

EDITOR'S CHOICE

Myelin and madness

Neuregulin 1 (NRG1) is a growth factor which binds to its receptor, erbB4, and by so doing mediates of its effects on normal development, especially of oligodendrocytes. Interestingly this system has been linked genetically to schizophrenia and bipolar disorders – disorders which some have considered to be neurodevelopmental in origin. In this study Roy et al have used mice in which erbB signalling in oligodendrocytes is blocked by expression of a dominant negative erbB receptor. These mice were then shown to:

- have alterations in oligodendrocyte morphology, number and function including thickness of myelin sheath, which was less in transgenic mice but with increasing numbers of smaller less branched cells, all of which reduced the conduction velocity of action potentials (at least in the optic nerve anyway);
- have increased levels of functional dopamine transporters and D1 receptors as evidenced by direct measurement and response to injections of amphetamines;
- exhibit behavioural alterations suggestive of neuropsychiatric disorders, such as hypoactivity in open field testing, with more time spent in the periphery suggestive of increased anxiety. Furthermore, using a social interaction test they found abnormalities in transgenic mice compared to wildtype.

This all suggests that abnormalities in normal oligodendrocyte development leads to subtle changes in defined neurochemical pathways with behavioural consequences and as such the problem in psychiatric disorders is as much to do with the white matter as anything else. Obviously this paper has focused on NRG1 erbB4 effects on oligodendrocytes and inferred its link to the other abnormalities when of course they may all be primarily affected by an abnormality in this pathway. It does though raise many interesting questions about how different neural elements speak to and affect each other and in particular how oligodendrocytes may instruct the dopaminergic system to behave normally. - **RAB**

Roy K, Murtie JC, El-Khodor BF, Edgar N, Sardi SP, Hooks BM, Benoit-Marand M, Chen C, Moore H, O'Donnell P, Brunner D, Corfas G.

Loss of erbB signalling in oligodendrocytes alters myelin and dopaminergic function, a potential mechanism for neuropsychiatric disorders.

PNAS

2007;104:8131-6.

COGNITION: The Green-eyed monster

*** RECOMMENDED

When a colleague does well (gets a grant, merit award, paper published) do you feel pleased or jealous? And if he or she does badly, do you gloat or commiserate? These 'social competitive emotions' have been studied by a group from Haifa, Israel. 48 subjects with focal brain damage and 35 age-matched controls were asked to judge whether a picture showed a face that was envious, gloating or sympathising with a person. The character in question was a little cartoon head called 'Yoni' for no clear reason. He was surrounded by photos of four different young women with various facial expressions. If Yoni smiled, whilst the woman he was looking at was sad, he was said to be gloating; if Yoni was sad when the woman he started at was happy, he was envious; and if Yoni shared the facial expression of the woman, he was identifying with her. The main result was that patients with ventromedial frontal brain damage lost the ability to work out when Yoni was being jealous or gloating, but could spot when he was identifying with the woman. And those with right-sided lesions had more trouble recognising envy, whereas those with bilateral or left-sided damage could not identify gloating. At p values of 0.074 (which ordinary people call non-significant, but this group describe as 'marginally significant') patient with left inferior parietal damage had impaired gloating recognition, but could identify envy easily. The authors says this fits with Davidson's 'valence theory' which seems altogether improbable to me, that the left hemisphere is dominant for 'positive' emotions (in the sense that gloating is pleasurable) whereas the right is domi-

nant for 'negative' emotions. The anatomical details are beside the point. What is remarkable is that the cognitive kits for recognising identification, envy and gloating are different. Should we read any moral 'design' into the fact that empathising seems to be a distributed function, difficult to disrupt, whereas envy, and even more so gloating, require complex intact pathways? -**AJC**

Shamay-Tsoory SG, Tibi-Elhanany Y, Aharon-Peretz J.

The green-eyed monster and malicious joy: the neuroanatomical bases of envy and gloating (schadenfreude).

BRAIN

2007 Jun;130(Pt 6):1663-78.

REHABILITATION: research of research on efficacy

Those working in the field of brain injury rehabilitation can sometimes feel as if the dominant force in research focuses on the efficacy of the intervention as a whole rather than an analysis of what particular aspects of rehabilitation work and why. Unfortunately as rehabilitation is often perceived as an optional attachment to good medical care rather than a core service, there is an ongoing anxiety on the part of those working in the field of brain injury rehabilitation to prove that what they do 'works' in the same way as a drug for hypertension or a new surgical technique. The variability in type of brain injury, the state of the pre-injured brain and the individual circumstances of the brain-injured individual mean that trying to pin down evidence-based conclusions in this population has proven very difficult. The large meta-analysis illustrates this point very well. As well as looking at the efficacy of inpatient rehabilitation per se, the authors have examined the available research surrounding some of the thorny questions that provoke such debate amongst rehabilitation professionals. When should rehabilitation start? how long should it go on for?, what should its intensity be? and does community or vocational rehabilitation work? Not surprisingly, the authors found that one of the main difficulties in answering these questions comes from the variability in outcome measures adopted by different research groups. In terms of measuring the effectiveness of inpatient rehabilitation, different groups had used the Barthel index, the FIM, the Ranchos Los Amigos level of Cognitive Functioning Scale, Glasgow Outcome Scale, length of hospital stay and return to work. The trials were almost all retrospective or single group intervention and indicated limited evidence for the effectiveness of inpatient rehabilitation, while the one randomised controlled trial demonstrated moderate evidence. The authors rightly state that there is a great variability of the programs and patient populations. This makes meaningful comparisons difficult. As one could probably predict, the other conclusions from the analysis revealed that there was evidence, albeit limited, to support earlier, more intense rehabilitation that continued in the community and was supported by a vocational element. The authors conclude that standardisation of outcome measures would allow more meaningful comparisons between studies. Perhaps more pertinently, however, they speculate that "...further research may well find that optimal timing and duration of rehabilitation is unique to each patient..." - **LB**

