

Emerging Therapies in Stroke Rehabilitation

Sherry Young,¹MD, Keng He Kong,²MBBS, MRCP (UK)

Abstract

Traditionally, practitioners of stroke rehabilitation are taught that benefits of rehabilitation are achieved primarily through training patients in new techniques to compensate for impairments, and that neurological recovery is predominantly spontaneous in nature. Recent animal and human experiments have, however, indicated that the adult brain is capable of reorganisation and the term plasticity has been coined to describe this ability. Furthermore, it has been shown that cerebral reorganisation is use-dependent and can be manipulated via appropriate stimuli. This has resulted in a paradigm shift in the way stroke survivors should be rehabilitated and also given rise to several novel rehabilitation techniques.

Ann Acad Med Singapore 2007;36:58-61

Key words: Rehabilitation, Stroke

Introduction

Stroke is the fourth leading cause of death in Singapore since 1998.¹ While mortality due to stroke has steadily declined over the years with better care, stroke remains the leading cause of long-term disability in adults and the most common reason patients are referred for rehabilitation.

The main goal of rehabilitation is to optimise functional recovery. Conventionally, this is usually achieved through emphasis on reduction of disability and not impairment. Thus, if a stroke patient has difficulty caring for himself because of weakness of the affected arm, the emphasis will be on teaching him to compensate using the non-affected arm rather than spending time strengthening and re-educating the affected arm. Learning compensatory techniques to reduce disability leads to faster and earlier functional response compared to impairment reduction techniques. However, hasty compensation runs the risk of encouraging disuse in the affected limb which may affect long-term recovery, as will be discussed later.

The other aspect of conventional stroke rehabilitation programmes is the reliance on natural or spontaneous recovery as the basis for treatment protocols. However, recent animal and human studies indicate that this is not necessarily the case and rehabilitation is actually capable of influencing the process of post stroke recovery.

Mechanisms of Recovery

Advances in neuro-imaging techniques such as functional magnetic resonance imaging (fMRI), positron emission tomography (PET) and transcranial magnetic stimulation (TMS), in addition to animal studies on neurological injury, have helped further our understanding of how the brain recovers after an insult such as a stroke. We now know that the adult brain is capable of reorganising itself after suffering a stroke. This process of change and reorganisation is referred to as plasticity.

In animal studies, the changes noted include increased dendritic branching,² synaptogenesis,³ reduced GABAergic inhibition and increased hyperexcitability in both perilesional and distant cortex.⁴ The process of cerebral reorganisation is activity or use-dependent and can be potentially manipulated. Furthermore, it is now known that even in the chronic stages of a stroke, the brain is still “plastic” and can reorganise in response to appropriate stimulus.

These findings have marked implications on the practice of neurorehabilitation. Firstly, it challenges conventional wisdom that benefits from rehabilitation can only be achieved through training patients in new techniques to compensate for impairment rather than impairment reduction. Moreover, the fact that cerebral reorganisation

¹ Department of Rehabilitation Medicine, Changi General Hospital, Singapore

² Department of Rehabilitation Medicine, Tan Tock Seng Hospital, Singapore

Address for Correspondence: Dr Kong Keng He, Department of Rehabilitation Medicine, Tan Tock Seng Hospital, C/o Ang Mo Kio Hospital, 17 Ang Mo Kio Ave 9, Singapore 569766.

Email: keng_he_kong@ttsh.com.sg

is use-dependent further stresses the importance of impairment reduction. Secondly, it offers the distinct possibility of manipulation of neurological recovery through other means apart from physical therapy. Finally, rehabilitation should be considered even in patients with a chronic stroke.

We will next discuss some of the emerging therapies in stroke rehabilitation.

a. Constraint-induced Movement Therapy (CIMT)

Studies in monkeys showed the phenomenon of “learned non-use” when a single forelimb is deafferented leading to deprivation of somatic sensation. Since the animal is unable to feel, it stops using the affected limb right after injury and learns to get along with the 3 remaining limbs. As time goes on, even after the affected limb heals, the monkey exhibits “learned non-use” when the limb becomes potentially useful again. This “learned non-use” can be reversed with restraining of the intact forelimb and training to use the affected limb.^{5,6} This forced use of the unaffected limb is known as constraint-induced movement therapy (CIMT).

