

EDITOR'S CHOICE

AUTOIMMUNITY: mimicking one's self

Hartmut Wekerle's team, from the Max Planck Institute of Neurobiology, Martinsried, are responsible for some seriously important immunological observations over the years. And this is another one....

Firstly, remember what you learnt about one possible cause of autoimmune disease at college...that an invading bacteria looks very like an ordinary part of "self" so that the appropriate immune response against the bug mistakenly leads to auto-damage. Hence "molecular mimicry".

Now, consider this. Wekerle's team have been playing around with a mouse whose entire T cell repertoire consists of one response: to the myelin peptide MOG. In theory, it should only respond to MOG. Through the mechanism of molecular mimicry from an invading bug, it can be induced to get EAE. But, when the mouse is further trans-gened not to be able to produce MOG, you would expect that it could not get EAE, because there is no MOG target to get inflamed about. However, these animals continued to develop EAE spontaneously. After a lot of fancy purification, it turns out that T cells from these animals were targeted at two neurofilament proteins. One, NF-M, turns out to contain a sequence of 7 amino acids that is nearly identical to a sequence in the core of the MOG molecule. So, one class of T cells, that should only respond to MOG, were also targeting neurofilaments. Wekerle's team have coined this "self-mimicry".

The main thing you need to know to understand the significance of all of this is that the strain of mice used (C57BL/6) is notoriously resistant to most attempts to induce autoimmunity. So Wekerle speculates that the mice's particular susceptibility to MOG-induced EAE is because one autoimmune response (against MOG) actually ends up targeting two self-antigens: a two-pronged attack. The other implication (which isn't mentioned and I thought up all myself) is that an immune attack against myelin can also, of itself, induce an immune attack against neurons (for NF-M is a neuronal antigen). Hence perhaps, an explanation for the attrition of nerves in the predominantly demyelinating disease of multiple sclerosis.

It is hard to think of a clinical application for this discovery. But I think there is a good case for us to include this paper in ACNR because of that "wow" factor.... just when we thought we knew everything, something quite unexpected comes along. Who'd have thought.... – **AJC Krishnamoorthy G, Saxena A, Mars LT, Domingues HS, Mentele R, Ben-Nun A, Lassmann H, Dornmair K, Kurschus FC, Liblau RS, Wekerle H.**

Myelin-specific T cells also recognize neuronal autoantigen in a transgenic mouse model of multiple sclerosis.

NATURE MEDICINE

2009 Jun;15(6):626-32.

COGNITIVE Dyspraxia feel the quality

Qualitative research can be a difficult concept to digest to those of us reared on the milk of the double-blind crossover trial paradigm. The lack of a p-value at the end of the results section leaves us feeling adrift and disorientated. Certain concepts do not lend themselves particularly well to the concept of quantitative research, however. A literature search for articles on "dyspraxia" will throw up a bewildering array of concepts pertaining to speech, motor control and cortical mapping. Different disciplines working within the sphere of neurological rehabilitation would, no doubt, vary in their definitions of the condition. Given rehabilitation is based around addressing the problems that the patient sees as important rather than treating abstract diagnoses, determining the particular impact of dyspraxia on an individual's daily life is an important part of planning and providing appropriate rehabilitation strategies to them.

The authors, here, provide a concise summary of the current concepts of ideational (difficulty with the conceptual organising of task sequencing) and ideomotor (difficulty with the performance of a complex task or gesture) dyspraxia. Given that approximately 50% of people with nondominant hemisphere strokes are thought to develop ideomotor dyspraxia, there is a need to have a meaningful concept of the condition in terms of its affects on an individual. To this end, eight participants were filmed giving interviews after completing one or two activities that revealed the extent of their dyspraxia. The interviews could, therefore, focus on the particular difficulties encountered in functional situations and, also, correlate with specific life events. These

videos were then analysed to identify specific themes and experiences. The findings were then presented in various settings to multi-disciplinary groups who confirmed the validity of the findings. Unfortunately, no more detail is given of the latter part of this process and this seems somewhat open-ended.

The interviews revealed a common theme of struggle. This struggle was perceived as being both "within" (pacing oneself, thought processes, control) and "without" (using tools, communicating, relationships). The interviews revealed self-directed compensatory and functional approaches employed in order to overcome the difficulties that were being experienced. Compensatory approaches included environmental adaptations, such as the use of Velcro shoes while functional strategies included breaking activities down into their component parts. These approaches mirror those employed in the rehabilitation setting.

As is often the case with qualitative research, there isn't an obvious "take home message", but what this study does demonstrate is the need to adopt an individualised approach and to work with patients to find strategies that they can use in overcoming the difficulties arising from dyspraxia. It is a shame that some of the concerns and ideas generated in such research could not be taken forward by qualitative methodologies. – **LB**

Blijlevens H, Hocking C, Paddy A.

Rehabilitation of adults with dyspraxia: health professionals learning from patients.

DISABILITY AND REHABILITATION

2009;31(6):466-75.

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POST-POLIO SYNDROME: To rehabilitate or not to rehabilitate?

Post-polio syndrome (PPS) is a complex of symptoms occurring late in polio survivors. One of the challenging aspects in planning the rehabilitation of these patients is the difference in emphasis between management of their original polio and the PPS. For polio, exercise and activity are generally encouraged. This is not the case for PPS where energy conservation and fatigue management are important.

This pilot study looked at the effectiveness of a group rehabilitation programme for PPS sufferers using a comprehensive range of outcome measures that could serve as a useful pointer for research into more "clinical" interventions in chronic neurological disease. The rehabilitation, itself, was a comprehensive three week residential programme which involved physical exercise, education and peer support. Given that this study was a pilot, control groups were not employed, although the patient group were divided into three cohorts of 10 of whom only three dropped out by the end of the six-month follow-up period.

