraining movement in patients following stroke and benefits have been demonstrated in a few small studies.

One such study is reported in the first issue of Clinical Rehabilitation this year. The authors of this study were interested to see if mental practice would help patients in a stroke unit. 10 patients were given daily mental practice for two weeks and their rate of improvement on the Motricity index score for the upper limb was compared before, during and after the two weeks mental practice.

The rate of recovery was increased over the intervention phase in eight of the patients, in one patient no change was seen and change in the remaining patient was not analysed because performance over the baseline phase was not stable. The study has limitations: it is small and there is an inherent difficulty in checking compliance to mental practice. Patients were their own controls rather than there being a control group and the status of the asses-

sor (blinded or not to the phase of study) was not reported. However the results of this pilot study are very promising and if substantiated mental practice may provide a simple and inexpensive means of supplementing therapy. Even in stroke units patients have little opportunity to carry out real practice so with adequate training those who are cognitively able may at least be able to do mental practice while they sit by their beds. -AJT

The adjunctive role of mental practice in the rehabilitation of the upper limb after hemiplegic stroke.

Crosbie JH, McDonough SM, Gilmore DH, Wiggam MI

CLINICAL REHABILITATION

2004; 18: 60-68

SPEECH: Treating aphasia

Two rather distinct approaches to aphasia therapy have emerged over recent years. The first, based on strong cognitive neuropsychological models, focuses on a specific aspect of the language impairment, e.g. semantic processing, with little direct attention to generalisation into everyday communication. The second has a much broader perspective, in which language is viewed as only one aspect of overall communicative ability. It has been easier to demonstrate improvements using the first approach but a query remains over the extent to which this really helps people. Conversely, the second approach, while firmly rooted in real communication, is much more difficult to measure.

This study (the second in a series of three) contributes to what is as yet a very small literature where the two approaches have been investigated together. In the full study six patients were taken through two baseline assessments, and two major periods of therapy, one termed 'lexical therapy' and the other 'communicative'. The previous paper reported the results of the lexical therapy; this paper has a focus on the combination of lexical and communicative therapy, in which tasks moved gradually from picture naming, to exercises involving the transmission of specific information and on to natural conversation. Within the broad range of results there were different patterns of gain across the lexical and communicative therapy phases. One participant did not benefit from the communicative therapy (but had from the earlier lexical therapy) while the pattern was reversed in another. The authors were able to conclude that overall gains were made via the combined therapy for five of the six participants.

The small number of previous studies involving both approaches to therapy is at least partly attributable to the complexity of issues involved. This study produces interesting and informative results in its own right and advances some of the methodological issues to promote more work in the field. -RB

Combining lexical and interactional approaches to therapy for word finding deficits in aphasia.

Herbert R, Best W, Hickin J, Howard D and Osborne F.

APHASIOLOGY

2003; 17: 1163-1186

REHABILITATION: A "holistic wellness program" for people with spinal cord injury

This interesting study from a US university centre demonstrated the benefit of a 7 month "wellness programme" for patients with spinal cord injuries (SCI), many of the features of which seem to constitute an integral part of "the standard" rehabilitation programme offered by centres this side of the Atlantic. This was a randomised controlled trial for patients with SCI of a series of six 4-hr (outpatient) workshop sessions over a 3 month period with telephone follow-up and support for the following four months. The study group were a mean of 14 years since their injury and 43 out of 67 starters completed the 7-month trial. Though difficult to ascertain exactly the content and how the sessions were conducted, it consisted of four modules which were "didactic & experiential": lifestyle management, physical activity, nutrition and prevention of secondary complications. The workshops were facilitated by two staff members with SCI and there were individual coaching sessions by the teachers for 3 of the 4 modules.

They based the design of their programme on Stuijbergen's self-efficacy model, defined as the "degree of confidence that one can successfully perform a specific behaviour". Their outcome measures included Self-Rated Abilities for Health Practice and other such scales to assess this model. The other outcome measures related to the modules described above and a standard ASIA neurological examination conducted at entry, at 2 weeks and 4 months after the workshops. Using regression analysis the standardised measures for each of health-related self efficacy, nutritional awareness and behaviour, stress management and physical fitness as well as secondary conditions all showed significant improvements with the intervention, supporting their model. However there were no changes in physiological (some may say more objective) measures which the authors attributed to the short time frame involved.