The first report of the effectiveness of CIMT for hemiparesis in humans was by Ostendorf and Wolf in 1981.⁷ This was followed subsequently by a number of case series and small randomised controlled trials. CIMT in these studies consisted of intensive training of the affected upper extremity for 6 hours a day for 10 consecutive weekdays, restraint of the less affected extremity for a target of 90% of waking hours during the 2-week treatment period, and application of a number of other techniques designed to produce transfer to the life situation. The results of these studies were generally impressive. Taken together, they showed that CIMT can produce a large improvement in the amount of use of the impaired arm in patients with chronic stroke.⁸⁻¹² This improvement is of interest because it is reported to transfer to the life situation and persist for ≥ 2 years. Furthermore, it has been shown on transcranial magnetic stimulation studies, that after CIMT, there is almost doubling of the excitable cortex on the affected hemisphere which parallels clinical improvements.¹⁰ Despite these, there were still doubts about the efficacy of CIMT, largely because these studies involved only small patient numbers and were single centre trials.

In the largest, multicentre, randomised controlled trial of CIMT to date, 227 patients who had a first stroke within the previous 3 to 9 months were assigned to either a 2-week programme of CIMT (wearing a restraining mitt on the unaffected hand while engaging in repetitive task practice and behavioural shaping with the hemiplegic hand) or usual and customary care (this could range from no treatment to pharmacologic or physiotherapeutic interventions).¹³ The outcome measures were the Wolf Motor Function Test

which measures functional ability of the upper extremity, the Motor Activity Log which measures how often 30 common daily activities are performed, and Stroke Impact Scale (hand domain) which measures self-perceived hand function difficulty. The CIMT group demonstrated statistically significant improvements in all outcome measures that persisted for at least 1 year.

For patients to benefit from CIMT, it is recommended that they have intact cognition and also meet the minimum motor criteria of being able to extend the impaired wrist and fingers to 20 and 10 degrees respectively. The challenge now is to establish the role of CIMT during acute rehabilitation and the ongoing VECTORS study (www.strokecenter.org/vectors) should answer this question.

b. Rehabilitation Pharmacology

Rehabilitation pharmacology refers to the use of medications in combination with rehabilitative training to improve function. Several potentially useful medications have been identified in animal and human experiments and the 2 most studied are amphetamine and levodopa.

In animal studies, amphetamine has been shown to enhance post stroke recovery possibly because of increased noradrenergic neurotransmission and facilitation of activity-dependent neuro-plasticity.^{14,15} It has also been shown to upregulate neural sprouting and synaptogenesis in peri-infarct cortex and contralateral cortex.¹⁶ Maximum improvement occurs when drug administration is coupled with task-specific practice.¹⁷ A dose-response effect has also been identified and multiple doses on an intermittent basis appear most effective.

In humans, 10 mg amphetamine facilitates the effects of motor training on use-dependent plasticity as measured by transcranial magnetic stimulation, suggesting that this dose is sufficient for producing a measurable neurophysiological effect.¹⁸ Small trials have demonstrated safety, feasibility, and proof-of-concept for the use of amphetamine in post stroke rehabilitation for carefully selected patients, but clinical efficacy is uncertain.¹⁹⁻²⁵ This uncertainty is probably a result of the small sample sizes and imbalances in prognostic variables inherent in these studies. The ongoing multicentre, randomised, placebo-controlled Amphetamine Enhanced Stroke Recovery (AESR) study may provide much needed clarity on the efficacy of amphetamines in stroke recovery.

