REVIEW ARTICLE

Progress in Clinical Neurosciences: Stroke Recovery and Rehabilitation

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ABSTRACT: ***Background:*** Recent literature has provided new insights into the role of rehabilitation in neurological recovery post-stroke. The present review combines results of animal and clinical research to provide a summary of published information regarding the mechanisms of neural recovery and impact of rehabilitation. ***Methods:*** Plasticity of the uninjured and post-stroke brain is examined to provide a background for the examination of brain reorganization and recovery following stroke. ***Summary and Conclusions:*** Recent research has confirmed many of the basic underpinnings of rehabilitation and provided new insight into the role of rehabilitation in neurological recovery. Recovery post stroke is dependent upon cortical reorganization, and therefore, upon the presence of intact cortex, especially in areas adjacent to the infarct. Exposure to stimulating and complex environments and involvement in tasks or activities that are meaningful to the individual with stroke serves to increase cortical reorganization and enhance functional recovery. Additional factors associated with neurological recovery include size of stroke lesion, and the timing and intensity of therapy.

RÉSUMÉ: Récupération et réadaptation après un accident vasculaire cérébral. La littérature récente apporte un nouvel éclairage sur le rôle de la réadaptation dans la récupération neurologique après un accident vasculaire cérébral (AVC). Cette revue combine les résultats de la recherche animale et de la recherche clinique pour réaliser un sommaire de l'information publiée sur les mécanismes de la récupération nerveuse et l'impact de la réadaptation. ***Méthodes :*** Nous examinons la plasticité du cerveau non lésé après un accident vasculaire cérébral afin de mettre en contexte l'examen de la réorganisation cérébrale et de la récupération après un AVC. ***Sommaire et Conclusions :*** Des recherches récentes confirment plusieurs des principes de base de la réadaptation et fournissent un nouvel éclairage sur le rôle de la réadaptation dans la récupération neurologique. Après un AVC, la récupération dépend de la réorganisation corticale et donc de la présence d'un cortex intact, spécialement dans les zones adjacentes à l'infarctus. L'exposition à un environnement stimulant et complexe et la participation à des tâches ou à des activités qui sont significatives pour l'individu atteint d'un AVC servent à promouvoir la réorganisation corticale et à améliorer la récupération fonctionnelle. Plusieurs autres facteurs ont un impact sur la récupération neurologique, entre autres la taille de la lésion et le moment et l'intensité du traitement.

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Evidence derived from animal studies and new imaging techniques has served to increase our understanding of neurological recovery and the role of rehabilitation therapies in promoting such recovery. An increasing number of clinical trials has indicated the importance of rehabilitation in this recovery. The present article provides an overview of the current evidence supporting the concept of brain plasticity as well as cortical reorganization in response to rehabilitation therapies post stroke. We will also discuss intrinsic and extrinsic factors that influence recovery.

Plasticity of the Uninjured Brain

The Brain has an Inherent Capacity for Plasticity

Brain capacity has been shown to be dependent upon the number of synaptic connections rather than the number of neurons *per se*.[1,2] Synaptic connections develop as a consequence of genetic programming and a lifetime of experience. They are inherently resistant to change following the loss of a large number of functional connections,[1] such as that which may occur due to stroke. The inherent capacity for cortical reorganization or development of new functional connections in response to learning and experience is referred to as plasticity. It is the capacity for plasticity within the cerebrum that allows for recovery of lost function following the loss of neurons and associated functional connections.[3]

Enriched Environments and Motor Learning

Over half a century ago, Hebb[4] published observations that rats placed in a stimulating environment exhibited improved problem-solving skills when compared to rats raised in standard laboratory cages. Since that time, researchers have demonstrated that motor learning results in morphological changes to the

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motor cortex.[5-8] Animals raised in complex or enriched environments have greater brain weight, thicker cortical tissue, greater neuron size, a greater degree of dendritic branching, higher dendritic spine frequency, larger synaptic contacts and more synapses per neuron.[6,9-15] Learning and experience lead to an expansion of cortical representation while failure to maintain training results in a contraction of cortical representation.[16-18] Repetitive unskilled movements that do not require motor learning do not produce changes in the rat or monkey motor cortex.[19,20] This has significant implications for stroke rehabilitation, where patients need to re-learn physical functions that have been lost.

