A Review of Brain Neuroplasticity and Implications for the Physiotherapeutic Management of Stroke

Key Words
Stroke Recovery, Neuroplasticity, Rehabilitation

The brain continually organizes itself from birth, during learning and development and during skill acquisition in adulthood. The brain can recruit adjacent undamaged areas, supplementary and association areas and ipsilateral pathways to varying degrees in response to brain injury. This occurs throughout life but is more evident when injury occurs at an earlier age and is highly variable among patients. Enriched or impoverished environments, sensory inputs and motor skill practice can influence brain plasticity. There appears to be evidence for rehabilitative strategies to be employed for patients with varying degrees of hemiparesis and at different stages of recovery. Recent findings indicate that the stroke patient benefits from physiotherapy however more research is required to identify the ability of specific therapies to influence neuroplasticity and the critical time lines.

Le cerveau s’organise continuellement depuis la naissance, pendant l’apprentissage et le développement et pendant l’acquisition de compétences à l’âge adulte. Le cerveau peut recruter des zones adjacentes n’ayant pas subi des lésions, des régions supplémentaires et d’associations et des voies homolatérales à des degrés divers en réponse à un traumatisme crânien. Ce processus survient durant la vie, mais il est plus évident lors d’un traumatisme à un plus jeune âge et varie considérablement parmi les patients. Les environnements stimulants ou non stimulants, les données sensorielles et la pratique d’habilités motrices peuvent influer sur la plasticité du cerveau. Il existe des données sur des stratégies de réadaptation à utiliser chez les patients souffrant de divers degrés d’hémiparésie et à différents stades de récupération. Des observations récentes indiquent que chez le patient ayant subi un accident cérébro-vasculaire, la physiothérapie a des effets bénéfiques, mais des recherches plus approfondies sont nécessaires pour identifier la capacité des thérapies spécifiques à influer sur la neuroplasticité et sur la période critique.

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Health Canada reports that there were over 49,000 hospitalizations due to stroke in 1997.1 Hemiparesis contralateral to the side of the lesion, is the most common deficit after stroke acutely affecting 80% of patients and greater than 40% chronically.2 Recovery of the hemiplegic upper extremity is one of the main challenges in the rehabilitation management of stroke. For many years clinicians have held the view that brain tissue had little or no potential for recovery.3 However despite this belief, in the rehabilitation setting, stroke patients showed continued functional improvement beyond the “window of recovery” often considered to be six months post-injury. Over the past ten years, advances in experimental techniques and brain mapping technology have shown that the adult brain continues to be modified with experience and after injury.4,5 This can be examined at a molecular or cellular level and on a larger systems level. This paper will review current brain plasticity research in humans and animals, examine the influence of rehabilitative techniques, particularly in the upper extremity, and discuss the implications in the physiotherapeutic management of stroke. This is a scientific review rather than a systematic one, so although the literature search is comprehensive, one cannot be assured that every research paper has been cited.

What is Neuroplasticity?
Neuroplasticity is a broad term describing alterations in neural function that are long lasting. It is used to describe change in the neural system at many levels, molecular, morphological, synaptic, cortical and functional. A fundamental notion in neuroscience is that a change in the synaptic efficiency between two neurons is a substrate for learning and memory and that the increase in strength and number of synapses and the activation of latent synapses underlies cortical neuroplasticity. A classic example of neuroplasticity is long term potentiation (LTP). This phenomenon refers to a prolonged change in synaptic strength that has been proposed to be the basis for enduring memory and learned behaviors in animals.6 This change in neuronal function in response to input is probably the basis of cellular neuroplasticity.7 LTP is described as following “Hebbian rules” hypothesized by psychologist D. O. Hebb in 1949.8 The theory is that presynaptic cells that provide input to the postsynaptic cell will have their synaptic connection strengthened. Those connections that are not active will gradually have their influence weakened.

**Part I: Neuroplasticity in the Intact Adult Brain**
**Environmental Enrichment**
There have been numerous studies examining the effects of sensory impoverishment and sensory and social stimulation on the rodent brain. Mice housed in enriched environments with climbing and manipulative toys9 or with free access to a running wheel10 typically have increased number of neurons in the hippocampus. Voluntary running has also been shown to increase the levels of brain-derived neurotrophic factor in the rat brain.11 Black12 examined the cerebellar neurons of rats placed in four housing conditions for 30 days: 1) obstacle course (AC); 2) forced treadmill exercise (FX); 3) voluntary wheel running (VX); and 4) individual cages (IC). The groups with the highest activity, FX and VX, had increased capillary density in the cerebellum while the AC rats had dramatic increases in the synapses per neuron of the cerebellar Purkinje cells. Similar findings were reported by Kleim et al.13 in the rat motor cortex with acrobatic training and there is reported increased number of bifurcating and multi-headed spines in neurons of the caudate nucleus of rats housed in enriched environments.14 Others have shown that environmentally influenced neuronal modification also occurs in the brains of aged mice although to a lesser degree than adults.15,16 Overall, these studies indicate there is evidence in animals that various parts of the brain including hippocampus, cerebellum, cortex and striatum are changed in response to environmental stimulation and exercise.