As usual for a rehabilitation study it was limited by small sample size and

heterogeneity of the sample but did achieve statistical significance in a number of areas with high satisfaction ratings from participants. Whilst acknowledging Prof. Derek Wade's concerns about opening the "black box of rehabilitation" this study adds some evidence to understanding the vital components of a comprehensive rehabilitation programme. It would be interesting to compare the outcomes (including economic) of the "short-sharp" sub-acute rehabilitation programmes commonly on offer in the US along with this programme, with "the standard" programmes on offer in the British Isles and Europe. - JJMACF

Assessment of a Holistic Wellness Program for Persons with Spinal Cord Injury.

Zemper ED, Tate DG, Roller S, Forchheimer M, Chiodo A, Nelson SV, Scelza W.

AMERICAN JOURNAL OF PHYSICAL AND MEDICAL REHABILITATION
2003;82:957-968

GUILLAIN-BARRÉ SYNDROME: What lies between GBS and CIDP?

By definition, patients with Guillain-Barré syndrome reach their worst point within four weeks from the start of their neurological symptoms, and people with chronic inflammatory demyelinating polyneuropathy have a progressive decline (with or without relapses) over months. However not every case fits these criteria and there has always been some debate about whether an additional entity, subacute inflammatory demyelinating polyneuropathy (SIDP), exists. In this paper Oh and colleagues examined patients with SIDP based on their history (progression with nadir between 4 and 8 weeks from onset with no relapse on follow-up) and neurophysiology. Using these criteria they identified 16 definite and 13 probable cases, and showed that cranial nerve involvement and respiratory failure were rare features and that most responded to steroids with complete recovery in two thirds of cases. They therefore suggested that SIDP was more like CIDP than GBS, but that there was a higher rate of antecedent infection and a higher recovery rate in SIDP.

This paper claims to show that SIDP is different from CIDP and GBS, but to my mind this claim remains unproven. Nevertheless on a pragmatic level it does suggest that patients progressing beyond 4 weeks with "GBS" might well benefit from steroid treatment. -RAB

Subacute Inflammatory Demyelinating Polyneuropathy.

Oh SJ, Kurokawa K, de Almeida DE, Ryan HE, Claussen GC.

NEUROLOGY

2003; 61: 1507-1512.

GUILLAIN-BARRÉ SYNDROME: Steroids along with IVIG for GBS?

I clearly remember the conclusion of the presentation of the Dutch GBS group at the ENS in 2002: IV methylprednisolone combined with IVIG improved the outcome of GBS when compared to IVIG alone. I even reported this result in ACNR. However, by the time their work was acceptable to the Lancet reviewers, the researchers' claims had sobered up: steroids offered no significant increased efficacy to IVIG treatment. The study involved 233 people with GBS who were unable to walk independently. There was no difference between the groups in the primary outcome measure: disability at 4 weeks. However, if the results were adjusted for age and disability, factors which were unbalanced at baseline, a treatment effect emerged although even then the stats are unimpressive. There is the usual plea in the last paragraph for more trials, but few people can share their enthusiasm, as Richard Hughes's commentary amply demonstrates. - AJC

Effect of methylprednisolone when added to standard treatment with intravenous immunoglobulin for Guillain-Barre syndrome: randomised trial.

van Koningsveld R, Schmitz PI, Meche FG, Visser LH, Meulstee J, van Doorn PA; Dutch GBS study group.

LANCET

2004 Jan 17;363(9404):192-6.

☆☆☆ RECOMMENDED

ALZHEIMER'S: the role of APP in A β toxicity

It is now 20 years since the first characterisation of amyloid β -peptides (A β) from Alzheimer's disease (AD) brain. Although evidently toxic in cell culture, the precise role of A β in AD pathogenesis has remained uncertain, one consequence of which has been the sometimes acrimonious debate surrounding the use of so-called A β vaccines for the treatment of AD. That A β toxicity may depend in some way on its parent molecule, amyloid precursor protein (APP), a transmembrane protein which might have an intracellular signalling function, has been postulated (the "reciprocity hypothesis"; BioEssays 1995; 17: 819-24). Certainly A β toxicity is attenuated in APP deficient neurones (Nature Neuroscience 2000; 3: 460-4)