Dopaminergic activity is one of the mechanisms implicated in memory formation. Floel et al²⁶ studied the effects of a single oral dose of levodopa administered in a randomised, double-blind, placebo-controlled cross-over design on formation of a motor memory in patients with a chronic stroke, and found that levodopa enhanced the

ability of motor training to encode an elementary motor memory relative to placebo. They suggested that up-regulation of dopaminergic function may enhance motor memory formation, which is crucial for successful rehabilitation. In a randomised, double-blind study of 53 stroke patients, a single dose of levodopa 100 mg in combination with physiotherapy for 3 weeks resulted in better motor recovery compared to placebo, and this was independent of the initial degree of impairment.²⁷

Larger studies are needed before one can justify the routine use of either amphetamine or levodopa to facilitate post stroke recovery.

c. Transcranial Magnetic Stimulation (TMS)

Repetitive transcranial magnetic stimulation (rTMS) has recently been used to facilitate motor recovery after stroke. It is hypothesised that in the normal brain, there is interhemispheric or transcallosal inhibitory drive between both motor cortices.²⁸ When a motor cortex is damaged as a result of a stroke, it results in excessive inhibitory drive of the contralesional motor cortex on the ipsilesional motor cortex. It is believed that this excessive inhibitory drive retards recovery of the affected limb and conversely, a reduction in inhibitory drive should result in better recovery.

This balance of interhemispheric inhibition can be manipulated by rTMS. It is known that low-frequency (1 Hz) rTMS has inhibitory effects on the motor cortex while high-frequency (5 Hz or more) rTMS has excitatory effects. Thus, the imbalance in interhemispheric inhibition theoretically, can be redressed either by low-frequency rTMS of the contralesional motor cortex or high-frequency rTMS of the ipsilesional motor cortex. Clinical studies of rTMS in chronic stroke patients (both low and high-frequency stimulation) do support the hypothesis of interhemispheric inhibition.²⁹⁻³¹ However, as a potential therapeutic tool, the overall procedure of rTMS remains to be optimised, in particular regarding the number of rTMS sessions. Furthermore, as existing studies only evaluated patients with a chronic stroke, its role acute and subacute stroke remains to be defined.

d. Robotics

Over the last few years, there has been considerable research looking at the role of interactive robotic devices in rehabilitation, especially in the area of upper limb recovery. One such device, developed at Massachusetts Institute of Technology, involves placing the impaired arm into a brace that is in turn attached to the “arm” of the robot.^{32,33} A therapist physically guides the patient through a given exercise and the session is recorded by the robot. The robotic device is then capable of reproducing the exercise and guides the patient through it. As the patient begins to recover and starts to initiate some movement on his own,

the robot can measure how much force the patient is applying and adjust the amount of resistance it provides.

Body weight supported treadmill therapy (BWSTT) has also made inroads into the area of post stroke gait training. Typically, the robotic system consists of a motor driven exoskeleton which is attached to the patient’s legs, a body weight support suspension system from which the patient is suspended and a treadmill. The motor driven exoskeleton moves the patient’s legs through position-controlled trajectories that mimic normal human gait patterns. This is accomplished by utilising high quality computer-controlled motors that are precisely synchronised with the speed of the treadmill.

Compared to conventional exercises that are provided by a therapist, interactive robotic devices are capable of delivering repetitive controlled, reproducible sensorimotor training that not only allows precise intensity and duration of training but also crucial timely responsiveness that is correlated with the patient’s sensory experience. Although preliminary studies evaluating robot-assisted motor rehabilitation has been encouraging so far,³⁴⁻⁴⁰ larger, randomised, controlled studies are necessary before they can be adopted as standard treatment.

Conclusion

The field of stroke rehabilitation has undergone major paradigm shifts as a result of our understanding on how the brain recovers after a stroke. This has also led to new and promising rehabilitative treatment and modalities and the future of stroke rehabilitation has never been more exciting.

REFERENCES

1. Health facts Singapore, Ministry of Health, 2005. Available at: <http://www.moh.gov.sg/corp/publications/statistics/index.do>. Accessed 10 December 2006.
2. Jones TA, Schallert T. Overgrowth and pruning of dendrites in adult rats recovering from neocortical damage. *Brain Res* 1992;581:156-60.
3. Jones TA, Kleim JA, Greenough WT. Synaptogenesis and dendritic growth in the cortex opposite unilateral sensorimotor cortex damage in adult rats: a quantitative electron microscopic examination. *Brain Res* 1996;733:142-8.
4. Buchkremer-Ratzman I, August M, Hagemann G, Witte OW. Electrophysiological transcortical diaschisis after cortical photothrombosis in rat brain. *Stroke* 1996;27:1105-9.
5. Knapp HD, Taub E, Berman AJ. Movements in monkeys with deafferented forelimbs. *Exp Neurol* 1963;7:305-15.
6. Uswatte G, Taub E. In: Stuss DT, Winocur G, Robertson IH, editors. *Cognitive Neurorehabilitation: A Comprehensive Approach*. New York: Cambridge University Press, 1999.
7. Ostendorf CG, Wolf SL. Effect of forced use of the upper extremity of a

