

EDITOR'S CHOICE

Alcoholism is linked to disruption of the biological clock

Alcohol and drug addiction are complex disorders with environmental, drug-induced and genetic components. It is likely that multiple genes contribute to the development of an addictive disease. There is a growing body of evidence implicating circadian clock genes in mechanisms of drug-abuse related behaviours. The clock genes, including, *Per1*, *Per2*, *Cry1* and *Cry2*, underlie the ability of the biological clock to provide endogenous rhythms of physiological functions with a periodicity of 24 hours, without any environmental cues. These genes regulate oscillations in the levels of the transcription factor complex, CLOCK-BMAL1, in the suprachiasmatic nucleus of the hypothalamus. Such oscillations are generated by inhibitory feedback loops, in which the protein products of the clock genes down-regulate their own transcription. This study by Spanagel focuses on one such clock gene, *Per2*, and its role in alcoholism. They investigated a *Per2^{brdmi}* mutant mouse, in which the *Per2* protein is rendered non-functional. As a result, neurochemically these mutant mice exhibited serious disturbances in the glutamatergic system. A significant reduction in the astrocytic expression of the EAAT1 glutamate transporter, which clears glutamate from the synaptic cleft, produced a three-fold increase in extracellular glutamate in the ventral striatum. On a behavioural level, the *Per2^{brdmi}* mutant mice voluntarily consumed more alcohol compared to wild-type mice. On administration of acamprosate, an anti-relapse drug, the *Per2^{brdmi}* mutants showed a reduction in augmented extracellular glutamate levels in the nucleus accumbens and their alcohol consumption was normalised to below wild-type levels. This latter finding lends support to the theory that acamprosate acts by reducing the hyperglutamatergic state in alcohol-dependents. In humans Spanagel found that the *Per2* gene had an analogous function in the regulation of alcohol consumption. By sequencing the *Per2* gene of alcohol-dependents, they identified a haplotype of four gene variants associated specifically with the subjects with low alcohol consumption. In summary, Spanagel identifies glutamate to be the link between disruption of the *Per2* and increased alcohol consumption. It is proposed that glutamate alters the alcohol reinforcement processes in the brain, most likely via modulation of the dopamine reward pathways. In the clinic, acamprosate increases abstinence rates in just 10-20% of cases compared to placebo. Further research is required to determine if certain polymorphisms in the *Per2* gene confer a positive acamprosate response. Thus it would be possible to predict if a patient would benefit from this therapy. - *LMS & SJT*

Spanagel R, Pendyala, Abarca C, Zghoul T, Sanchis-Segura C, Magnone M, Lascorz J, depner M, Holzberg D, Soyka M, Schreiber S, Matsuda F, Lathrop M, Schumann G, Albrecht U.

The clock gene Per 2 influences the glutamatergic system and modulates alcohol consumption.

NATURE MEDICINE
2005;11:35-42.

MOTORNEURON DISEASE: VEGF treatment of ALS

*** RECOMMENDED

Amyotrophic lateral sclerosis (ALS) is a paralysing progressive disorder that kills within five years of onset. It can present in one of two forms: the first is limb-onset ALS, which is characterised by initial muscle weakness of extremities and the second, more aggressive form is bulbar-onset ALS, in which patients have difficulty swallowing and breathing. This disease results from selective loss of motor neurons in the spinal cord and brainstem but the underlying pathogenic mechanism has not yet been identified. Furthermore, there is currently no cure for this devastating illness. To date, neurotrophin treatment of motor neuron degeneration, although rational, has proved unsuccessful in prolonging survival of ALS patients. Storkebaum and colleagues have now published very encouraging data indicating that vascular endothelial factor (VEGF) may be an effective therapy for ALS. In a mutant SOD1 transgenic rat model, which mimics the more severe bulbar-onset disease, they have found that continuous intracerebroventricular (i.c.v) delivery of recombinant VEGF improves motor performance compared to controls. When administered before onset of symptoms, onset of paralysis was delayed by 17 days and survival was improved by 22 days. They demonstrate that through their novel mode of delivery VEGF diffuses from the site of delivery in the CSF to spinal motorneurons, where it is

anterogradely transported in axons. Whilst they show that VEGF prolongs motorneuron survival via a direct neurotrophic action, it is proposed that VEGF is a more effective therapy compared to other neurotrophic factors due to its additional angiogenic activity whereby increasing blood flow to the microenvironments of the brain and spinal cord. I.c.v. VEGF administration offers protection to cervical neurons in particular and thus represents an ideal therapy for bulbar-onset ALS and final stage limb-onset disease. This route of administration offers advantages, in that dosing and duration of treatment can be controlled. Whilst these results are highly promising, it must be noted that only a modest improvement in survival was observed when i.c.v VEGF was administered at the time of disease onset. - *LMS & SJT*