In the series of experiments reported in this paper, it is shown that soluble

A β potentiates APP homodimerization, forming A β /APP dimer complexes. This step does not require the cytoplasmic (C-terminal) domain of APP. Caspase-8 is then recruited to the complex, cleaving APP at position 664, leading to the generation of cytotoxic C-terminal APP peptides including C31, known to be proapoptotic. The time course of these binding and cleavage processes correlates with cell death. Furthermore, a preliminary study of AD brains (n = 3) showed a correlation between levels of caspase-cleaved APP fragments and soluble A β .

These findings suggest that soluble A β -induced multimerization of APP at the cell surface may transduce a cell death signal, through recruitment and activation of caspase-8. Since it is increasingly appreciated that soluble A β , rather than the fibrillar species in plaques, best correlates with the severity of AD, this mechanism may be of relevance to AD pathogenesis and suggests possible points for therapeutic intervention. These might include not only anti-apoptotic agents but also small molecules antagonising Ab-APP binding. -AJL

Amyloid β protein toxicity mediated by the formation of amyloid- β protein precursor complexes.

Lu DC, Shaked GM, Malsiah E, Bredesen DE, Koo EH.

ANNALS OF NEUROLOGY

2003;54(12):781-789

EPILEPSY: Steroids for parasites in the brain?

There is something particularly horrible about a parasite growing in your brain, but it remains probably the most common cause of epilepsy in places where the pork tapeworm is found. In the UK cases are seen regularly in centres where travel to endemic areas is common, particularly among the Asian community. Surprisingly, although treatment is indicated in certain situations, it is not clearly established whether it affects the development of epilepsy in those with from one to a few parenchymal cysts. The first two randomised trials of treatment and the effect on seizures have just been published. In the study by Garcia *et al*, 120 patients were selected. They all had a history of seizures for less than 10 years and all had evidence of viable *Taenia Solium* cysts on CT or MRI, some with signs of inflammation. Patients were randomised to albendazole plus dexamethasone or placebo and followed for 30 months. The number of patients with partial seizures was similar in the two groups but treatment significantly reduced secondarily generalised seizures (23% of treated patients and 37% of placebo patients). Patients who had no active lesions at 6 months had 62% fewer seizures than those who had active lesions. In the placebo group, nearly all the non-inflamed viable cysts persisted whereas in the treatment group, less than half persisted. The authors argue that these results support treatment although they do not establish whether the effective agent was albendazole or steroids.

Mall *et al* studied a slightly different group of 97 patients with new onset seizures (<11 days) and a single cyst. They randomised patients to prednisolone 1mg/kg for 10 days or placebo and followed up clinically and with neuroimaging at 1 and 6 months. Both groups received anti-epileptic drugs. After 6 months, lesions had disappeared in 88% of prednisolone-treated patients but only in 52% of placebo patients. Seizure recurrence was associated with abnormal CT scans in 81%, including persisting lesions and calcified or regressed lesions. So steroids seem to help scan resolution, and scan resolution is associated with lower seizure recurrence in both studies. Does this mean that it was actually the steroids that were effective in the Garcia study? The patient groups were different so it is difficult to be sure. A study of albendazole plus steroids versus steroids would clearly answer the question. Worries about a Herxheimer type reaction mean that albendazole is rarely used alone. -MRAM

A trial of antiparasitic treatment to reduce the rate of seizures due to cerebral cysticercosis. Garcia H.

Pretell EJ, Gilman RH *et al*.

NEW ENGLAND JOURNAL OF MEDICINE

2004;350:249-257.

Short course of Prednisolone in Indian patients with solitary cysticercus granuloma and new-onset seizures.

Mall RK, Agarwal A, Garg RK, Kar AM, Shukla R.

EPILEPSIA

2003;44:1397-1401

EPILEPSY: PET of DNETs?