**Motor Learning**
It is now generally accepted that the mammalian brain is capable of change throughout the lifetime in response to the environment and subsequent sensory experience. Investigators have used a number of brain mapping techniques to examine brain topography modification.

Positive Emission Tomography (PET) scanning is used to measure regional cerebral blood flow (rCBF). Specific tracers are either injected or inhaled by subjects and while they move a particular body part their brain is scanned. Increased tracer uptake reflects areas with enhanced rCBF as a result of increased metabolic activity from the movement related neural activity.17,18 Focal transcranial magnetic stimulation (TMS) typically involves using a figure-of-eight coil placed over the skull to apply a stimulus to the cortex. The motor response to this stimulus is then recorded peripherally using EMG electrodes placed on the target muscles. In this way researchers can not only map brain regions but also record amplitude and latency of the motor evoked potential (MEP). Higher MEP amplitude and short latency are indicative of efficient cortical transmission.19 Functional magnetic resonance imaging (fMRI) measures small changes in blood flow that accompany brain activation during performance of a task. Brain structure and blood flow can be measured simultaneously using fMRI.20

Specific sensory enrichment causes plastic change in the
corresponding cortical map. A number of fascinating studies investigated cortical map enlargement of preferentially used digits, specifically the index finger of Braille readers and the digits of the playing hand of string players.\textsuperscript{27,28} It appears that the cortical territory serving the preferentially used digits in these individuals expands and the enhancement is temporally dependent, since it occurs to a greater degree when the practice is initiated at an early age and for longer periods. An interesting phenomenon in the proficient Braille readers is that the representation for the reading finger appeared to be enlarged at the expense of the remaining fingers. As well, the same researchers\textsuperscript{24} examined cortical maps of Braille proof readers and showed that the map enlargement was larger on work days indicating the brain was capable of making a rapid change in response to input (or need).

Motor task learning can be described as specific sensory and environmental enrichment since motor tasks are accomplished using repetitive sensory feedback to learn and refine the skill. Pascual-Leone\textsuperscript{25} and Karni\textsuperscript{26} trained adult human volunteers on finger and/or thumb repetitive movements. The training groups had progressively larger cortical outputs to the involved muscles along with improved task performance. Pascual-Leone’s group\textsuperscript{25} had a subsequent decrease in map size back to baseline after the motor sequence was learned in map size back to baseline after group\textsuperscript{25} had a subsequent decrease in performance. Pascual-Leone’s muscles along with improved task performance. The training volunteers on finger and/or thumb repetitive movements. The training groups had progressively larger map size back to baseline after the motor sequence was learned in map size back to baseline after group\textsuperscript{25} had a subsequent decrease in performance. Pascual-Leone’s muscles along with improved task performance. The training volunteers on finger and/or thumb repetitive movements. The training groups had progressively larger map size back to baseline after the motor sequence was learned in map size back to baseline after group\textsuperscript{25} had a subsequent decrease in performance. Pascual-Leone’s muscles along with improved task performance. The training volunteers on finger and/or thumb repetitive movements. The training groups had progressively larger

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Sensory/environmental impoverishment also appears to induce cortical change.\textsuperscript{10,13} Amputees, in particular, have been studied to determine the extent of cortical change as a result of removal of input to the cortex from the amputated body part. Cohen\textsuperscript{34} and Flor\textsuperscript{35} used magnetic source imagery (magnetic responses to stimuli of the digit cortical representations of the amputated hand) to show change in cortex topography. They demonstrated a mean shift in cortical responsivity to facial stimulation indicating that the somatotopic representation of the missing limb was “taken over” by that of the face. Another study by Florence used neural tracers to map the hand representation of four monkeys with chronic upper extremity injury. The findings were similar to Flor,\textsuperscript{35} with the face and remaining upper limb maps expanding into the cortex representing the damaged limb.

Two studies examined the speed and topography of cortical plasticity during short term deafferentation using a blood pressure cuff on the arm and leg of normal human subjects.\textsuperscript{37,38} Within minutes MEPs from more proximal unaffected muscles increased then returned to baseline once the cuff was removed. The cortical representation area for the muscle proximal to the tourniquet was enlarged. Is the cortical map change due to peripheral nerve impairment or decreased use of the particular muscles or both? Liepert\textsuperscript{39} examined individuals with ankle immobilization following ankle injury without peripheral nerve damage. The immobilization caused a decrease in the cortical map representation for the tibialis anterior muscle which quickly returned to baseline with muscle contraction.

