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Introduction to the ACNR Stroke Series

Upper limb impairment is one of the most important challenges for clinicians, researchers and stroke survivors. Improving outcomes is a key goal. In this next article in our stroke series, Nick Ward, Kate Kelly and Fran Brandner – from the innovative Queen Square specialist upper limb clinic team - offer a clear and concise summary of recent developments and promising new directions. They make a strong case for increasing the amount and intensity of neurorehabilitation, as well as outlining new approaches to augment the response to interventions. This article reminds us of the importance of working as a multidisciplinary team in stroke neurorehabilitation, and of the challenges in translating neuroscience findings to pragmatic and effective treatments.

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The future of stroke rehabilitation: upper limb recovery

The impact of stroke-related impairment around the world remains high.[1] In particular, residual upper limb dysfunction after stroke is a major clinical, economic and societal problem. In the UK alone, the economic burden of stroke is estimated at over £5 billion a year and so improving outcomes after stroke is an important clinical and scientific goal. Nearly three-quarters of stroke survivors experience upper limb symptoms after acute stroke and in the first six months only 20% or so achieve some functional recovery.[2,3] Management of the upper limb after stroke can be complex, requiring approaches that avoid complications, promote recovery and provide compensatory strategies in varying combinations depending on severity and time post-stroke.[1]

The wrong dose of rehabilitation?

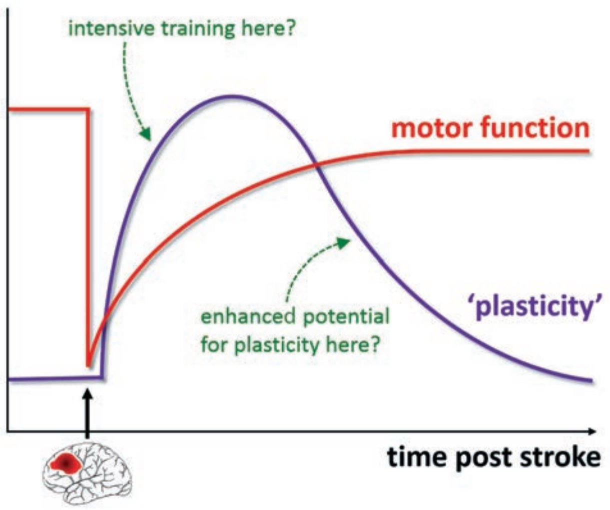
There is concern that the dose and intensity of upper limb rehabilitation after stroke is too low. During early inpatient rehabilitation, the time spent engaged in activities, especially functional upper limb movements, is surprisingly low.[4,5] Several studies have examined whether increasing the time spent on upper limb therapy makes a difference. For example, an additional two to three hours of arm training a day for six weeks reduced impairment and improved function by clinically meaningful amounts when started one to two months after stroke,[6] but anything less than this does not appear to provide much benefit on average.[7,8] It seems likely that when it comes to upper limb therapy, more is better.

However, the intensity (amount of activity), as well as the overall dose (time spent in therapy) is important. Data from work in rodent models of stroke suggest that changes in synaptic density (a marker of the neuroplastic reorganisation that is the substrate for recovery) in the primary motor cortex occur after hundreds but not tens of repetition.[9] In human stroke patients, the typical number of repetitions in a therapy session can be much lower.[4] It may be the case that there is a threshold of activity below which the neuroplastic reorganisation of surviving motor networks supporting recovery is unlikely to occur.[10]

How to increase the dose of rehabilitation?

One way of increasing dose is to implement a treatment programme that patients can administer themselves. The self-administered 'graded repetitive arm supplementary program' (GRASP) has the advantage of being flexible enough to use in patients with a range of impairments. When started early after stroke in an in-patient setting, four weeks of GRASP led to improvements in upper limb function compared to patients undergoing an education programme. These gains were maintained at five months post-stroke. GRASP is easy to administer, cost-effective and feasible to implement in a number of health care settings on a large scale.[12]

Constraint-induced movement therapy (CIMT) also increases the dose of functionally relevant training. Patients are required to wear a sling or mitten restricting use of the unaffected upper limb resulting in increased use of the affected hand/arm in functional tasks. CIMT led to improvements in the performance of functional tasks compared to standard (less intense) treatment.[13] Despite its apparent simplicity, it is not always tolerated well if worn for six hours per



A change in the potential for experience dependent plasticity after stroke has implications for (i) when intensive neurorehabilitation training should be delivered and (ii) when 'plasticity-enhancing' interventions might be used.

day (standard protocol) and so modified protocols have been used, although less well studied.