Dysembryoplastic neuroepithelial tumours are increasingly recognised as a cause of refractory epilepsy. They are benign lesions and are difficult to diagnose with certainty with conventional radiological techniques. Follow-up scans are usually needed to help exclude low grade gliomas. Resection of DNETs results in a high (80-90%) rate of seizure remission in some series. A method of distinguishing them from progressive lesions would be very valuable. In this small study of 7 patients with benign temporal lobe lesions and

epilepsy, the authors used [11C]Methionine PET and related them to histological diagnosis after resection. Four patients with DNET all had low uptake in the lesions, whereas 3 patients with other lesions (low grade astrocytoma, pleomorphic astrocytoma and ganglioglioma) all had high uptake. If this finding is confirmed, it may prove a useful ancillary investigation for this small group of patients. -MRAM

Usefulness of [11C]Methionine PET in the diagnosis of dysembryoplastic neuroepithelial tumor with temporal lobe epilepsy.

Maehara T, Nariai T, Kawai K, Shimuzu H, Ishii K, Ishiwata K, Ohno K.

EPILEPSIA

2004;45:41-45

THE BIZARRE: the neurology of out-of-body experiences

The pages of Brain are not the likeliest place for a discussion of the whacky and wonderful. But this is a truly classical account from Geneva of out-of-body experiences (where people feel they are outside of themselves and see their own body within the world) and autoscopia (the experience of remaining within one's body but seeing another copy of one's body outside of one self). 6 clinical cases are presented in which 4 definitely had epilepsy, one had hemiplegic migraine and one case was undiagnosable but certainly had migraine. In all but one, the experience was vivid and felt to be real at the time. In out-of-body experiences, the body lay on the bed whereas in autoscopia, the body was upright. This was accompanied usually by a feeling of dizziness or lightness and fear (although one patient reported joy). Three patients also experienced body part illusions (such as limb shortening). Combining anatomical and electrical lesion data, the authors suggest that these unusual experiences can arise from unilateral lesions in the temporo-parietal junction of either hemisphere. They go on to speculate on the mechanism. They argue that we assimilate multiple sensory sources into a representation of ourselves which is contained within our defined personal space. If this representation "escapes" the confines of cognitive personal space, then we see an illusory duplication of ourselves. A fantastic read. -AJC

Out-of-body experience and autoscopia of neurological origin.

Blanke O, Landis T, Spinelli L, Seeck M.

BRAIN

2004;127 (Pt 2):243-58.

☆☆☆ RECOMMENDED

MULTIPLE SCLEROSIS: brain plasticity and effect of cholinesterase inhibitors

Colleagues from the multiple sclerosis (MS) clinic occasionally ask me whether cholinesterase inhibitors (ChEI) might have a role in the treatment of cognitive problems in MS. My formulaic answer has been "there is no evidence", but this may change if the findings of this paper from Oxford are corroborated. Ten MS patients without significant neuropsychological impairment as assessed by a battery of tests, but with subjective complaints of poor concentration and memory, were studied along with 11 controls using fMRI whilst performing the counting Stroop test, performance of which is impaired with frontal lobe damage. The patients showed a distinct, and abnormal, pattern of brain activation relative to the controls, with reduced right inferior frontal (Brodmann area 45) and right basal ganglia activation, but increased left medial prefrontal (Brodmann areas 8, 9, 10) activation. The magnitude of these differences correlated with normalised parenchymal brain volume, a measure of disease burden. Since behavioural performance was similar in the two groups, the authors suggest that these activations reflect adaptive functional neuroplasticity in response to brain injury.

Double blind administration of the ChEI rivastigmine (3 mg), one of the licensed treatments for mild-to-moderate Alzheimer's disease, 150 minutes before fMRI, resulted in normalisation of the pattern of activation in all 5 MS patients tested, but had no effect in the 4 controls tested. No change in patients' behavioural performance was noted following rivastigmine, but numbers were small. These findings suggest that cholinergic agonism rapidly modulates functional changes, perhaps by facilitating processing associated with right prefrontal activation and consequently reducing adaptive left frontal responses, perhaps by unmasking latent pathways.

Of course, functional imaging is one thing and clinical neurology is quite another, but these findings do suggest that clinical trials of ChEI in cognitively impaired MS patients may be of interest. -AJL

Potentially adaptive functional changes in cognitive processing for patients with multiple sclerosis and their acute modulation by rivastigmine.

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