These studies may indicate that cortical maps are changing on a daily and even minute-to-minute basis depending on increase or decrease in sensory input and motor activity. It suggests that when a body part is injured, immobilized or missing, there is a neuronal change along with the more readily acknowledged musculoskeletal impairments. Garraghty and Muja\textsuperscript{40} have proposed that deafferentation in primates probably occurs in two phases; in the first phase some deprived neurons immediately express new receptive fields while in the second phase the remaining majority regain responsiveness over weeks or months. These changes in cortical representation are proposed to be mediated at the synaptic level via unmasking of latent synapses or an increased responsivity of synapses in the short term and modified synaptic morphology in the long term. In summary, these research findings suggest that:

- Acquisition of motor skill is mediated by change in cortical map topography.
- An inability to move or perform a task due to physical injury causes brain topography modification. Therefore, patients with musculoskeletal injury likely have neuroplastic change as well.
- Specific skill training and practice may be integral to reacquire the skill and the corresponding cortical map representation. True intrinsic (automatic or unconscious) motor skill learning seems to occur when the activity becomes subcortical.

Part II: Neuroplasticity in the Damaged Adult Brain

If neuroplasticity occurs in the normal brain, does the damaged brain undergo similar processes and is neuroplasticity related to functional outcome? There are a number of morphological changes...
that have been demonstrated in cortically lesioned rats. For example, in the intact hemisphere there is evidence for increased cortical thickness, dendritic branching and number of synapes per neuron. These changes result from the combined effects of the lesion itself and the ensuing forelimb asymmetry.41,42

Role of Motor Association Areas
Weiller and colleagues in two separate studies43,44 used PET to study organizational changes after recovery from subcortical (internal capsule and striatum) stroke in ten and eight subjects respectively compared to controls. Regions such as the basal ganglia, thalamus, sensorimotor cortex contralateral to the recovered hand, and the ipsilateral cerebellum, had decreased rCBF indicating the dysfunction related to the ischemic lesion. Regions that had increased rCBF compared to controls were the prefrontal cortex, insula, cingulate and inferior parietal cortex of the damaged hemisphere and the premotor cortex, basal ganglia and cerebellum of the undamaged hemisphere. The patterns of activation were variable among subjects and among infarct sites but a common theme was the finding of increased activity in areas remote from the lesion and their involvement in movement of the recovered hand. Other studies have confirmed these findings45-48. Notably the structures involved during movement of the recovered hand in these studies are primarily, cortical supplementary and association areas, striatum (bilaterally) and the cerebellum contralateral to the recovered hand.

It has been suggested that different motor areas operate in parallel. Fries et al.45 identified in monkeys, descending pathways from multiple topographically organized cortical maps that pass through the internal capsule in an orderly manner. Descending fibres from the supplementary motor area (SMA) and limbic motor fields pass through the anterior limb of the internal capsule, the premotor cortex fibres through the ventral posterior limb and primary motor fibres through the middle third of the posterior limb. The authors suggest that these parallel cortical maps are able to substitute for each other functionally. Non-primary motor areas may play an increased role in generating voluntary movement during recovery from brain injury.46 This has been further supported by Seitz et al.47 using TMS, MRI and PET in seven patients with middle cerebral artery (MCA) infarct. These researchers found that motor recovery appeared to rely on activation of premotor cortical areas of both cerebral hemispheres. Dettmers and colleagues48 report similar findings and suggest that the increased recruitment of executive cortical areas in tasks that require little demand in normal subjects may be the reason many stroke patients experience an increased sense of effort and ensuing fatigue with motor task practice. When infarcts damage either large portions of the cortex or capsule, the brain may rely on the less functional, ipsilateral pathways. The authors correlated these findings with quantitative motor recovery in 23 patients with various infarcts of the internal capsule and striatum.49 Ischemic lesions in the internal capsule, therefore, can have a relatively large effect on multiple motor maps. This may explain the fact that patients with subcortical (internal capsule, basal ganglia and thalamus) are reported to have less favourable outcome than those with cortical stroke.50

Role of Ipsilateral Connections
Interestingly, stroke has also been associated with both neurophysiological and functional impairments in the so called “unaffected” hand51 which may lend some evidence for the role of ipsilateral pathways in limb control and recovery from stroke.

One of the most remarkable cases for studying the role of ipsilateral pathways in recovery from brain damage is the patient with hemispherectomy (or hemidecorticate).52 This procedure has been performed on patients with severe epilepsy or tumor and the post-operative motor function depends largely upon the age when the surgery is performed. The functional recovery after hemispherectomy is much better in the infantile versus adult onset group.53 The motor recovery seen in hemispherectomy patients is proposed to be mediated via ipsilateral corticospinal projections and the cortico-reticulospinal pathway.

Benecke54 used TMS to show the existence of both pathways in early and late brain damaged groups with hemispherectomy and severe hemispheric lesions but identified primarily the cortico-reticulospinal pathways in the late onset group. Both groups had more impairment (increased latency and decreased amplitude of MEPs) of the distal muscles suggesting that these ipsilateral pathways may predominantly activate proximal muscles. It is interesting that stroke patients frequently show a proximal to distal gradient with control of proximal musculature returning (i.e. sitting balance, bed mobility, and gait) before dexterous limb activity.