Storkebaum E, Lambrechts D, Dewerchin M, Moreno-Murciano M-P, Appelmans S, Oh H, Van Damme P, Rutten B, Man W, De Mol M, Wyns S, Manka D, Vermeulen K, Van Den Bosch L, Mertens N, Schmitz, Robberecht W, Conway EM, Collen D, Moons L, Carmeliet P.

Treatment of Motorneuron Degeneration by Intracerebroventricular delivery of VEGF in rat model of ALS.

NATURE NEUROSCIENCE
2005;8:85-92.

COGNITIVE IMMUNOLOGY: The cortical control of thymic function

*** RECOMMENDED

There is a lot of very poor science in the field of neuro-endocrine-immune interactions and, accordingly, it is given a wide berth by most respectable laboratories. But no less a figure than Norman Geschwind drew attention in the 1980s, with Peter Behan, to the possible lateralisation of neocortical control over the immune system. Vahe Amassian, in New York, has been working up this story for more than a decade and now has produced a compelling animal study. Amassian's group studied rats in whom a permanent stimulating electrode had been placed over either temporo-parietal cortex. A permanent catheter in the right atrium allowed frequent blood sampling. A four hour stimulation of the left cortex increased circulating T and B lymphocyte numbers; whilst exactly the opposite occurred with stimulation of the right temporo-parietal cortex. This difference was most marked during periods of increased behavioural activity, such as at night. The effect of cortical stimulation was abolished by thymectomy or lesions of the cord above T7. These data suggest there is an anatomical pathway from the cortex through the

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upper thoracic spinal cord to the thymus which controls lymphocyte generation. Furthermore, there is cortical lateralisation of function of this pathway.... But, what on earth does this mean? Frustratingly, the authors have not revealed whether there is any difference in phenotype of the newly generated lymphocytes. (I am sure they will have looked). Nor do they say if the altered lymphocyte numbers lead to any difference in immune responses. - *AJC*

Moshel YA, Durkin HG, Amassian VE.

Lateralized neocortical control of T lymphocyte export from the thymus I. Increased export after left cortical stimulation in behaviorally active rats, mediated by sympathetic pathways in the upper spinal cord.

JOURNAL OF NEUROIMMUNOLOGY

2005;158:3-13.

NEUROIMMUNOLOGY: Inflammation in the brain is good for you

Much effort is spent suppressing inflammation in the brains of people with multiple sclerosis. Yet there has always been a kernel of sceptics who have cautioned that this may be throwing out the baby with the bathwater, because inflammation promotes remyelination. It is true that, in the 1990s, it was shown that remyelination is often found close to inflammatory lesions. And, experimentally, remyelination is impaired in the absence of T cells, Class II expression or the cytokines IL-1 and TNF- α . Yet who can really argue that the dominant effect of cerebral inflammation in multiple sclerosis is bad? Robin Franklin at the Vet School in Cambridge has studied the beneficial effects of inflammation by using a model in which demyelination is induced by a toxin, with any inflammation therefore being a secondary response. He has previously shown that depletion of macrophages from the animals, using clodronate-liposome, impaired oligodendrocyte remyelination. Now his group has adopted a different approach. They studied the effect of minocycline treatment on the repair of demyelinated cerebellar lesions induced by ethidium bromide. Minocycline is an antibiotic, but it also has multiple anti-inflammatory actions. These were confirmed in this study by the reduced activation of microglia (as shown by reduced Class II and OX42 expression) in the minocycline-treated animals. The crucial results were that oligodendrocyte precursor numbers in the lesion were also reduced in these animals, accompanied by reduced histological remyelination. What makes this study so interesting is that minocycline is being trialled in the treatment of multiple sclerosis, having shown promising efficacy in suppressing EAE. Whilst minocycline might effectively reduce the immune attack on myelin (which of course is deliberately missing from the Franklin model), it might also reduce repair. Indeed might suppressed remyelination be a generic problem with anti-inflammatory treatments of multiple sclerosis? Having said which, an hour or two in a MS clinic soon brings home the indisputable point that leaving inflammation unchecked in the brain is not a good thing. Clearly the way forward is to dissect from the complex mechanisms of inflammation those that promote repair and those that are harmful. - *AJC*