As demonstrated in animal research, experience and learning or lack thereof can lead to changes in the human motor cortex.[21-23] With the use of functional MRI (fMRI), researchers are able to identify those parts of the human brain activated during specific tasks. For instance, practicing a known sequence of finger movements can produce a progressive expansion of finger representations in the primary motor cortex within 30 minutes that persists for at least eight weeks following training.[24,25] Learning a new skill, such as tracking a movement target with the dominant hand or learning to play the piano, has been associated with increasing motor representation of the hand on fMRI as the new skill improved.[26,27] While motor learning and experience are associated with an expansion of cortical representation, lack of movement may produce the opposite effect.[28] A similar pattern of cortical reorganization has been identified within the somatosensory cortex in studies of both animals and humans.[29-35]

Reorganization of the Brain Post-Stroke

Recovery post-stroke is dependent on several factors. The three most important factors appear to be stroke severity, age of the patient and the availability of specialized interdisciplinary stroke rehabilitation. For instance, the Copenhagen Stroke Study reported that the rate of neurological recovery was directly related to the initial stroke severity.[36,37] As a general rule, the severity of the initial deficit is inversely proportional to the prognosis for recovery.[37,38] All of these factors are directly related to the likelihood of cortical reorganization taking place following the stroke in an attempt to compensate for the injured area of the brain.

Spontaneous Recovery Post-Stroke

Recovery from stroke is often attributed to the resolution of edema and return of circulation within the ischemic penumbra.[39] The penumbra is defined as "ischemic peri-infarct tissue that lies between the thresholds of electrical failure and membrane integrity".[40] Spontaneous recovery can be prolonged well beyond the resolution period of these acute stroke changes,[41] with recovery typically continuing for 4-6 weeks post-stroke.[36,37,42] Furthermore, animal and human trials have indicated that the cerebral cortex undergoes functional and structural reorganization for weeks to months following injury with compensatory changes extending up to six months in more severe strokes.[43]

Reorganization of the Affected Hemisphere Post-Stroke

Nudo[44] noted that neuroplasticity post-stroke is based on three main concepts: 1) In uninjured brains, acquisition of skilled movements induces predictable functional changes within the motor cortex; 2) A motor cortex injury post-stroke results in functional changes in the remaining cortical tissue; 3) After a cortical stroke, these two interact so that acquiring motor skills influences functional neurological reorganization in the undamaged cortex. When damage occurs to a portion of the cortex (as in a stroke), much of the surrounding undamaged cortex will be impacted due to the loss of intracortical projections both to and from the area of injury.[44] Hence, a process of brain reorganization can be anticipated in the areas both adjacent and connected to the damaged area.

Reorganization of the cortex post-stroke is dependent not only on the site of the lesion itself but also on remote brain areas that have structural connections with the area damaged by the stroke. The greater the damage to reciprocal intracortical pathways, the greater the plasticity seen in secondary intact areas; however, these secondary cortical areas must be preserved for recovery to take place. In animals, recovery after brain injury is strongly associated with dendritic growth in intact adjacent brain.[3,45,46] Motor recovery is dependent upon the presence of intact cortex adjacent to the infarct. This would mean that larger strokes, which often damage both primary and secondary motor areas, would markedly reduce the capacity for compensatory reorganization.

Johansen-Berg et al[47] demonstrated that therapy-related improvement in the mobility of the upper extremities in humans following a stroke to the primary motor cortex was associated with increased fMRI activity in the premotor cortex, the supplementary motor area and secondary somatosensory cortex contralateral to the affected limb. Similarly, Cramer et al[48] observed that patients with the greatest motor recovery from a stroke showed a progressive increase in activity of the peri-infarct areas of the supplementary motor area and the primary motor cortex contralateral to the affected hand. This peri-infarct area coincides with that area referred to as the penumbra, as defined earlier. This dependence on peri-infarct areas for cortical reorganization post-stroke demonstrates the importance of maintaining the integrity of the neurons within the penumbral region.