Role of Map Representation Changes in the Lesioned Hemisphere
Mapping techniques have identified areas of increased activation in the lesioned hemisphere in the motor association areas and surrounding cortex.21 There appears to be a correlation between enlargement of the motor map of the hand and the degree of clinical improvement.66,57

Using intracortical recording techniques, Jenkins and Merzenich58 have demonstrated that in various species of monkeys, restricted cortical lesions are followed by dramatic reorganization of cortical maps. Regions surrounding the damaged area gain
new receptive fields in which much of the skin surface formerly represented in the infarcted cortex becomes represented around the rim or penumbral zone of the infarct. This finding is supported by another study using PET to examine rCBF changes in patients with tumors occupying the hand area of the motor cortex. These patients retained their ability to use the hand and rCBF activity was identified solely around the edge of the tumor rather than at more remote sites. Rossini et al. used a relatively new mapping technique, magnetoencephalography, which measures the magnetic field distribution over the scalp during peripheral nerve stimulation. This showed the same enlargement and shift of hand distribution areas in the affected hemispheres as the PET, fMRI and TMS studies. Not all studies are in agreement however, a later study by Nudo and Milliken using intracortical mapping techniques in squirrel monkeys, showed that movements formerly represented in the infarcted zone did not appear in the cortical sector surrounding the infarct, at least in the absence of post-infarct training. They showed an apparent increase in proximal limb representations that may have accounted for the animals’ recovery. In summary, motor recovery can be mediated through a number of neural pathways.

- Cortical map reorganization involving tissue surrounding the infarct mediated by unmasking of latent synapses and/or growth of new intracortical connections.
- Association motor areas in the lesioned cortex
- Association motor areas in the opposite cortex that probably have redundant collosal connections
- Uncrossed pyramidal and reticulospinal pathways in the opposite cortex.

### Part III: Effect of Training on Plasticity in the Damaged Brain

#### Enhancement of Recovery in Animals

As previously discussed, environmental and sensory enrichment can induce plastic changes in the normal adult brain. Can manipulation of the environment through treatment influence plastic changes in the damaged brain? The answer is yes, there is ample evidence in animal and human studies supporting an active role of rehabilitation in remodeling cortical maps.

Xerri and colleagues performed intracortical mapping procedures in adult owl and squirrel monkeys, trained to master small object retrieval, before and after primary somatosensory cortex lesions. Their goal was to gain insight into the specific neuro-physiological processes that mediated behavioral recovery. Lesioned monkeys had the expected impairments in dexterity of the affected upper limb however they were able to accomplish the task post lesion as they were previously trained to do. Monkeys then initiated compensatory use of the opposite upper limb for the task but this resulted in a performance drop. The monkeys then re instituted the affected limb and exhibited gradual recovery of function over several weeks. This recovery was paralleled by striking enlargement of the motor and sensory representation of the fingers in the damaged hemisphere. There was no significant change in the intact hemisphere. Nudo and Milliken used similar methods to show that map remodeling around the infarct did not occur. However, the studies are different in that Xerri’s animals with behavioral training showed increased hand map representation while Nudo’s untrained monkeys did not. In another study by Nudo and colleagues in fact, they demonstrated that retraining of skilled hand use after infarct resulted in prevention of loss of hand territory adjacent to the lesion suggesting that rehabilitative training can indeed shape the reorganization of cortical tissue. Others have had similar findings in skilled motor activity training in animals, visuospatial training in hemineglect and aphasia training in humans.

Friel and Nudo also discuss the issue of compensation versus recovery. They examined monkeys attempting to retrieve food pellets following minute ischemic cortical lesions of the primary motor cortex. Frame by frame video analysis revealed that some monkeys, although achieving pre-lesion performance levels, used slightly different movement strategies. These monkeys had slightly larger lesions and more distal limb involvement than the monkeys that made a full recovery. These authors as well as others propose that compensatory strategies in the affected limb may be a natural course of functional return but should not be equated to ‘true’ recovery.

Johansson and Ohlson have examined environment, social interaction and physical activity as determinants of functional outcome after cerebral infarction in rats. In their first study lesioned rats were placed in three groups; Group A were in single cages, Group B were in enriched cages (elevated boards, chain, swing, blocks, etc.) and Group C were in enriched cages both before and after the lesion. Overall, animals with pre- and post-lesion enrichment improved sooner and to a slightly higher degree than the other rats. The rats housed in individual cages had the poorest scores on measures of functional outcome. The authors suggested that perhaps the pre-lesion environment had a neuroprotective effect. Further, the same researchers’ second study attempted to differentiate between the benefits of the social group housing and the enriched environment. Group A rats were
housed in groups in enriched environments, Group B rats were housed together in the same size cage with no toys and Group C rats were housed in individual cages with free access to a running wheel. In terms of recovery measured on behavioral testing (climbing, balance beam, etc.), social interaction was superior to wheel running but an enriched environment combined with social interaction resulted in the best performance. It may be that the combination of social interaction in group activities and the more intensive approach toward therapeutic activities found in typical specialized stroke units mimic these enrichment studies. Indeed it appears that functional outcome and long term survival is significantly better in stroke units compared with general wards.

