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Background Concepts in Stroke Rehabilitation

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Abstract

Evidence that neurological and functional recovery occurs in both the acute and chronic phases post-stroke. Rehabilitation has been shown to be most beneficial when started early; however, recovery of stroke-related impairments are still possible months and even years later. Stroke recovery is influenced by a variety of intrinsic and external factors which influence the likelihood and degree of neurological reorganization. Of pertinent interest are the effect of early initiation of rehabilitation, increased therapy intensity, and enriched environments on stroke recovery.

Key Points

- Cortical plasticity depends on the damaged area of the brain as well as areas connected to the damaged area.

Post-Stroke Recovery

- Most recovery occurs early on and is influenced by age and lesion size.
- Post-stroke neurological recovery peaks within the first 3 months.
- Some improvement in function can occur between 6 months to 3 years post-stroke.

Neuroplasticity

- Brain capacity is dependent on the number of functional connections, i.e. synapses.
- In animal studies, enriched environments result in a greater number of synapses.
- In animal studies, motor learning results in changes to the motor cortex.
- In animals, somatosensory cortical maps can be changed by changing sensory input to the motor area
- Clinical studies show that learning and experience result in an expansion of cortical representation.
- Clinically, sensory stimulation may facilitate motor recovery.

Hemispheric Involvement in Neuroplasticity

- In animals, the greater the damage to a specific brain area, the greater the brain plasticity in adjacent areas.
- In animal and clinical studies, ipsilateral motor pathways involving the unaffected hemisphere are recruited when infarcts are so large that the affected hemisphere cannot recover.
- Clinically, stroke recovery is primarily associated with brain plasticity in the adjacent cortex.
- Clinically, greater motor recovery is seen with brain plasticity involving the affected hemisphere.
- Aphasia recovery is associated with bilateral hemispheric involvement.

Therapy Intensity

- In animal studies, more intensive training increases brain plasticity.

- Clinically, more intensive rehabilitation therapies result in improved functional outcomes.

Early Therapy

- In animal studies, very early therapy, if done intensively may worsen outcomes.
- In animal studies, early therapy results in greater brain plasticity; later therapy does not.
- Clinically, earlier rehabilitation therapy is associated with better outcomes.
- Stroke Size and Age Affect Post-Stroke Recovery
- In animal studies, there is an inverse relationship between stroke size and recovery.
- Younger animals show a more complete and rapid recovery post-stroke.
- Clinically, age is inversely related to recovery but the impact is small.

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Table of Contents

Abstract.....	1
Key Points.....	2
Table of Contents	4
3. Recovery Post Stroke	5
3.1 Impact of Stroke	5
3.2 Classifying Outcomes Post Stroke	5
3.3 Defining Recovery and Time Course Post-Stroke	7
3.3.1 Defining Different Types of Recovery	7
3.3.2 Mechanisms of Neurological Recovery	8
3.3.3 Time Course of Recovery	10
3.3.4 Recovery of Specific Functions.....	12
3.3.5 Maintenance of Stroke Recovery	13
3.4 Plasticity of the Cortex.....	14
3.4.1 Human Brains Have More Functional Connections	14
3.4.2 Learning, Experience and Motor Reorganization	14
3.4.3 Somatosensory Reorganization and Stimulation	17
3.5 Mechanisms of Reorganization Post Stroke.....	19
3.5.1 Reorganization of the Affected Hemisphere Post-Stroke.....	19
3.5.2 The Role of Ipsilateral Pathways in Stroke Recovery	22
3.5.3 Aphasia.....	23
3.6 Influence of Rehabilitation on Post Stroke Reorganization	24
3.6.1 Training and Cortical Representation	24
3.7 Reorganization After Stroke: Other Factors Influencing Recovery	25
3.7.1 Effect of Time on Brain Activation Post-Stroke.....	25
3.7.2 Size of the Lesion Influences Recovery	27
3.7.3 Age Effects Recovery	28
3.8 Summary.....	30
References.....	34