Li WW, Setzu A, Zhao C, Franklin RJ.

Minocycline-mediated inhibition of microglia activation impairs oligodendrocyte progenitor cell responses and remyelination in a non-immune model of demyelination.

JOURNAL OF NEUROIMMUNOLOGY

2005;158:58-66.

REHABILITATION: Functional electrical stimulation for stroke recovery

Treatment methods in rehabilitation can take decades to develop, test and become part of clinical practice. Functional Electrical Stimulation (FES) has been advocated by a passionate few as a method for improving walking since the 1960s. Over the last decade support has become more widespread. Sophisticated stimulating systems being researched for the benefit of people with spinal cord injuries have received attention in the press and it is becoming more common for therapists to use simple systems in clinical practice as a gait training tool after stroke. 2005 sees evidence, from a good randomised controlled trial, of the benefit of FES used as a treatment early after stroke. Yan, Hui-Chan and Li recruited 46 patients from a single centre in Hong Kong. The patients were within 3 weeks of stroke (mean 9 days) and only 5 were able to walk before the treatment. They were randomly allocated using a minimisation method to either standard rehabilitation plus FES, 30 minutes a day, 5 days a week for 3 weeks, or to a placebo group who had sham stimulation for 60 minutes a day plus standard rehabilitation, or to a control group who received standard rehabilitation only. The stimulation was carried out not during gait training but with the patient positioned on their side lying with the affected leg in a sling. Quadriceps, hamstrings, tibialis anterior

and gastrocnemius were stimulated using an activation sequence that mimicked the gait cycle. Spasticity, isometric strength of the ankle dorsiflexors and plantar flexors and the amount of their co-contraction was measured along with walking ability weekly during the treatment period and also at a follow up 8 weeks after stroke. The assessor was blinded to the individual subject's intervention. Significantly greater improvements in impairment level outcomes were found in the FES group compared with the other two groups. Significantly more subjects in the FES group were able to walk after treatment than in the other two groups. These differences were evident at week 2, 3 of the treatment and 8 weeks after stroke. Patients in the FES group were also able to start walking in the hospital an average of two days earlier than those in the other two groups. This trial shows that sensorimotor stimulation requiring no active participation on the part of the patient but which mimics the gait cycle can help prepare patients for walking early after stroke. The adoption of FES as a treatment in clinical practice is restricted in part by the cost of stimulators and of training therapists in their use, but also by lack of evidence of its effect from good quality randomised controlled trials. The results of this study should increase the support for a treatment that has been forty years in the making. - *AJT*

Yan T, Hui-Chan CWY, Li LSW.

Functional Electrical Stimulation improves motor recovery of the lower extremity and walking ability of subjects with first acute stroke.

STROKE

2005;36:80-5.

