Harnessing experience-dependent plasticity for CNS repair and regeneration

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Future Neurology

Conference Scene

7th World Congress of Neurorehabilitation

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The 7th World Congress of Neurorehabilitation was held from 16–19 May, 2012, in Melbourne, Australia. Melbourne produced the largest attendance of any meeting thus far for this biennial congress of the World Federation of Neurorehabilitation. The congress provided a diverse range of presentations, from environmental interventions in animal models of brain disorders, to new techniques for rehabilitation and clinical trials. While stroke, traumatic brain injury and spinal cord injury featured prominently, there were also many other presentations on rehabilitation for neurodegenerative diseases and other neurological disorders. Here, we focus on a selection of novel findings reported at this congress.

New insights from animal models of CNS disorders

The congress provided insightful examples of how high-quality studies in valid animal models can lead to translation and refinement of clinical trials. The congress opened with an excellent Michael P Barnes lecture delivered by Randolph Nudo (Kansas University Medical Center, Kansas City, KS, USA). Dancause and Nudo have developed some innovative approaches for the development of new treatments to enhance neural plasticity, and hence recovery, following brain injury, building on recent work from this group [1]. One exciting new technology described involved detection of neural activity on one hemisphere of a traumatic brain injury (TBI) model that controlled neural stimulation adjacent to the injury site. This demonstrated significant beneficial effects, including a behavioral reaching task. The interface between neural plasticity and neuroengineering holds great promise for TBI and other CNS disorders.

In another session focused on animal models, Michael Nilsson (Hunter Medical Research Institute, University of Newcastle, Newcastle, Australia) provided an enlightening overview of the beneficial effects of environmental enrichment, which enhances cognitive stimulation and physical activity, in animal models of brain injury, as well as in clinical settings. The promising data from animal models of stroke [2] have recently been taken into clinical trials [3]. Michael Selzer (Shriners Hospitals Pediatric Research Center, Temple University School of Medicine, PA, USA) described novel approaches to inducing axonal plasticity and repair for the treatment of spinal cord injury (SCI). Selzer *et al.* have previously developed a lamprey model of spinal axon regeneration, which incorporates live imaging approaches [4]. They have since used this model system to understand specific molecular mechanisms regulating axonal regeneration and sprouting. Their findings identify potential targets guiding development of future therapeutics for SCI and related CNS disorders. Finally, a presentation from Anthony Hannan discussed the beneficial effects of environmental enrichment and experience-dependent plasticity in various mouse models of brain disorders. These experimental paradigms have been used to model brain and cognitive reserve as well as experience-dependent functional compensation [5]. A recent systematic review in stroke models showed the superiority of enriched environments for functional and cognitive recovery [2]. Furthermore, Hannan has proposed that environmental enrichment can be used to identify 'enviromimetics', drugs that mimic or enhance the beneficial effects of enhanced cognitive stimulation and physical activity [6]. Trials of rehabilitation-enhancing drugs are emerging, with a number of large Phase III trials (e.g., FOCUS and AFFINITY) planned.

A further session on animal models focused on the preclinical development of specific environmental and pharmacological approaches for TBI and SCI. Cristina Morganti-Kossmann and Nicole Bye (National Trauma Research

Keywords

■ animal models ■ brain repair ■ depression ■ environmental enrichment ■ exercise ■ spinal cord injury ■ stroke ■ traumatic brain injury

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Institute, Alfred Hospital, Melbourne, Australia) described recent findings involving rodent models of TBI. One particularly interesting area is the role of neuroinflammation, including specific chemokines and their receptors, in TBI [7]. Additional data were presented on the effects of TBI on adult neurogenesis and associated identification of potential molecular targets for therapeutics, such as BDNF. Anthony Kline (Physical Medicine and Rehabilitation, University of Pittsburgh, PA, USA) has provided important insights into the optimization of environmental enrichment and other approaches for TBI [8]. In this talk, he presented new data on pharmacological modulators of TBI, including antipsychotic drugs such as aripiprazole. Camilia Fiore (Melbourne School of Health Sciences, University of Melbourne, Australia) presented new data on the effects of treadmill training in a mouse model of SCI. These kind of animal model approaches are now being used to inform clinical rehabilitation strategies.