An important recent study combined environmental enrichment and skilled reaching activity for two months beginning 15 days after ischemic injury in rats with the objective of enhancing dexterous limb activity. Despite a large ischemic injury to both cortex and striatum, animals in the treatment group had significantly greater dendritic branching of pyramidal neurons in the intact cortex (See Figure 1) and better functional outcome than the control animals. Interestingly, little spontaneous recovery was observed in animals unless they were exposed to the enrichment plus skilled reaching therapy.

All of these studies suggest that following brain injury, social interaction and complex exercise have an effect on the mechanisms underlying neural plasticity. Current evidence suggests that in animal models of brain injury and neurodegeneration, exercise induces the brain uptake of insulin-like growth factor-I (IGF-I), a neurotrophic hormone that has been shown to be neuroprotective. Exercised animals perform better on behavioral tests and demonstrate neuronal preservation in a number of brain regions compared to sedentary animals. Ivanco and Greenough state, “If experience can influence plasticity (anatomical and physiological) in the injured brain, we are on strong empirical grounds to suggest behavioral therapies following brain injury.”

The question is, what specific tasks promote plasticity and at what point in the recovery process should these be undertaken? An interesting phenomenon occurred in Johansson and Ohlsson’s study. After the lesion, the rats displayed locomotor hyperactivity when given unlimited access to a running wheel and only three of the nine rats survived the 13 week testing period. It was thought that the intensive exercise although voluntary was too stressful for the animals. Recent studies have found that for about 7 days after brain lesions in rats, extreme behavioral demand placed on the affected limb (i.e. forced use) caused an exaggeration of neuronal injury and further tissue loss. It was found that the excitatory neurotransmitter glutamate was probably involved since increased levels of this neurotransmitter may cause cell death in the early post-lesion period. Accordingly, glutamate receptor blockers spared the neural tissue during forced use and enhanced functional recovery. The authors suggest that although behavioral experience and therapy can enhance neuronal growth after brain injury, the region surrounding the injury may be particularly vulnerable to behavioral pressure (or stress) in the early post-lesion period.

Jones and Schallert also reported that directly following the lesion to the rat sensorimotor cortex there was an increase in dendritic arborization of the pyramidal neurons of the opposite cortex. This reached a maximum about 18 days post-lesion which closely paralleled a measured overuse of the unimpaired limb. Once the animals began to use their affected limb again, there were pruning of the dendrites and functional recovery. The researchers restricted either the ipsilateral unaffected limb or

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**Figure 1 – Representative reconstructions of layer V pyramidal cells respective of treatment condition (IE, IS and SE).** Note the increased basilar dendritic arbor in the IS group compared with the SE group and even greater complexity in the IE condition. Scale bar, 100mm. (Biernaskie J, Corbett D. Enriched rehabilitative training promotes improved forelimb motor function and enhanced dendritic growth after focal ischemic injury. J Neurosci 2001:21:p.5276. Reprinted with permission from Journal of Neuroscience)
the contralateral affected forelimb to examine the effects on dendritic arborization. Restriction of the contralateral limb in the first 15 days post lesion had no effect but restriction of the ipsilateral side reduced neuronal arborization and was associated with poorer performance on tests of bilateral sensorimotor function afterwards. The authors suggest that complete restriction of the intact limb acutely post stroke may worsen overall function. There may be a specific time period when the development of compensatory strategies involving the use of the nonimpaired limb is optimal.

Bury and colleagues further investigated the effect of constraint of the unaffected forelimb on plasticity after lesions to the corpus callosum in rats. Lesioned or sham operated rats were either forced to use the affected forelimb (via a plaster of paris one-holed vest) or permitted to use both forelimbs normally for eight days directly post surgery. Histological examination of the affected sensorimotor cortex showed increased density of proteins associated with the astrocytic changes and plasticity in the lesioned-only animals and the forced-use only animals but was greatest in the lesioned + forced-use animals. Basic fibroblast growth factor (bFGF), a neurotrophic growth factor, was also increased by lesion and forced use alone but was not further enhanced by the combinations of the conditions. These findings suggest that astrocytic reactions post cortical lesion can be shaped by behavioral demand which may ultimately lead to enhancement of neural growth following injury. This is in contrast to the previous study by Jones and Schallert suggesting early tissue loss in response to excessive behavioral demand. Perhaps this represents a balance of intensity of the rehabilitation program or that larger lesions are more vulnerable to excitotoxicity.