- hemiplegic patient on changes in function. *Phys Ther* 1981;61:1022-8.
8. Taub E, Miller NE, Novack TA, Cook EW III, Fleming WC, Nepomuceno CS, et al. Technique to improve chronic motor deficit after stroke. *Arch Phys Med Rehabil* 1993;74:347-54.
 9. Van der Lee JH, Wagenaar RC, Lankhorst GJ, Vogelaar TW, Deville WL, Bouter LM. Forced use of the upper extremity in chronic stroke patients: results from a single-blind randomized clinical trial. *Stroke* 1999;30:2369-75.
 10. Liepert J, Bauder H, Wolfgang HR, Miltner WJ, Taub E, Weiller C. Treatment-induced cortical reorganization after stroke in humans. *Stroke* 2000;31:1210-6.
 11. Taub E, Lum PS, Hardin P, Mark V, Uswatte G. AutoCITE: automated delivery of CI therapy with reduced effort by therapists. *Stroke* 2005;36:1301-4.
 12. Taub E, Uswatte G, King DK, Morris D, Crago JE, Chatterjee A. A placebo-controlled trial of constraint-induced movement therapy for upper extremity after stroke. *Stroke* 2006;37:1045-9.
 13. Wolf SL, Winstein CJ, Miller JP, Taub E, Uswatte G, Morris D, et al; EXCITE Investigators. Effect of constraint-induced movement therapy on upper extremity function 3 to 9 months after stroke: the EXCITE randomized clinical trial. *JAMA* 2006;296:2095-104.
 14. Feeney DM, Gonzalez A, Law WA. Amphetamine, haloperidol, and experience interact to affect rate of recovery after motor cortex injury. *Science* 1982;217:855-7.
 15. Hovda DA, Fennel DM. Amphetamine with experience promotes recovery of locomotor function after unilateral frontal cortex injury in the cat. *Brain Res* 1984;298:358-61.
 16. Stroemer RP, Kent TAA, Hulsebosch CE. Enhanced neocortical neural sprouting, synaptogenesis, and behavioral recovery with D-amphetamine therapy after neocortical infarction in rats. *Stroke* 1998;29:2381-95.
 17. Goldstein LB, Davis JN. Post-lesion practice and amphetamine-facilitated recovery of beam-walking in the rats. *Restor Neurol Neurosci* 1990;2:311-4.
 18. Butesfisch CM, Davis BC, Sawaki L, Waldvogel D, Classen J, Kopylev L, et al. Modulation of use-dependent plasticity by d-amphetamine. *Ann Neurol* 2002;51:59-68.
 19. Crisotomo EA, Duncan PW, Propst M, Dawson DV, Davis JN. Evidence that amphetamine with physical therapy promotes recovery of motor function in stroke patients. *Ann Neurol* 1988;23:94-7.
 20. Walker-Batson D, Smith P, Curtis S, Unwin H, Greenlee R. Amphetamine paired with physical therapy accelerates motor recovery after stroke. Further evidence. *Stroke* 1995;26:2254-9.
 21. Martinsson L, Wahlgren NG. Safety of dexamphetamine in acute ischemic stroke: a randomized, double-blind, controlled dose-escalation trial. *Stroke* 2003;34:475-81.
 22. Sonde L, Nordstrom M, Nilsson CG, Lökk J, Viitanen M. A double-blind placebo-controlled study of the effects of amphetamine and physiotherapy after stroke. *Cerebrovasc Dis* 2001;12:253-7.
 23. Treig T, Werner C, Sachse M, Hesse S. No benefit from D-amphetamine when added to physiotherapy after stroke: a randomized, placebo-controlled study. *Clin Rehabil* 2003;17:590-9.
 24. Martinsson L, Eksborg S, Wahlgren NG. Intensive early physiotherapy combined with dexamphetamine treatment in severe stroke: a randomized, controlled pilot study. *Cerebrovasc Dis* 2003;16:338-45.