3. Recovery Post Stroke

3.1 Impact of Stroke

The impact of stroke is again increasing as the number of deaths attributable to stroke is beginning to rise again after decades of decline. This trend is felt to be a result of the aging of Canada's population and hence is likely to continue as our population continues to age (Heart and Stroke 1997). Flick (1999) notes that in the United States, *“there are 300,000 to 400,000 stroke survivors annually (Stineman et al. 1997, Alexander 1994). Many are left with significant impairments and disability. Fortunately, 78% to 85% regain the ability to walk, with or without an assistive device; 48% to 58% regain independence with their self-care skills (Gresham et al. 1995, Segal and Whyte 1997); 10 to 29% are admitted to nursing homes (Gresham et al. 1995)”*. The implications of an expected rise in stroke incidence is significant as the burden of the disability associated with stroke is high. Rehabilitation offers the opportunity to reduce this burden of disability; however, given the resource-intensive nature of rehabilitation, it is imperative that it be utilized in a systematic and cost-effective manner, in accordance with the best scientific evidence.

Not all stroke patients make it to a formal rehabilitation program. Mayo et al. (1999) reported that of the approximately 35,000 individuals hospitalized for acute stroke each year in Canada, 20% die before leaving acute care, 50% are discharged home, 10% go to inpatient rehabilitation programs and 15% of patients require long-term care.

Table 3.1 Mayo et al. (1999) Discharge Destination of Quebec Stroke Patients Based Upon Stroke Severity

Discharge Destination For Stroke Survivors	Stroke Severity Level		
	Non-ambulatory	Function With Assistance	Independent
Home	26%	66%	86%
Transfer to another acute care hospital	22%	7%	3%
Rehabilitation facility	22%	11%	3%
Any long-term care facility	30%	16%	8%
Total	100%	100%	100%

Tran et al. (1999) reported 56% of stroke survivors in a Toronto hospital were discharged home (compared to 33% in 1993), 32% to rehabilitation (compared to 41% in 1993), and 11% directly to nursing home or long-term care (compared to 26% in 1993). The last decade has seen an increasing number of stroke patients discharged directly home, with a substantial number sent to rehabilitation programs.

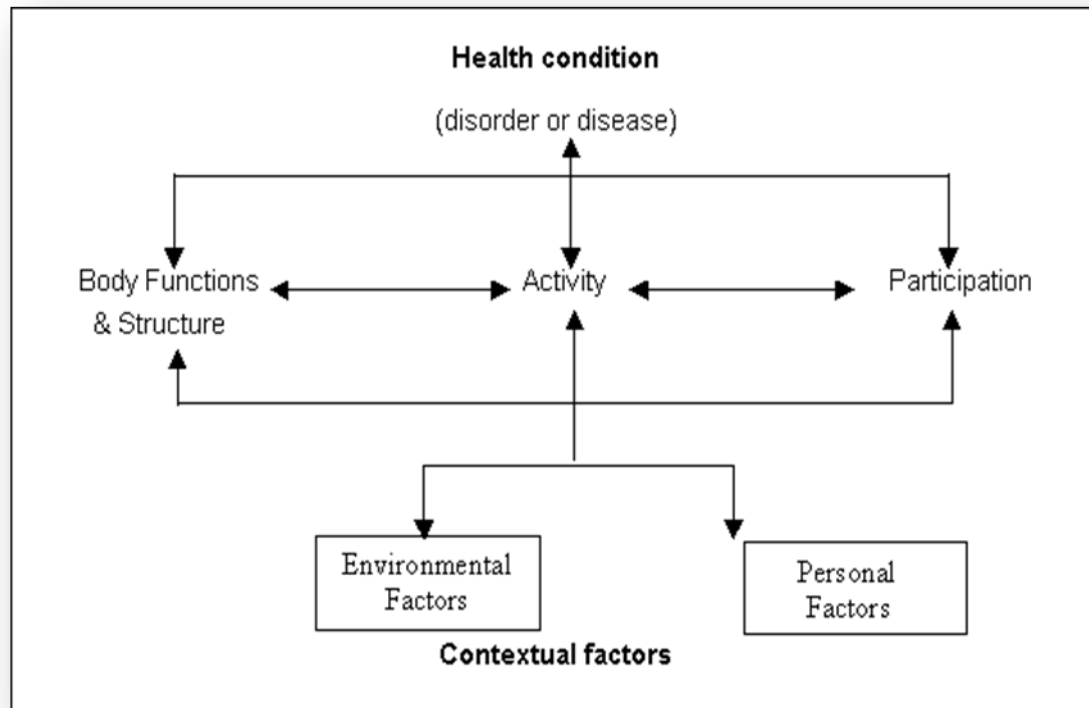
Conclusions: As the population ages, there will be an increased number of stroke survivors with impairments and disabilities who may benefit from rehabilitation.