Role of Ipsilateral Pathways in Stroke Recovery

Ipsilateral motor pathways can make a contribution to motor recovery, but only when more efficient contralateral pathways are too damaged to be activated. As the size of the infarct increases, cortical reorganization occurs over a wider area, with less efficient projections and less recovery.[49] When reorganization in the adjacent or surrounding cortex is not possible, activation of the unaffected or ipsilateral cortex may occur.[49-52]

Somatosensory Reorganization and Stimulation Post-Stroke

Cortical reorganization is not confined to the motor cortex. Reorganization associated with somatosensory changes post-stroke has been observed in both animal[53-56] and human[57-59]

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studies. Studies have demonstrated that within hours, days or weeks of a focal cortical injury, neurons adjacent to and distant from the lesion responded to stimulation of skin regions formerly represented by neurons within the damaged area. Human-based research has suggested that this reorganization is not simply a redirection to healthy tissue, but a reorganization of available neural substrate.[57,58] Clinical trials assessing the impact of increased sensory stimulation achieved via acupuncture or Transcutaneous Electrical Stimulation (TENS) on stroke outcomes, such as motor recovery, improved Activities of Daily Living (ADLs) or improved spasticity, have reported conflicting results[60,61] and the clinical correlates of improvement post-stroke in animal studies is not as impressive as it is for motor recovery.

Intrinsic Factors Influencing Post-Stroke Brain Reorganization

Size of Lesion

In animals, it has been demonstrated that functional recovery following cortical lesions is dependent upon reorganization of the remaining cortex. This reorganization includes increased dendritic arborisation and increased spine density.[62] Kolb[3] noted that, in the case of smaller lesions, motor recovery could be ascribed primarily to changes in the surrounding intact motor cortex. This process occurs over weeks to months post-stroke.[63] In contrast, animals with larger cortical lesions demonstrated a much slower rate of recovery with less complete return of function.[64] In larger lesions when activation and reorganization are forced to occur in more distant cortical regions, compensatory movements during recovery appear to play a much more important role.

Results from clinical studies support the association between lesion size and recovery post-stroke. It is well known that individuals who experience smaller strokes make a more complete recovery. However, with small strokes, rehabilitation appears to have limited impact due to the relative ease with which the remaining unaffected cortex can reorganize to take over the lost function, creating a “ceiling effect”. The so-called “middle band” of patients, those who have experienced moderately severe stroke exhibit the greatest improvement as a result of rehabilitation interventions.[65-69] While moderately severe strokes tend to involve larger areas of the brain, adjacent areas are often spared thereby providing the basis for reorganization and recovery. Recovery, in this group of patients, is not as complete as in the case of smaller strokes; however, in the absence of a ceiling effect, rehabilitation appears to have a much greater impact, stimulating cortical reorganization which otherwise might not have occurred. As reorganization within the damaged hemisphere, in particular peri-infarct activity, is associated with the best recovery,[48,70] individuals experiencing severe stroke have the worst prognosis for recovery due to a lack of adjacent, unaffected cortical regions where cortical reorganization for the lost function would otherwise be possible.

Age and Recovery

Older animals often exhibit a rapid and relatively complete recovery post-stroke, although, in general, recovery is more rapid and more complete the younger the animal.[71] This trend corresponds to the decline in the formation of new neuronal connections and synaptogenesis that occurs with aging.[72-76] While the age of an animal may not be a consistent predictor of eventual functional recovery overall, increasing age does have a negative impact on recovery.

Age has been demonstrated to be a factor in diminished post-stroke recovery in clinical settings.[77,78] Studies of the impact of age on recovery post-stroke have determined that the impact of age is small but significant on both the speed and completeness of recovery.[79,80] Older stroke patients do demonstrate signs of recovery of the lost function, albeit at a slower rate. Given that the impact of age is relatively small, it is now regarded as a poor independent predictor of functional recovery when compared to the size of the lesion.