Cullen N, Chundamala J, Bayley M, Jutai J.

The efficacy of acquired brain injury rehabilitation.

BRAIN INJURY

2007 Feb;21(2):113-32.

PARKINSON'S DISEASE: Falling asleep with PD

There has been a great deal of interest in the prevalence, type and cause of sleep disturbance in Parkinson's disease, perhaps triggered by the issues of somnolence with dopamine agonists some 5-10 years ago. Whilst abnormalities of sleep are now recognised and may even precede the onset of Parkinson's disease, the aetiology underlying it is not fully understood, although the role of hypocretin/orexin in this has been an active area of research. It is therefore timely that two papers in Brain have recently reported on the loss of orexin in Parkinson's disease. In both papers the authors demonstrate that there is a loss of orexin neurons in the hypothalamus. In addition Fronczek et al showed that there are Lewy bodies in the hypothalamus and reductions in CSF as well as prefrontal orexin levels, whilst Thannickal et al have shown that the loss of orexin neurons increases with disease progression and is associated with the loss of melanocyte stimulating hormone producing neurons in the hypothalamus as well. This latter population of neurons has also been associated with actions in controlling

Journal reviewers

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the sleep wake cycle. Therefore these two papers both point to pathology in the hypothalamic orexin system in Parkinson's disease and as such a possible explanation for the number of sleep problems in PD. Of course these studies have only shown an association and to prove causality will be a bit more tricky. - **RAB Thannickal TC, Lai Y-Y and Siegel JM.**

Hypocretin (orexin) cell loss in Parkinson's disease.

BRAIN.

2007 Jun;130(Pt 6):1586-95.

Fronczek R, Overeem S, Lee SYY, Hegeman IM, van Pelt J, van Duinen SG, Lammers GJ and Swaab DF.

Hypocretin (orexin) loss in Parkinson's disease.

BRAIN

2007 Jun;130(Pt 6):1577-85.

BRAIN INJURY: poor effort on test results and its relation to distress, personality and litigation

The assessment of the cognitive performance of an individual following traumatic brain injury is of fundamental importance in delineating the deficits that may be present and hence planning further rehabilitation and re-integration into society. While certain parameters such as the extent of damage identified on brain imaging, duration of coma and post-traumatic amnesia are all considerations in the prognostication of brain injury survivors, they do not tell the whole story. An assessment of possible deficits through a battery of validated neuropsychological tests is felt to represent a reasonably 'objective' picture of the state of an individual's cognitive performance. This paper examines the effects of poor effort on performance in neuropsychological testing, and how this may be assessed. Of 618 patients attending an emergency department following mild traumatic brain injury, 110 agreed to undergo formal neuropsychological testing 6 months later. The Amsterdam Short Term Memory Test (ASTMT) was used to assess bias or poor effort. This involves reading five noun words aloud and then repeating them to the assessor after a short distraction task. Validation studies have previously demonstrated high average scores for healthy subjects and patients with closed severe head injuries. The other assessments performed included memory, general intelligence, processing speed and attention. Poor performance in these areas was associated with poor effort as determined by the ASTMT. Poor effort was also associated with depressive symptoms, post-traumatic stress, fatigue and reduced motivation. While the authors are clear that these results need to be interpreted with caution, given the relatively low number of participants and the potential bias in symptomatic patients putting themselves forward for evaluation, their findings do provoke an interesting discussion about the robustness of cognitive evaluation methods in brain injured patients. Effort testing may be important in delineating cognitive deficits occurring as a consequence of brain injury and pre-existing issues unrelated to the injury which can affect performance in formal assessments. - **LB**

Stulemeijer M, Andriessen TM, Brauer JM, Vos PE, Van Der Werf S.

Cognitive performance after mild traumatic brain injury: the impact of poor effort on test results and its relation to distress, personality and litigation.

BRAIN INJURY

2007 Mar;21(3):309-18.

STROKE: Mirror therapy for the – is it the illusion that counts?