The brain as a network

The need to understand the effect of structural damage on functional brain networks was a prominent message throughout the conference, and was perhaps most eloquently put by Maurizio Corbetta (Washington University, St Louis, MO, USA). Corbetta presented his model of spatial neglect that is based on dorsal and ventral processing systems, without localization to any one area. A stroke lesion can cause imbalance in these networks, creating abnormalities in functional connectivity in distributed brain networks, which manifests as neglect [9]. Stroke is one way that functional connectivity can be interrupted, but interruption can be expected whenever neuronal connectivity is compromised (e.g., TBI, multiple sclerosis and dementia). Corbetta also demonstrated the importance of connectivity in the healthy brain, reporting that stronger functional connectivity in the visual cortex is not only associated with better performance on a difficult visual task but also with a better capacity for learning.

Understanding residual functional connectivity has implications for post-stroke motor recovery. Cathy Stinear (University of Auckland, Auckland, New Zealand) has developed an algorithm (PREP) for predicting motor recovery after stroke [10]. The stepped algorithm begins with a clinical assessment of function, followed by transcranial magnetic stimulation to determine integrity of the corticospinal tract, followed by MRI to identify descending white-matter pathways. Arm function measured at 12 weeks post-stroke was remarkably well predicted by the algorithm taken within 2 weeks of stroke. Leeanne Carey (Florey Neuroscience Institutes, Melbourne, Australia) demonstrated how knowledge of functional brain activity can be used to inform rehabilitation of sensory function after stroke. The SENSe approach is aimed at achieving task specific training effects, then establishing the transfer of training effects to novel stimuli. Carey reported that this rehabilitation approach was effective in improving functional sensory discrimination in a randomized controlled trial [11] and also that training-facilitated recovery of touch sensation was associated with changes in brain activity. While preliminary, Dominic Pérennou's team (Grenoble, France) has begun to understand the brain regions/networks responsible for problems with 'visual-vertical' perception. This phenomenon involves alteration to the perception of what is upright, and results in patients leaning away from and resisting movement towards their unaffected side. It is challenging to treat and recovery is slow. Understanding the problem could hold the key to improving treatments.

Innovative ways to treat depression & fatigue

Depression and fatigue are very common after brain injury and other CNS disorders, with deleterious impacts on rehabilitation and recovery. Nadina Lincoln (University of Nottingham, Nottingham, UK) presented positive findings from a randomized controlled trial of social support groups for low mood in multiple sclerosis [12]. Improvements in the treatment group were maintained at 8-month follow-up, and the intervention was shown to be cost effective (largely as a result of reduced general practitioner visits in the treatment group). Lincoln also reported encouraging results from a trial of behavioral therapy, based around increasing communication, in stroke patients with low mood and aphasia (CALM). The treatment group exhibited greater improvement over time than controls on aphasia-friendly mood scales. Given how little is known about how to treat fatigue, it was exciting to see preliminary research on light therapy in TBI patients. Kelly Sinclair (Monash University, Melbourne, Australia) compared short-wavelength (blue) light – hypothesized to reduce fatigue as it stimulates arousal rather than visual areas – to middle-wavelength (yellow) light and

no light. Exposure to blue light significantly reduced fatigue and daytime sleepiness, though the maintenance of these benefits over time was unclear.

Conclusion

The final day of the conference held a reminder that scientific breakthroughs were impotent without change in clinical practice. Robert Teasell (University of Western Ontario, London, Canada) used the context of stroke rehabilitation to stress that we already have a large evidence base [101]. He reported a recent trial of implementation of stroke guidelines across 20 sites in Canada (SCORE-IT), where it was found that simply implementing existing guidelines increased discharge to home from 60 to 70%. We will see much more implementation science in this arena. At the close of this congress, the panel of eminent clinician scientists, when asked to gaze into the future for neurorehabilitation, saw stronger linkages between basic scientists and clinicians as imperative. The prescience of these scientists, and progress in this fast-moving field, will be revisited when the 8th World Congress of Neurorehabilitation is held in Istanbul (Turkey) in 2014.

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