Training and Stimulation in Post-Stroke Recovery Brain Reorganization

Use It or Lose It

Using both animal and clinical models, it has been shown that training and rehabilitation increases cortical representation and functional recovery.[60,63,81-85] Animals exposed to enriched environments and training demonstrated improved functional outcomes[50,86,87] when compared with animals that did not receive enrichment or training. Exposure to an environment with social interactions has also been associated with improved recovery.[50,87,88] Based upon animal models, key factors in the promotion of neurological recovery are skilled learning and exposure to a stimulating and social environment.

Stroke Units

Clinically, stroke rehabilitation units represent the closest available approximation to the enriched environments created in animal research. These specialized rehabilitation units are designed to provide stroke patients with daily, individualized, skill training interventions by therapists with special expertise in stroke rehabilitation. Reviews of studies examining the effectiveness of specialized inpatient stroke units have reported that stroke unit care is associated with reductions in death, dependency and the need for institutionalized care[85,89] when compared to conventional care usually provided on a general medical ward. An extensive review by Teasell et al[60] concluded that treatment within specialized interdisciplinary stroke rehabilitation units was associated with improved functional outcomes.

Too Inactive and Alone

Despite available evidence demonstrating the value of providing rehabilitation interventions within a stimulating environment, a number of studies have reported that the majority of a patient’s time on a stroke rehabilitation unit is spent idle and alone.[90-93] Given the evidence arising from animal studies that increased stimulation and social interaction are associated with better recovery, there is clearly an opportunity for improving the stroke rehabilitation experience to maximize post-stroke recovery by improving the opportunity for cortical re-organization.

The Role of Timing and Intensity of Rehabilitation Therapies

The Earlier the Better

Schallert et al[50] noted that the brain appears to be "primed" to "recover" early in the post-stroke period. In animal studies, it has been shown that if therapy is delayed for several weeks post-stroke, dendritic arborisation is markedly reduced.[3,94-98] Biernaskie et al[49] induced a small, focal ischemic lesion in rats that were then randomly assigned to social housing or enriched rehabilitative training for 5 weeks beginning at 5, 14 and 30 days post-stroke. Animals receiving enriched rehabilitative training at day 5 demonstrated a marked improvement in recovery while those animals that received similar training at day 30 improved no more than those exposed to social housing alone. The same authors examined dendritic morphology in the undamaged animal cortex contralateral to the stroke lesion. Enriched rehabilitation at day 5 was associated with an increased number of dendritic branches and greater complexity of layer V neurons when compared to animals beginning rehabilitation at day 30 and those exposed to social housing only. The authors concluded that the post-stroke brain was more responsive to rehabilitation early post-stroke, and that responsiveness declines linearly with time. Delayed rehabilitation (beginning at day 30 in rats) was no more effective than social housing alone.[49] Based on these results, it appears there is a limited period of time during which the brain is primed for recovery where failure to provide adequate timely therapy represents an opportunity lost for achievement of maximal recovery. While delays may serve to diminish the effects of therapy, gains may still be made through active practice.[16,17,99]

While the results of animal studies are not always reproducible in a clinical setting, retrospective studies of stroke survivors have demonstrated a clear association between early intervention and improved functional outcome,[100-106] although this relationship may be mediated by other variables such as stroke severity.[107,108] Although no consensus exists regarding the optimal time for commencement of rehabilitation, it has been suggested that rehabilitation begin as soon as the patient is medically stable.[105,108,109] Based on the results of both animal and clinical studies, waiting lists for entry to rehabilitation care may result in an irretrievable loss of recovery potential.