In summary, environment and skill practice have an effect on neuroplasticity post-stroke. Animals exposed to enrichment, socialization and skilled activity have better functional outcome, increased complexity of neuronal branching and enhanced cortical activation. In the early days of recovery, intense use of the affected limb especially in large lesions may be contraindicated. Therefore bilateral and reciprocal activities early post stroke may be recommended then progressing to more focused intense treatment of the impaired limb itself.

The Constraint-Induced Therapy Paradigm

Taub investigated the effect of restraint of the intact upper extremity and recovery of function of primates in the late 60s and 70s. He proposed that animals with chronic deficit had “learned non-use” of the affected limb since attempts to use the hand post injury were unsuccessful and reinforced or conditioned. Taub and others have now used the “forced use” paradigm in human stroke patients. In these studies patients were typically one to 20 years post left-sided infarct, right-handed with partial recovery of wrist and finger extensors and no cognitive or perceptual deficits. Patients wore either a sling, a splint or both to restrict movement of the intact upper extremity for 90% of their waking hours. They engaged in six hours of motor relearning or “shaping” therapy, five days per week, as well as using the affected extremity during ADL at home. All studies showed marked improvement on subjective and objective testing of recovery and function. The researchers suggested that this recovery was new and not associated with spontaneous recovery since so much time had elapsed post-stroke and the patients’ recovery had “plateaued” pre-treatment. Further to this, with the advent of TMS mapping procedures, Taub and others have examined the cortical change resulting from this treatment. Consistently, subjects had recruitment of motor areas adjacent to the lesion as indicated by increased motor output area and increased MEP amplitudes. Another study used EEG and showed an anterior shift of the hand cortical map into the supplementary motor area of the affected cortex with forced-use therapy. At three-month follow-up the affected hand movement source actually shifted to the opposite or ipsilateral hemisphere. The authors suggest that this may have reflected the recruitment of ipsilateral pathways. In a forced-use study that had follow-up, patients maintained their acquired skill up to two years post-intervention.

It is unknown which aspect of the treatment contributed most to recovery, the six hours per day spent in direct therapeutic activities or the remaining six to eight hours of restraint. The former could have accounted for the significant improvement since other studies have documented the benefit of massed practice in physiotherapy or perhaps the latter, since a preliminary TMS study has demonstrated increased motor cortex excitability with forced-use plus conventional therapy without the 6 hours per day of “shaping.” In a review article by Taub et al., it was suggested that when “conventional” physiotherapy is administered six hours per day for ten consecutive days there is a similar increase in arm use seen in CI therapy. The conclusion was that some chronic and subacute patients, who are able to tolerate it, could greatly benefit from physiotherapy if they received multiple hours of motor skill practice per day.

Since the CI therapy technique is useful in chronic stroke patients, it may be even more effective in patients involved in active rehabilitation programs. In fact two recent studies have shown that cortical activation is significantly greater when forced-use therapy is
combined with skilled arm training two weeks post-infarct in humans and primates. In a recent randomized clinical trial, patients began two weeks of constraint-induced movement therapy within 14 days of their stroke versus traditional therapy. The CI group had less impairment on some outcome measures without any adverse reactions to the treatment.97

For rehabilitation professionals, forced-use offers more treatment options for patients without cognitive or perceptual problems and some motor recovery in the hand. More research needs to be undertaken in acute and rehabilitation settings since the stress of such a treatment may affect these patients as previously documented in animals.77,98 It is also possible that the compensatory strategies learned in rehabilitation contribute to the learned non-use of the affected limb.99,100

**Motor Relearning**

Cramer and Chopp101 suggest that in the past ten years research supports the hypothesis that recovery from stroke resembles stages in childhood development. They state that motor recovery follows the proximal (bilateral) to distal gradient from gross motor function to fine motor function and this is paralleled by cortical map plasticity and molecular events that resemble those in the developing brain. They suggest that different recovery stages probably call for different clinical approaches, an emphasis on bilateral activity initially and unilateral skilled activity in later rehabilitation or in mild hemiparesis. The developmental approach to management of stroke was developed by the Bobaths in the 1960s and the motor relearning (skilled activity acquisition) approach by Carr and Shepherd in the 1970s. Perhaps the approaches are not mutually exclusive but can be combined. Initially, moderate to severe patients would benefit from the symmetrical postural activities, especially of the trunk (Bobath) and later skilled task learning (Carr and Shepherd).104 In fact, a preliminary study indicates that bilateral movement activates the damaged hemisphere in acute stroke significantly more than unilateral limb activity.105