COGNITION: Better than one for the phrenologists

Most people acquire a 'collection' of one sort or another during their lives. Animals ranging from crows to hamsters may also accumulate non-food items, often shiny ones. Experimental lesion studies implicate a number of subcortical sites in this behaviour. In humans, however, it is thought that the drive to collect is modulated by cognitive processes presumably occurring in the cortex. Several clinical conditions are associated with maladaptive collecting behaviour including schizophrenia, obsessive-compulsive disorder and various dementias. Famously, after suffering frontal lobe trauma, Phineas Gage developed a 'great fondness' for animals and souvenirs. Collectors of cortical areas to which a function has been ascribed will enjoy the study by Anderson and colleagues in the January issue of *Brain*. The key data-sets are profiles of collecting behaviour, and maps of static cortical lesions in a group of 63 subjects. Nine were deemed to have abnormal collecting behaviour. Perhaps surprisingly, in view of the varied nature of collections in general, independent raters showed 100% agreement when deciding on the normality or otherwise of an individual's collecting behaviour. General neuropsychological testing confirmed that global impairment was not present; the 'collectors' scored somewhat better on tests of executive function and worse on tests of memory. The study draws upon an important resource, already used in a language study (*Damasio et al, 2004*). Structural MR images of all patients have been reconstructed such that the lesions are mapped to allow voxel-by-voxel comparison of overlaps. The resulting anatomical data can be analysed alongside any cognitive or behavioural indices. In this instance, maximal lesion overlap in 'collectors' versus 'non-collectors' was the mesial and inferior prefrontal region bilaterally, which included anterior cingulate cortex and extended to involve the frontal pole on the right. There was no evidence of damage in subcortical structures associated with acquisition behaviour in rodents. The inference is that activity in mesial prefrontal structures is necessary for regulation of collecting tendencies that originate in subcortical bioregulatory nuclei and that the normal operation of this multitiered system underlies the ubiquitous tendency of humans to create socially acceptable collections. Comparison of Anderson's paper and a single case study that showed impairment of mentalising abilities with bilateral anterior cingulate lesions (*Bird et al, Brain 2004, also reviewed in ACNR*) highlights the burgeoning literature on localisation of cerebral function and the need for care in its assimilation. - *RRD*

Anderson SW, Damasio H, Damasio AR.

A neural basis for collecting behaviour in humans.

BRAIN

2005;128:201-12.

PARKINSON'S DISEASE: A stimulating new approach

The surgical treatment of Parkinson's disease (PD) has concentrated on either neural transplantation (*see ACNR 2(6)*) or deep brain stimulation (*ACNR 2(6)*). However there is an emerging realisation that many of the features of PD may occur through alterations of synchronised oscillatory neuronal activities in corticostriatal circuits. With this in mind, Drouot et al

posed the unusual hypothesis that direct interference of the basal ganglia associated motor cortical areas, by using implanted electrodes adjacent to the cortex, may actually lead to functional recovery in PD. This they investigated using the chronic MPTP primate model of PD, and a high frequency stimulating epidural electrode placed unilaterally on the motor cortex, but at an intensity below that required for producing muscle twitching in the contralateral muscles. Amazingly this approach worked, with a significant bilateral improvement in bradykinesia, in association with an increase in metabolic activity in the supplementary motor area (SMA) using FDG-PET – an area that is known to be underactive in the bradykinesia of PD. In addition there was a normalisation of firing rates from neurons within the output nuclei of the basal ganglia and a reduction in synchronised oscillatory activities between the cortex and basal ganglia. All of this was achieved without side-effects. Of course whether this is the whole story behind its actions is not known, but the authors attribute the success of their approach to the normalisation of aberrant neuronal activity downstream of the striatum. Whatever the mechanism, this approach is exciting and may lead to a radical rethink of the surgical treatment of movement disorders as well as the role of cortical stimulation in other basal ganglia related disorders. - **RAB**

Drouot X, Oshino S, Jarraya B, Besret L, Kishima H, Remy P, Dauguet J, Lefaucheur JP, Dolle F, Conde F, Bottlaender M, Peschanski M, Keravel Y, Hantraye P, Palfi S.

Functional recovery in a primate model of Parkinson's disease following motor cortex stimulation.

NEURON

2004;44:769-78.