 25. Gladstone DJ, Danells CJ, Armesto A, McIlroy WE, Staines WR, Graham SJ, et al; Subacute Therapy with Amphetamine and Rehabilitation for Stroke Study Investigators. Physiotherapy coupled with dextroamphetamine for rehabilitation after hemiparetic stroke. *Stroke* 2006;37:179-85.
 26. Floel A, Hummel F, Breitenstein C, Knecht S, Cohen LG. Dopaminergic effects on encoding of a motor memory in chronic stroke. *Neurology* 2005;65:472-4.
 27. Scheidtman K, Fries W, Muller F, Koenig E. The effect of levodopa in combination with physiotherapy on functional motor recovery after stroke: a prospective, randomised, double-blind study. *Lancet* 2001;358:787-90.
 28. Murase N, Duque J, Massocchio R, Cohen LG. Influence of interhemispheric interactions on motor function in chronic stroke. *Ann Neurol* 2004;55:400-9.
 29. Mansur CG, Fregni F, Boggio PS, Riberto M, Gallucci-Neto J, Santos CM, et al. A sham stimulation-controlled trial of rTMS of the unaffected hemisphere in stroke patients. *Neurology* 2005;64:1802-4.
 30. Takeuchi N, Chuma T, Matsuo Y, Watanabe I, Ikoma K. Repetitive transcranial magnetic stimulation of contralesional primary motor cortex improves hand function after stroke. *Stroke* 2005;36:2681-6.
 31. Fregni F, Boggio PS, Mansur CG, Wagner T, Ferreira MJ, Lima MC, et al. Transcranial direct current stimulation of the unaffected hemisphere in stroke patients. *Neuroreport* 2005;16:1551-5.
 32. Krebs HI, Hogan N, Aisen ML, Volpe BT. Robot-aided neuro-rehabilitation. *IEEE Trans Neural Syst Rehabil Eng* 1998;6:75-87.
 33. Krebs HI, Aisen ML, Volpe BT, Hogan N. Quantisation of continuous arm movements in humans with brain injury. *Proc Natl Acad Sci USA* 1999;96:4645-9.
 34. Aisen ML, Krebs HI, Hogan N, McDowell F, Volpe BT. The effect of robot-assisted therapy and rehabilitative training on motor recovery following stroke. *Arch Neurol* 1997;54:443-6.
 35. Volpe BT, Krebs HI, Hogan N, Edelstein OL, Diels C, Aisen M. A novel approach to stroke rehabilitation: robot-aided sensorimotor stimulation. *Neurology* 2000;54:1938-44.
 36. Ferraro M, Palazzolo JJ, Krol J, Krebs HI, Hogan N, Volpe BT. Robot-aided sensorimotor arm training improves outcome in patients with chronic stroke. *Neurology* 2003;61:1604-7.
 37. Fasoli SE, Krebs HI, Stein J, Frontera WR, Hogan N. Effects of robotic therapy on motor impairment and recovery in chronic stroke. *Arch Phys Med Rehabil* 2003;84:477-82.
 38. Werner C, Von Frankenberg S, Treig T, Konrad M, Hesse S. Treadmill training with partial body weight support on an electromechanical gait trainer for restoration of gait in subacute stroke patients: a randomized, crossover study. *Stroke* 2002;33:2895-901.
 39. Tong RK, Ng MF, Li LS. Effectiveness of gait training using an electromechanical gait trainer, with and without functional electric stimulation, in subacute stroke: a randomized, controlled study. *Arch Phys Med Rehabil* 2006;87:1298-304.
 40. Hesse S, Schmidt H, Werner C. Machines to support motor rehabilitation after stroke: 10 years of experience in Berlin. *J Rehabil Res Dev* 2006;43:671-8.