*** RECOMMENDED

Recently there has been considerable interest in applying mirror therapy to stroke rehabilitation. The interest was sparked by Ramachandran's work with amputees who suffer phantom limb pain. His patients reported that they could move and relax the painful phantom limb by viewing their contralateral limb through a mirror. The mirror was positioned so that the unimpaired limb 'appeared' to occupy the place of their phantom. Since this discovery researchers have tried using the mirror trick to enhance the sensory input relating to stroke patient's efforts to move in the hopes that this would improve motor recovery. Reports of small studies have held promise for mirror therapy in improving movement in paretic arms and hands. Now a randomised controlled trial of 40 patients has reported benefits for leg recovery from using mirror therapy. Sütbeyaz and colleagues treated comparable groups of stroke patients with impoverished lower limb movements with mirror therapy or with a sham treatment. Patients in the intervention group were positioned in a semi reclined sitting position on a bed. A mirror was placed between their legs and perpendicular to the midline and the patient was asked to move both feet in and out of dorsiflexion while watching the image of the unimpaired limb in the mirror. The mirror was reversed in the control sham treated group so that the non-reflecting side was used. Patients practised moving like this for 30 minutes a day, five days a week for four weeks. This intervention was in

addition to their normal rehabilitation programme. Significant differences between groups in leg movement recovery and function measured by the FIM were found six months after treatment. This is a remarkable result; differences between groups in rehabilitation trials are not often so long lasting. However it is not clear from the study whether viewing the unimpaired foot through a mirror would be better than viewing actual movements of the affected foot. Both groups were effectively denied sight of the impaired foot because it would have been behind the mirror. A second control group is needed to determine whether the sight of an unimpaired limb superimposed on the place of the affected one is better than the actual sight of the impaired limb itself. What the study does suggest is that visual information about lower limb movements helps their recovery. This is important because very often patients are not positioned so that they can see either of their feet moving. - **AJT**

Sütbeyaz S, Yavuzer G, Sezer N, Koseoglu BF.

Mirror Therapy Enhances Lower-Extremity Motor Recovery and Motor Functioning After Stroke: A Randomised Controlled Trial.

ARCHIVES PHYSICAL MEDICINE AND REHABILITATION

2007;88:555-9.

COGNITION: Ventrolateral frontal cortex and eye movement control

*** RECOMMENDED

The frontal lobes of the cerebral cortex have long been associated with the ability to inhibit stimulus driven actions and this includes eye movements. Indeed in 1985 Guitton et al were the first to examine the performance of frontal lobe damaged patients in antisaccade tasks. In such a task individuals are prompted to execute a saccadic eye movement in the opposite direction to the direction of the stimulus presented to them. However, which point of the prefrontal cortex mediates this effect is not known. In this recent study Hodgson et al addressed this issue using a group of 23 frontal lobe damaged patients who were tested in a rule switching task. All patients had isolated focal lesions rather than multiple infarcts and an age-matched control group of 21 individuals were also studied. 16 out of the 23 patients also completed the pro and antisaccades tasks and eye movements were recorded using a video based pupil tracker and were visualised off line. With the use of a custom software program saccades were identified and artefacts removed.

The rule switching task consisted of three boxes outlined in black on a dark grey background which were presented either in the center or 9 degrees to the right or left of the central fixation spot. A coloured circle was presented in the central box which instructed the individual according to the colour (red/blue) where to look, right or left. For the pro/antisaccades the trials were formed by the initial presentation in the center of the screen of a white spot of 0.5 degrees diameter. After 500msecs the spot was extinguished and then reappeared in either the left or the right response box. For the antisaccades trials individuals were instructed to look to the opposite direction to the target stimulus while for the prosaccadic trials individuals were required to fixate on the target stimulus. Results from this study clearly indicated that damage to the ventrolateral frontal cortex significantly impaired performance in both the oculomotor rule switching task and the standard antisaccades task. In particular, in the case of the rule switching task, patients with left ventrolateral damage had increased contralateral saccade errors in the task but were able to correct these errors in 68% of the trials. On the other hand, patients with right ventrolateral damage were able to correct only 30% of these errors. For the antisaccades task patients with either left or right ventrolateral damage appeared to be equivalently impaired and patients presenting with any other type of frontal damage had increased contralesional errors.

The results from this study support the initial hypothesis that the ventrolateral frontal cortex plays a crucial role in the inhibitory control of action during cognitive tasks as well as having a role in the inhibitory control of the saccadic eye movements. Any damage to this region either in the left or right hemisphere seems to contribute in failures to suppress stimulus-cued saccades in an antisaccades task as well as in the rule switching tasks. Why do patients with a right ventrolateral region seem to significantly fail to correct for response errors? As the authors suggest this could be due to an additional functional specialisation for the monitoring and controlling of behaviour on arbitrary task rules. Could deficits in inhibitory control over saccades have potential consequences for patients in the real world? - **CA**

Hodgson T, Chamberlain M, Parris B, James M, Gutowski N, Husain M, Kennard C.

The role of the ventrolateral frontal cortex in inhibitory oculomotor control.

BRAIN

2007 Jun;130(Pt 6):1525-37.