EPILEPSY: Out of Africa

In a region with a population approaching 1 billion, there are 75 EEG machines and 25 CT scanners, roughly equivalent to 1 scanner for the population of England and at any one time many are broken. Half the population are under the age of 15 and life expectancy is 45. Mortality below age 5 is 16.4%. Against this setting, with little health care infrastructure, simple epidemiological questions are difficult to answer. This review of epidemiology relied only on door-to-door surveys. The prevalence of epilepsy in two studies of villages 20km apart in Nigeria, with similar ethnic and age structures were 0.5% and 3.7% - population sizes were admittedly small. Reviewing all the studies from this part of the world the prevalence ranges from 0.5-7.4% with most studies falling out at 1-2% (cf Western populations around 0.5%). Some of these may be underestimates as young women especially have to hide their epilepsy in order to get married. There are less data on the mortality of epilepsy but in a small study in Ethiopia it has been estimated to be 3.16% (cf 1.64% without epilepsy) with status epilepticus and burns being the modes of death attributed directly to seizures. I imagine that SUDEP goes unrecognised in this society. Seizures start below the age of 20 in 60% of the population, but this may reflect the population structure of the region. Treatment (usually phenobarbital) is effective in this environment, but compliance is poor and may contribute to later relapse. In small studies where investigation has allowed epilepsy classification, 40% have focal seizures, half generalised seizures, usually from a focal onset and 9% were unclassifiable. Perinatal factors are important in the aetiology of epilepsy in all countries but are difficult to evaluate in this region as studies rely on personal recall by patients' mothers. The real significance of cysticercosis is difficult to establish as few patients will have a CT scan, but prevalence of seropositivity ranges is 0.3% in predominantly Muslim areas but much more in other regions. In a case control study from Burundi, an association was found with seizures but seropositivity was 35.1% of controls as well. Other postulated but unproven associations include malaria (the commonest cause of febrile seizures), filariasis and onchocerciasis. Eradication of *Taenia solium* could give a 50% reduction of epilepsy in this region. As in the history of health care in the developed world, a single public health care measure can do much more than thousands of doctors and prescriptions and is probably cheaper, but requires a more coordinated effort. - **MRAM**

Preux PM and Druet-Cabanac M.

Epidemiology and aetiology of epilepsy in sub-Saharan Africa.

LANCET NEUROLOGY

2005;4:21-31.

MULTIPLE SCLEROSIS & DEVIC'S DISEASE: Defined by a new antibody

*** RECOMMENDED

A monophasic neurological disease characterised by bilateral optic nerve involvement and myelitis occurring in rapid succession was first described by Eugene Devic in the late 19th century. Since then a relapsing form of the

illness has been identified and there has been much philosophising about whether this represents a variant of multiple sclerosis, or whether it is a distinct disease. To the cynics' "so what?" came the important rebuttal in the late 1990s from the Mayo clinic, that attacks of Devic's disease, but not multiple sclerosis, may respond to plasma exchange (*Keegan, M. Neurology 2002;58:143-6*). This discovery led the hunt for an antibody that might mediate Devic's... and here it is. Brian Weinschenker's group at the Mayo has managed the extraordinary feat of collecting serum from 45 patients with Devic's disease and 35 with "forme frustes" of the disease: recurrent transverse myelitis or optic neuritis. They compared these to serum from 22 people with classical multiple sclerosis, found an antibody and then tested it out in two other cohorts. They discovered that serum from most Devic's patients (33/45) contains a distinct immunoglobulin they called "NMO-IgG", that was found in only 2/22 multiple sclerosis controls and in higher proportions of those with recurrent transverse myelitis (14/27) or optic neuritis (2/8). NMO-IgG bound to mouse pia and subpia, outlined the Virchow-Robin space and microvessels in white and grey matter, and also to subependymal white matter and the subpial layer of midbrain. Co-labelling showed that the antibody bound to the abluminal face of microvessels and in extracellular matrix protein in pial and perivascular locations. These findings correlate nicely with the vasocentric pattern of immunoglobulin and complement deposition seen in the spinal cords of people with Devic's. The crucial questions are: what is the molecular target of the antibody and why does it pick on the optic nerves and spinal cord? If the Mayo team know the answers, they are certainly not telling... - **AJC**

Lennon VA, Wingerchuk DM, Kryzer TJ, Pittock SJ, Lucchinetti CF, Fujihara K, Nakashima I, Weinschenker BG.

A serum autoantibody marker of neuromyelitis optica: distinction from multiple sclerosis.

