It ain't what you do, it's the pace that you do it...

Reviewer – Dr Lloyd Bradley, Consultant in Rehabilitation Medicine, Western Sussex Hospitals NHS Foundation Trust, UK

There is an unwritten law of rehabilitation research that the more obviously beneficial an intervention, the harder it can be to identify a good evidence base. Is it better for Speech Therapists to conduct therapy sessions using the same language as the patient they are working with? Are the outcomes for hydrotherapy better in warm rather than freezing water? No, I don't know either. There's no evidence to say so, we just assume.

There is certainly a lot of research around the levels of physical activity within inpatient rehabilitation units. Perhaps unsurprisingly many patients are observed to spend significant amounts of time being physically inactive in spite of the fairly well evidenced(!) benefits of physical activity in a number of different domains. Engaging in social interaction is also felt to be important in the context of rehabilitation, but with a significantly less-well developed evidence base. The researchers begin this interesting study of the effects of environment on stroke recovery with reference to animal models. Although there is probably something to be said for drawing analogies around neuronal remodelling and cellular changes from mouse models of stroke, determining what constitutes an ideal environment for social activity from murine preferences is probably a less secure paradigm. The idea of an "enriched environment" is a fairly nebulous one but most of us would intuitively feel there is value in a setting that promotes social interaction and cognitive activity.

In order to determine the benefit of an "enriched environment" two (fairly small) groups of stroke patients within an inpatient neurorehabilitation facility were compared. One group were given access to communal activities and individual opportunities for stimulation such as newspapers, games consoles, board games, music and books. The other group received "standard care" (one wonders how rigorously the control group could be denied personal stimulation). Predictably the experimental group spent significantly more time engaged in "activity" than the control group. Unfortunately there is no longitudinal data around the effect that engaging in this activity may have had on length of stay or more meaningful functional outcomes.

No one working within an inpatient care setting can fail to appreciate how the traditional ward environment of being in a bed ministered to passively promotes dependence and adversely affects engaging in the normal activities of daily living. While perhaps animal models are not the best sources of information for the benefits of environmental stimulation in human populations, there are clearly many unanswered questions around the optimum environment for rehabilitation to take place in. Promoting independent social activity and interaction, may, in the end be as important as the regimental daily 45 minutes of face-to-face contact with a therapist in facilitating longer term gains. It is heartening that the focus could switch back to the patient "doing" rather than being "done to" in promoting recovery.

Janssen H, Ada L, Bernhardt J, McElduff P, Pollack M, Nilsson M, Spratt NJ. An Enriched Environment Increase Activity in Stroke Patients Undergoing Rehabilitation in a Mixed Rehabilitation Unit: A Pilot Non-Randomised Controlled Trial. DISABILITY AND REHABILITATION 2014;36(3):255-62.

Parkinson's Disease

Reviewer – Dr Thomas Foltynie, Consultant Neurologist and Senior Lecturer at the National Hospital for Neurology & Neurosurgery

The quest towards finding a neuroprotective agent for Parkinson's disease continues apace. The two main strategies can be broadly separated into those which aim to identify "de-novo" drugs with a specific action on the neurodegenerative process of PD, and those that aim to "repurpose" agents already licensed for the treatment of another human disease, that may have additional relevant effects. The latter strategy has appeal in that agents are far less likely to fail because of intolerable side effects and their efficacy verses futility (on relevant processes such as mitochondrial function or neuro-inflammation) can be determined more quickly and cheaply. There are trials in set-up or in progress using Isradipine, Inosine, Exenatide, Deferiprone, Ursodeoxycholic acid among others as examples of "repurposing".

The former strategy in comparison, is notoriously long-winded in terms of the laboratory selection process, carries high risk of failure because of potential toxicity, and is hugely expensive. It has been estimated that bringing a brand new agent to licensing takes approximately 17 years and costs over $1bn. In the past year however some further progress towards the development of a couple of "de-novo/tailor made" neuroprotective drugs for PD has been made focusing on agents that may have particularly relevance to individual patients with subtypes of PD.

The first targets the LRRK2 protein; mutations in the gene encoding for LRRK2 are the commonest cause of autosomal dominant PD, generally thought to result via a toxic gain of LRRK2 function. The relationship between LRRK2 and PD neurodegeneration appears to be more complex than simply excessive LRRK2 enzyme activity however (LRRK2 includes a GTPase domain, a carboxy terminal domain and a kinase domain and mutations in any of these, including mutations causing a loss of LRRK2 function can all lead to dominantly inherited PD). An important paper published this year by the Sheffield, UK group has suggested that one of the consequences of LRRK2 mutations in either of the first two domains, is on axonal transport via microtubule deacetylation. More importantly they showed that in Drosophila with such LRRK2 mutations (in the GTPase or carboxy terminal domains), enhancing microtubule acetylation through oral administration of a broad acting deacetylating inhibitor -Trichostatin A, could restore axonal transport and could restore abnormal locomotor behaviour even after the motor phenotype was established. Good news for the flies say the cynics…but perhaps also a critical finding towards developing a tailor made agent for patients with specific LRRK2 mutations, and to be considered alongside the concurrent exploration of a range of LRRK2 inhibitors that may have specific utility among the other subgroup of LRRK2 patients with mutations in the kinase domain.

The second paper has relevance for patients with mutations in the GBA gene – the causative gene for Gaucher disease, and recently discovered to also be the greatest single genetic risk factor for PD even when single mutated copies of the gene are inherited. GBA encodes the glucocerebrosidase (GCase) enzyme, and mutations in the gene lead to decreased GCase activity and consequently increased alpha synuclein aggregation. There is great interest in trying to boost GCase function using either repurposed or tailor made agents. AT2101 is an orally available, pharmacological chaperone, a small molecule which can specifically and reversibly bind GCase in the endoplasmic reticulum with high affinity, thus stabilising it, and increasing its trafficking to lysosomes where it has its functional interaction with alpha synuclein. In this paper by the Chesselet group, this AT2101 chaperone had clear effects on GCase stabilisation in an alpha synuclein overexpressing mouse model, which resulted in improved motor deficits and reduction in alpha synuclein neuropathology. This agent has already been the subject of trials in Gaucher patients (unpublished), and may become an agent with major potential relevance to PD neuroprotection in both GBA and possible even in some sporadic PD patients.

Godena et al. Increasing microtubule acetylation rescues axonal transport and locomotor deficits caused by LRRK2 Roc-COR domain mutations. NATURE COMMUNICATIONS 2014. Oct 15;5:5245.

Richter et al. A GCase Chaperone Improves Motor Function in a Mouse Model of Synucleinopathy. NEUROTHERAPEUTICS. 2014. Oct;11(4):840-56.