Interestingly, Nelles and colleagues106,107 have examined changes in rCBF post stroke. This in itself is not new, but whereas previous researchers studied recovered stroke patients, these investigators followed individuals for the first 12 weeks after their first cortical or subcortical stroke. Rather than patients performing a finger tapping task, the patients underwent passive elbow flexion and extension of the affected arm using a continuous passive motion (CPM) device. Remarkably these patients had activation of association cortices bilaterally as did the stroke patients moving their recovered hand actively in other studies. This is direct evidence of the benefit of passive range of movement acutely post stroke, a common treatment instituted to prevent musculoskeletal complications of immobility. An intriguing recent randomized control study by the same researchers108 using PET scanning investigated the effect of task-oriented arm training using motor learning techniques compared to passive ROM in nine severe hemiplegics about 22 days post subcortical stroke. Treatment was individually applied by physiotherapists and occupational therapists 45 minutes, four days per week for three weeks. Although the functional outcomes between the groups after the three weeks were not significant, the arm training group showed significantly more activation of the contralateral parietal cortex and primary motor area and bilateral premotor areas. This study, although small, presents compelling evidence that physiotherapy techniques influence cortical reorganization.

It appears that although passive and bilateral movement of the involved limb activates the damaged cortex (and association areas), when the patient is able to move the limb actively, active movement itself is the most effective method to stimulate neuroplasticity. This is confirmed in a study in which TCS mapping techniques were used to examine the effect of various physiotherapeutic techniques on MEPs of wrist and hand muscles in stroke patients.109 The researchers compared five treatment approaches to baseline and control subjects: 1) cutaneous stimulation of wrist extensors by tapping; 2) upper extremity weight bearing; 3) proximal activation of the shoulder; 4) maximum isometric contraction of contra-lateral wrist extensors; and 5) attempt to activate affected wrist and finger extensors. Patients were placed in three groups by severity of hemiplegia. Group 1 had severe impairment, Group 2 was moderate and Group 3 had mild hemiplegia. All approaches improved the frequency of occurrence of the MEPs. Attempting to isolate the affected wrist extensor in Approach 5 was overall the most effective at consistently generating MEPs in all groups. Approach 1, cutaneous tapping, was effective at raising the amplitude of the response potential in the most severe patients but had little effect in the other groups. Tapping was actually inhibitory in the healthy controls. Latencies of MEPs were diminished during the physiotherapeutic techniques and this benefit was most pronounced in the more hemiplegic groups. The exception was the cutaneous tapping techniques that lengthened latencies in Group 3 patients and healthy controls. In summary, direct activation of the target muscle induced the most facilitory effect. In a follow-up study110 these researchers assessed the effect of voluntary finger flexing and extension against various loads 15 minutes twice per day compared to the Bobath method of upper extremity weight bearing on motor outcome of the hemiplegic hand.
All 27 patients were three to 19 weeks post stroke, had some isolated movement in the fingers and they were placed randomly in the two groups. The patients undergoing the weight bearing approach alone did not experience a significant improvement on measures of strength and contraction velocities of the hand, whereas the hand exercise group did. The problem with this study is that patients at this relatively high level of function would not receive weight bearing alone as a focused treatment strategy. Many physiotherapists use weight bearing early in the rehabilitation program before skilled activity can be performed to facilitate more proximal muscle groups. Therapists often employ an eclectic individually tailored treatment program rather than a specific philosophical 'school' approach. (Bobath, Brunnstrom, PNF, Carr and Shepherd) The important point here is that patients had good outcomes with graduated strength training with only minimal therapy time (about 30 minutes per day). Another study reports increased motor output area to the abductor pollicis muscle following one 90-minute intense physiotherapy treatment for the impaired upper extremity.114 It should be noted again however that patients with sensory deficits, neuropsychological deficits and complete paralysis of the hand were excluded from these studies. Further, a randomized controlled study of 132 stroke patients also demonstrated that an enhanced therapy program consisting of self directed exercise, forced-use and biofeedback improved strength and speed of movement over a weight-bearing only treatment regime and the effects were sustained at a 12 month follow-up.115 Treadmill training in stroke patients is gaining increased interest in physiotherapy. Preliminary studies show that early intense treadmill training in stroke patients improves gait velocity and measures of gait parameters.114 In fact, there is evidence that treadmill training with partial body weight support during the acute rehabilitation phase of stroke may be more effective with regards to restoration of gait ability and parameters than conventional gait training.115-118 The method can be compared to both 'forced-use' and motor learning therapy since the patient is cued constantly by the moving belt during daily intense treatment sessions. It would be interesting to examine neuroplastic response to such a treatment.

In summary, there is a mounting body of evidence that indicates physiotherapeutic techniques ranging from PROM to intense motor skill training are able to directly impact cortical reorganization following stroke and that this modification is paralleled by functional recovery.