LANCET

2004 Dec 11;364(9451):2106-12.

PARKINSON'S DISEASE: What you eat is important

There is no doubt that modifying the environment can have effects on neurological disorders and this has perhaps been most explored clinically in rehabilitation therapy and in the laboratory with enrichment of the animal environment. However whilst attempts to manipulate the environment for the good of the individual are well known, how this is achieved at the cellular level has been less well explored. In this paper, Maswood et al have shown that in MPTP treated monkeys, dietary caloric restriction (CR) had a significant effect on the toxicity of the MPTP on the nigrostriatal dopaminergic network such that it afforded a degree of protection which was accompanied by an improvement in motor deficits. These investigators then demonstrated that this CR had a significant effect of the levels of GDNF in the caudate nucleus – implying that this may be the explanation for the observed recovery. However, in PD the greatest area of dopaminergic loss is the putamen rather than the caudate nucleus – a structure that is more associated with the cognitive, than motor, deficits of PD. Furthermore patients with PD often have difficulty maintaining their weight because of the difficulties with swallowing coupled to the increased metabolic rates induced by the movement disorder of this condition. Thus recommending CR in this patient group is not straightforward. However this study once more highlights the complex relationship that exists between our environment (including diet) and the state of our brain in health and disease. A relationship that is worth remembering when you are trying to lose those extra pounds from 2004, through your 2005 New Year resolutions. - **RAB**

Maswood N, Young J, Tilmont E, Zhang Z, Gash DM, Gerhardt GA, Grondin R, Roth GS, Mattison J, Lane MA, Carson RE, Cohen RM, Mouton PR, Quigley C, Mattson MP, Ingram DK.

Caloric restriction increases glial cell line derived neurotrophic factor levels and attenuates neurochemical and behavioral deficits in a primate model of Parkinson's disease.

PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES, USA.

2004;101:18171-6.

EPILEPSY: Stepping attacks

Unusual cases of epilepsy are curiosities but also give insights into the function of the brain. A 33-year-old man had a history of sudden falls. These were often precipitated by distractions such as unexpected loud noises or seeing a change in the floor material. His only symptom during the attacks was the sensation of loss of connection with his left lower limb. During the attacks, which were videoed, he would try to step over an obstacle with his right foot, but never his left foot, and then fall. Ictal scalp EEG revealed a midline 10-12Hz frontocentral discharge, lasting 1-3 seconds. He underwent intracranial

EEG and simultaneous EMG. The EMG showed no alteration in muscle activity or resting tone during attacks. Attacks were reproduced by stimulation of the right posterior parietal region and spontaneous discharges were also recorded from this area. The patient decided against resective surgery but underwent multiple pial transection, which was unsuccessful. The clinical manifestations of epilepsy never cease to amaze. I always ask myself in these sort of cases whether I would have thought of the diagnosis. - **MRAM**

So EL and Schaüble BS.

Ictal asomatognosia as a cause for epileptic falls. Simultaneous video, EMG and invasive EEG.

NEUROLOGY

2004;63:2153-4.

EPILEPSY: Anticonvulsants in the garden

Valerian is a perennial, widely distributed in Europe and North America. It is distinctive by its unpleasant smell and taste, so should make a good medicine. It was probably first used in the treatment of epilepsy by Fabio Colonna (1567-1650) of Naples, who himself suffered from epilepsy. He searched for a herb to help him and wrote a classic work "Phytobasanos" in which he described the efficacy of Valerian for his own condition. Willis only cited Valerian as an ingredient in one of his anticonvulsant concoctions in his work "Pathology of the Brain and Nervous stock: On convulsive diseases". Tissot in the 1770's described it as the best drug available for epilepsy and other European noteworthies also used it with success, such that it was in popular usage in the 18th and 19th centuries. John Cooke of London wrote in 1823 that valerian had "very little power" but Robert Bentley Todd (1849) thought more highly of it. Soon after it was superseded by the bromides and was not mentioned by Gowers in his monograph in 1885. It was used in WWII to relieve the stress of air-raids in London and is now used as a nocturnal sedative. In this role there have been a number of clinical trials, including one comparing it favourably with oxazepam but none of these is very satisfactory technically. Among the chemical ingredients of the plant are valepotriates, which may yield isovaleric acid, chemically related to valproic acid. Valerian extracts contain GABA and also valerianic acid, which inhibits GABA transaminase. So when the nth AED fails and you and your patient don't know where to go, you might try the garden. - **MRAM**

Eadie MJ.

Could Valerian have been the first anticonvulsant?

EPILEPSIA

2004;45:1338-1343.