The use of robotic technology in guiding highly specific training regimes might also allow a sufficient number of repetitions to be delivered in a motivating environment. Some devices allow weight support of the arm, so that skilled movements can be practiced even in the presence of significant shoulder weakness. Most clinical trials have been small and have involved chronic stroke patients. Two relatively large studies of upper limb robotic training in chronic stroke patients have recently been carried out.[14,15] Both achieved high numbers of repetitions but only improved impairment by a few points compared to usual (less intense) therapy, and results were not greatly different to standard therapy matched for dose. It is likely that robotics and other technology such as virtual-reality based rehabilitation will find use as adjunctive therapy, rather than replacement for hands-on therapy. In other words, technological solutions provide a way of providing massed practice, but hands-on therapy is crucial for turning benefits into functional gains. Advances in devices that can be used and monitored in a patient's own home will also be required before technological approaches to neurorehabilitation have a substantial impact.

What is the best time for neurorehabilitation?

One of the interesting things about stroke is the response to focal injury in the brain. There is evidence from animal models that a number of changes at molecular, cellular and systems levels reflect an upregulation of the potential for experience-dependent plasticity.[16] In particular, (i) widespread activation of genes normally seen during development and (ii) shifts in cortical excitability that support long-term potentiation and cortical map reorganisation. These changes probably support what has been termed 'spontaneous biological recovery' which refers to rapid, generalised improvement in impairment in the first few months after stroke and is in contrast to modest gains made in the chronic phase.[17] Limited evidence suggests the same critical window exists after stroke in humans. If so, this would provide a compelling reason to deliver the highest dose and intensity of neurorehabilitation in the first few weeks and months after stoke in order to effect the biggest improvement in the widest range of functional tasks (figure). Concerns over very early (within 24 hours) neurorehabilitation persist,[18] but early assessment and planning should start as early as possible, taking each patient's clinical status into consideration. Understanding the mechanisms underlying spontaneous biological recovery could provide novel therapeutic targets with the goal of enhancing, prolonging or even re-opening the critical period during which spontaneous biological recovery is most likely.

Enhancing plasticity

Training works through mechanisms of experience-dependent plasticity,[16] and there is now interest in enhancing the potential for plasticity to increase the efficacy of motor-skills training after stroke. A key determinant of the potential for plasticity in adults is the balance between cortical inhibition and excitation.[19] Reduced GABAergic-inhibition and/or enhanced glutamatergic-excitation can enhance long-term potentiation and facilitate downstream changes in neuronal structure, allowing remapping of sensorimotor functions to surviving cortical regions.[16] Knowing the profile of these longitudinal changes is crucial because it will impact on plasticity-mediated recovery, influence when training is best delivered and when plasticity-enhancement might be attempted.[20]

Several approaches to plasticity-enhancement for promoting the effects of training are of interest in stroke, including neuropharmacological and non-invasive brain stimulation (NIBS). These approaches and others, including mental imagery, action observation, bilateral movements, somatosensory stimulation and aerobic exercise, might be thought of as ways of 'priming' the brain (and specifically the motor cortex) just prior to more specific motor training.[21] Whilst brain stimulation has yet to repay early enthusiasm based on small studies, the neuropharmacological approach holds more realistic promise. The interest in selective serotonin reuptake inhibitors in promoting motor recovery after stroke is highlighted by the FLAME study[22] in which fluoxetine 20mg daily, started five to ten days after ischaemic stroke and continued for three months, enhanced upper limb motor recovery at three months. Dopamine-agonists are also currently under investigation in RCTs.[23] However, the implementation of strategies for post-stroke plasticity-enhancement in phase III trials lacks clear mechanistic rationale and is therefore premature. Without understanding 'who' and 'when' to treat based on mechanistic approaches, these trials are unlikely to succeed in delivering novel treatments into routine clinical practice.[24]

Summary

Management of the upper limb after stroke can be complex. At present the dose of upper limb neurorehabilitation is too low. Here we have outlined the rationale and approach for increasing both dose and intensity of treatment. Novel approaches to enhancing the potential for experience dependent plasticity may be available soon, if the required level of evidence comes from appropriately stratified clinical trials. Despite these potential advances, it is important to remember that reduced impairment needs to translate into functional improvements in everyday tasks, and that ongoing home based exercise or therapy programmes need to be embedded in self-management programmes[25] if patients are to truly benefit.

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