Role of Intensity of Therapy

Animals receiving training following stroke experience an increase in cortical motor representation while those who receive no training actually suffer a decline in motor representation[16] and may be significantly delayed in their recovery.[110-112] If training increases motor cortical representation and lack of training decreases it, then more intense training should be associated with greater benefit. Animal studies using constraint-induced motor therapy (CIMT) have demonstrated that increased intensity of therapy is associated with accelerated functional recovery and improved motor representation.[83,113-115]

In general, clinical studies have demonstrated that greater intensity of stroke rehabilitation therapies is associated with improved outcomes.[60,116,117] The greater the duration of exposure to various therapies, the better the outcomes; however, there is a tendency towards diminishing returns in that the correlation between increased intensity of therapies and improved recovery is not linear. In addition, the benefits of more intensive therapy may not be uniform. More intensive physiotherapy and occupational therapy results in improved overall functional outcomes and more rapid hospital discharge to home,[60,116-118] while more intensive language therapy results in improved aphasia outcomes.[119] However, studies of therapies specific to rehabilitation of the upper extremity have reported mixed results; some studies have demonstrated a benefit associated with increased intensity[120-123] while others have not.[124-126] This may reflect the difficulty in treating the upper extremity in patients who have experienced moderate to large middle cerebral artery strokes[127] and variations in intensity of therapy provided. More intense therapy in the form of CIMT has been associated with improvements in motor function, particularly among patients who have retained some active wrist and hand movements.[60]

The Role of Task-Specific Training in Rehabilitation Therapies

While it makes intuitive sense that practice is necessary in order to relearn any given task, repetition alone does not appear to be sufficient. In both animals[20,44,128,129] and humans,[130,131] activities must have meaning in terms of function or usefulness for functional reorganization to occur. Task-specific training, therefore, plays an important role in motor learning. Less intense (e.g. 30-45 minutes) task-specific training regimens with the more affected limb can produce cortical reorganization and associated meaningful functional improvements.[99,132-134] This has been demonstrated with regard to specific motor retraining, but task-specific training interventions designed to treat neglect may also result in improved perceptual functioning.[135]

Constraint-Induced Movement Therapy (CIMT)

Constraint-Induced Movement Therapy is based on the principle that stroke survivors may experience "learned non-use" of the upper extremity.[113] Used most often in the rehabilitation of the affected upper extremity of stroke patients, CIMT is designed to overcome learned non-use by restraining the unaffected arm while providing intensive, task specific training for the affected extremity for a minimum of two weeks. Animal studies have shown that CIMT accelerates recovery of paretic extremities and increases cortical representation.[17,113,114,136,137] Taub et al[137] demonstrated that, during the chronic period after a stroke, animals with paretic extremities demonstrated increased use of the affected limb when the unaffected limb was restrained. Clinically, the results of several randomized controlled trials have demonstrated a similarly positive impact for patients receiving CIMT.[138-142] However, functional benefits appear to be confined primarily to those individuals with some active wrist and hand movement, particularly among individuals experiencing sensory deficits and neglect.

Summary and Conclusions

These are extraordinary times in stroke rehabilitation. A confluence of animal research, functional neuroimaging and clinical trials have shown us that the brain, following stroke, has the capacity to reorganize and recover, facilitated by rehabilitation therapies. Despite overwhelming evidence of the

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benefits of timely, specialized stroke rehabilitation care, rehabilitation of stroke patients is often under-resourced and undervalued. Nevertheless, the research confirms what we have discovered empirically, through clinical practice. "Middle-band" patients improve the most with rehabilitation, "mild" strokes generally show a full or nearly full recovery but the impact of rehabilitation is limited by a "ceiling effect", while "severe" stroke patients, who experience the greatest deficit, make a much slower and inevitably incomplete recovery.

While age is an important factor, its role in post-stroke recovery tends to be over-rated. For rehabilitation, the focus should be on skilled learning within a stimulating social environment based on tasks of importance to the patient. Post-stroke recovery needs to be viewed as being time-sensitive, with earlier application of intensive therapies being required to maximize neurological recovery. Given the costs of stroke to the individual, family members and society at large, there is an urgent need to design stroke rehabilitation programs which limit the impact of a stroke by maximizing cortical reorganization and, therefore, recovery.

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