Perhaps unsurprisingly, given the nature of the disease, no differences were identified in muscle strength at follow-up. There were, however, significant improvements in levels of depression, fatigue and improvements in exercise endurance. Given that fatigue and endurance are two of the main ongoing problems for this patient group, it is encouraging that this relatively brief intervention may be of value in ameliorating these symptoms. A smaller subgroup also had significant improvements in general day to day functioning as measured by the Canadian Occupational Performance Measure. While this study is a pilot and, as such, lacks a control group, it is an illustration of the potential and lasting (to six months, at least) benefit of a multi-disciplinary intervention for this challenging patient group for whom no specific treatment in the typical medical sense has shown to be of benefit. – **LB**

Craig Davidson A, Auyeung V, Luff R, Holland M, Hodgkiss A, Weinman J.

Prolonged benefit in post-polio syndrome from comprehensive rehabilitation: A pilot study.

DISABILITY AND REHABILITATION

2009;30(4):309-17.

MEMORY: How did you remember that?

People are sometimes disappointed to realise that the rehabilitation of memory impairments can often involve nothing more complicated than a whiteboard, diary and a pager system. Although it would be easy to imagine that electronic "brain training" computer games could help restore cognitive function following a brain injury there is little evidence that such strategies actually work. In terms of active therapeutic intervention, the concept of "errorless learning" (EL) is becoming more widespread. This suggests that for patients with memory impairments occurring in the context of brain injury, new skills and information is best learnt in a didactic manner rather than by trial-and-error. This challenging approach or "errorful learning" (EF) involves learning from mistakes, but for patients with limited capacity to process and store information, these mistakes can be reinforced.

Although the effectiveness of EL relative to EF has been demonstrated in patients with memory disturbance, there is little correlative evidence of why this should be the case. This small study from Japan has looked at 13 patients with diffuse axonal injury (DAI) learning sets of words under EL and EF conditions and comparing them with healthy controls learning the same words under the same conditions. Functional MRI was carried out during the learning process on both groups and areas of the brain that required more activation for EF than EL were demonstrated by subtracting activity during the EL condition from that engendered under EF condition. For patients with DAI as well as healthy controls, activation of the precuneus was observed. While the control group also demonstrated recruitment of the posterior cingulate gyrus, the DAI group showed bilateral posterior parietal activation.

In the learning tasks, themselves, the DAI subjects (predictably) performed more poorly than controls under the EF conditions. The authors suggest that the neuroanatomical activation patterns in each group imply that this is due to reduced metabolism in the precuneus and posterior cingulate gyrus for the DAI group. The activation of the parietal lobes seen in this group may represent compensatory activity or disinhibition. Unfortunately, insufficient consideration is given to the dynamic processes of recovery and no clear relationship is sought between the time passed since the brain injury and learning patterns. The learning process, itself, is difficult to delineate, given that individuals tend to acquire information in unique ways. A further study looking at the changes in neuroanatomical activity over time in this patient group may be more useful in terms of the potential to translate to clinical practice. – **LB**

Ueno H, Maruishi M, Miyatani M, Muranaka H, Kondo K, Ohshita T, Matsumoto M.

Brain activations in errorless and errorful learning in patients with diffuse axonal injury: a functional MRI study.

BRAIN INJURY

2009;23(4):291-8.

MEMORY: Adult hippocampal neurogenesis – a phenomena looking for a function?

The role of adult neurogenesis in the dentate gyrus of the hippocampus is an area of intense debate. The fact that new neurons are born in this area of the mature CNS is not in doubt, but the problem is what do these cells do once they have matured and been incorporated into new circuits? A couple of papers have added to the literature in this area. The first by Kim et al investigated the consequences of preventing the death of these cells using a Bax-KO mouse, Bax being a pro-apoptotic gene (such that not having it would cause neurons newly born not to die by programmed cell death). Using this model (which of course assumes that most new neurons born in the dentate gyrus are lost through apoptosis), they found that there was a readjustment of synaptic connections with impairments in both electrophysiological and behavioural hippocampal function. In other words if a population of new born neurons in the hippocampus are not removed by natural cell death, they clog up the system and cause deficits which behaviourally involve memory acquisition and consolidation. This is consistent with the study of Truche et al who followed the fate of newly dividing (BrdU positive) neurons in terms of their integration and functional abilities. In this study the authors used the activity-dependent protein Zif268 in combination with high resolution confocal imaging and co-labelling with BrdU and the neuronal marker NeuN, to follow the fate of cells in the context of controlled behaviours involving the water maze. They found that these newly born neurons are recruited into neuronal networks involved with spatial memory and that once incorporated are involved in the updating and strengthening of that memory and thus contribute in part to its durability. Thus these cells are recruited under experience specific conditions and store those conditions as part of their contribution to the spatial memory of the hippocampus. Quite how this information is then used, updated and modified in the long term is not clear, but this and the other study of Kim et al does highlight that these new neurons do make a significant contribution to some aspects of hippocampal memory. – **RAB**

Kim WR, Park OH, Choi S, Choi SY, Park SK, Lee KJ, Rhyu IJ, Kim H, Lee YK, Kim HT, Oppenheim RW, Sun W.

The maintenance of specific aspects of neuronal function and behaviour is dependent on programmed cell death of adult-generated neurons in the dentate gyrus.

EUROPEAN JOURNAL OF NEUROSCIENCE

2009;29:1408-21.

Truche S, Bontempi B, Roulet P.

Rampon Recruitment of adult-generated neurons into functional hippocampal networks contributes to updating and strengthening spatial memory.

PNAS

2009;106:5919-24.