(with help from <http://ods.od.nih.gov/factsheets/Valerian.asp>)



EPILEPSY: Fracture risk

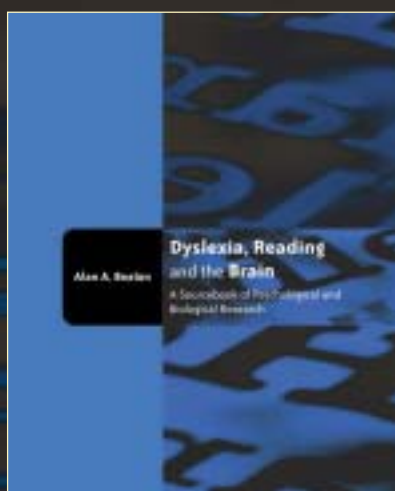
In Denmark all fractures are recorded on a central register, providing a unique opportunity to identify risk factors. From 1977 only inpatients were recorded but from 1995 outpatients were included. Medications prescribed and bought are also registered centrally to enable reimbursement of patients. For AEDs the amount taken by each patient from 1996-2000 could also be calculated. This study was conducted as a case-control study with fractures as the outcome and AED use as the variable. A further analysis was conducted to take account of different seizure types including generalised tonic clonic and focal seizures, IGE absences and status epilepticus. From Jan 01 2000 to Dec 31 2000 there were 124,655 fractures and for each case, three age and gender-matched controls were selected from a national database. The following factors were associated with a slight but significantly increased risk of fracture: lower income; divorced or unmarried status; being out of work or retired; more regular GP visits or ever having taken corticosteroids. Not surprisingly factors associated with a considerably higher risk were previous fracture or use of any treatment for osteoporosis such as HRT or biphosphonates. 2.5% of patients who had sustained a fracture had epilepsy, and 5.7% were taking AEDs compared with 1.3% of controls with epilepsy and 2.9% taking AEDs; these were particularly spine (10.3%) and hip fractures (9.9%). Odds ratios for specific drugs were calculated and a dose-response was sought. An increased risk of fracture was associated with carbamazepine, oxcarbazepine, clonazepam, valproate and phenobarbitone, but only phenobarbitone was associated with an increased risk of spine fracture. The increased risk, as measured by an adjusted odds ratio, was modest (1.18 for carbamazepine and 1.79 for Phenobarbital, which had the greatest effect). A clear dose-response effect with duration of drug exposure ($P < 0.01$) was seen only with carbamazepine and phenobarbital. This is a large study and important because it is population-based and likely to suffer little from failure of case ascertainment. A limitation of the study is the unknown duration of AED exposure before 1996; a reasonable hypothesis is that the longer a drug is taken the higher the risk of fracture. Also the study did not differentiate between epilepsy in remission and active epilepsy. Some other factors were not included such as smoking and alcohol history which impact on bone density and differ between epilepsy patients and controls. Nevertheless it provides evidence that there is a clear, if limited contribution to fractures in patients taking carbamazepine or phenobarbital. As evidence of this kind accumulates, we shall have to start to advise patients about bone protection, especially as we discharge them into the community on long-term treatment, without specialist follow-up. NICE guidelines also recommend bone densitometry for patients taking enzyme-inducing AED. - **MRAM**

Vestergaard P, Rejnmark L and Mosekilde L.

Fracture risk associated with the use of anti-epileptic drugs.

EPILEPSIA

2004;11:1330-7.



Dyslexia, Reading and the Brain

A Sourcebook of Psychological and Biological Research

By Alan A. Beaton, University of Wales, Swansea, UK

"This is an excellent book. The depth of detail, the broad range of research covered and the author's summaries of current viewpoints should be useful to the novice and expert alike. The book should be highly recommendable to those researching in the area of dyslexia and reading, but also to the student taking courses in these and related topics." - John Everatt, University of Surrey

Despite the wealth of literature available on the subject of dyslexia, there is little that explores the subject beyond a single theoretical framework. The need for a comprehensive review of the literature by both researchers and practitioners from different fields and theoretical backgrounds is the central motivation behind *Dyslexia, Reading and the Brain*. By combining the existing fragmented and one-sided accounts, Alan Beaton has created a sourcebook that provides the much-needed basis for a more integrated and holistic approach to dyslexia.

The comprehensive coverage and impartial approach mean that this sourcebook will prove an invaluable resource for anyone involved in study, research or practice in the fields of reading and dyslexia.

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