Functional Electrical Stimulation, Biofeedback, and Strength Training in Stroke

There is evidence that stroke patients despite having spasticity, can benefit from progressive resisted exercise. They experience a measurable improvement in strength without increases in spasticity.119,120 No study has shown that increased strength correlates with any neuroplastic change but one study120 showed that 60 to 90 minute physical training, three times per week, improved measures of overall gait speed 28% and stair climbing 37.4% in chronic stroke patients. The authors suggest that training specificity is required to improve functional tasks and their program incorporated actual task practice along with specific muscle strengthening. They state that since functional tasks require components of strength, balance and coordination, strength training alone is unlikely to improve functional ability. Patients in these studies had established isolated movement of the affected muscle groups before they began their training. Studies examining the benefit of functional electrical stimulation (FES) in stroke have been equivocal. A meta-analysis of four studies revealed that FES improves strength but there is no evidence that the treatment improved function.121 Another meta-analysis also supports that FES promotes the recovery of muscle strength after stroke and suggests that sustained improvement and functional change are promising as well.122 More recent examination of FES suggests upper extremity motor recovery after stroke is facilitated by FES especially during the rehabilitation stage,122-124 when worn for long periods (up to six hours, six days per week),122,124,125 and when the stimulated movement is augmented by volitional activation of the target muscles.124,125 Two studies using biofeedback in combination with FES demonstrated positive effects on measures of upper extremity motor recovery.126,127 Hummelsheim and colleagues have found that once the stroke patient has regained functional movement, FES is not as beneficial as active hand strengthening in improving measures of hand function. FES treatment does not appear to be as effective in chronic stroke deficit.126,127 Studies examining the use of FES with or without treadmill training to restore walking in stroke patients are preliminary but promising.126,130 Presently, studies examining biofeedback have not shown a significant benefit.131 Task specificity and incorporation of movements into function were not employed so these results are not surprising. Researchers have yet to examine neuroplastic change during FES or biofeedback treatment.

Part IV: Neuroscience Evidence-Based Practice

Physiotherapists have the skills and knowledge to influence and sculpt stroke recovery. (See Figure 2). They can employ rehabilitative intervention to influence the neuroplastic changes that lead to functional recovery. The efficacy of this intervention is determined by
the skill of the therapist, the patient’s motivation, his or her social support, and the pre- and post-stroke environments. Neuroscience evidence-based practice is constantly evolving based on sound neuroscience research in humans and animals and probably incorporates the following:

- The stroke patient within the first few days post-stroke may be vulnerable to a use-dependent increase in brain tissue loss.
- In the early days and weeks post-stroke, emphasis could be placed on bilateral and reciprocal activities. Passive range of motion (PROM) exercise of the affected limb likely has a direct effect on neuronal function even when the patient is unable to actively move the limbs. PROM and bilateral activity can be implemented to activate the cortex and other brain areas.
- Enrichment and exercise pre-stroke may have a neuroprotective effect. This is another sound reason for physiotherapists to encourage participation in an active lifestyle.
- Patients who have suffered a stroke should be in a stimulating, engaging environment with social support and physical activity to facilitate the recovery process.
- Patients in the early stages of recovery or with severe motor deficit may benefit from facilitory stimuli such as brushing, tapping and weight bearing and from FES.
- Patients who begin to have voluntary motor activity may benefit from therapy focused on repetitive active movement of the target muscles integrated into functional tasks. Patients should engage in these activities frequently throughout the day, everyday.
- If possible, patient and caregivers should be instructed in homework that specifically targets the problematic movement. It appears that task repetition is required for neuroplasticity to occur.
- Some patients, who have consistent isolated movement, may benefit from progressive strength training and constraint-induced therapy.

At this stage in our understanding of stroke recovery, there are certainly a number of unresolved questions that scientists and rehabilitation professionals may continue to contemplate.

- Does compensatory use of the unaffected limb, likely resulting in synaptic morphological change, occur at the expense of cortical plasticity in areas controlling the affected upper extremity?
- In the first days or weeks after stroke in humans, is there a vulnerable period? How much intervention and what specific intervention, if any, should be employed during this period?
- What specific rehabilitation practices should be undertaken to create an ‘enriched environment’ for stroke patients?
- How much therapy is required to obtain the optimal neuroplastic effect? The evidence varies from 15 minutes twice per day to 6 hours per day. Is targeted home exercise able to induce a similar cortical change?
• Do therapies such as strength training, FES, and biofeedback, (with adequate repetition and training specificity) induce neuroplastic changes?

• What therapies are the most effective for moderate to severe hemiplegia and for those stroke patients with cognitive and visuospatial impairment?

• At what point along the recovery continuum does the potential neuroplasticity end, if ever?

**Conclusion**

Research in animals has demonstrated that structural and functional neuroplasticity occurs in normal and damaged brains and is enhanced by enrichment and rehabilitative training. Using imaging technology, similar research is being undertaken in humans with encouraging results. The effectiveness of physiotherapy in management of stroke may be examined using standardized outcome measures as well as functional imaging techniques. It is important for physiotherapists to have a clear understanding of the science of neuroplasticity to provide rationale for specific physiotherapy practice in stroke.

**References**


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