3.2 Classifying Outcomes Post Stroke

The WHO International Classification of Functioning, Disability and Health (ICF: WHO, 2001, 2002) provides a multi-dimensional framework which was revised from the previous ICIDH -2. The ICF

framework (2001, 2002) identifies three primary levels of human functioning – the body or body part, the whole person and the whole person in relation to his/her social context.

Outcomes may be measured at any of these 3 levels: **body functions/structure** (impairment), **activities** (refers to the whole person, was formerly conceived as disability in the old ICIDH framework), **participation** (formerly referred to as handicap). Activity and participation are affected by **environmental and personal** factors (referred to as contextual factors within the ICF).



The ICF terms are defined as below:

ICF Terminology	Descriptions	Example
Body Function	Physiological functions of body systems (including psychological functions).	Conscious functions Orientation functions Muscle power functions Mental functions of language Attention functions Memory functions
Body structures	Anatomical parts of the body such as organs, limbs and their components	Structure of brain Structure of upper & lower extremity
Activity	Execution of a task or action by an individual Activity limitation are difficulties an individual may have in executing activities	Walking Speaking Toileting Eating Washing Dressing Communication
Participation	Involvement in life situation	Driving

		Return to work, gainful employment
Environmental factors	Physical, social and attitudinal environment in which people live and conduct their lives	Immediate family Health professionals Health services, systems and policies
Personal factors	Features of the individual that are not part of a health condition or state.	Gender, race, age, lifestyle, social background, education, occupation, and psychological characteristics. Such personal factors are not actually coded in the ICF framework itself, but are included in the conceptual model which underpins it.

The ICF Core Set for stroke include a comprehensive list of components including body functions (such as attention and memory), body structures, activities and participation, environmental factors (such as family and support systems) .The Comprehensive ICF Core Set for stroke is the largest of the ICF Core Sets developed for the 12 most burdensome chronic conditions. The large scope of categories included in the Comprehensive ICF Core Set reflects the important and complex impairments, limitations, and restrictions of activities and participation involved, as well as the numerous interactions with environmental factors.

Due to the length of this classification system, a Brief ICF Core Set for stroke has been defined and can be more readily used in clinical practice. The Brief Core Set represents a selection of ICF domains from the whole classification and includes a total of 18 categories (six on body functions, two on body structures, seven on activities and participation, and three on environmental factors) and account for the fundamental and most striking aspects of stroke-related functioning. The relatively larger number of categories relating to restrictions in activities and participation reflects the relevance of these limitations to everyday activities in people with stroke.

Category	Comprehensive ICF Core set for stroke	Brief ICF Core set for stroke
Body Function	41	6
Body structure	5	2
Activities and Participation	51	7
Environment	33	3
Total categories	130	18

3.3 Defining Recovery and Time Course Post-Stroke

3.3.1 Defining Different Types of Recovery

Spontaneous or Intrinsic Neurological Recovery

As a general rule, the severity of the initial deficit is inversely proportional to the prognosis for recovery. Most spontaneous recovery occurs during the first 3-6 months after the stroke. The course of recovery negatively accelerates as a function of time and is a predictable phenomenon (Skilbeck et al. 1983). Skilbeck et al. (1983) studied 92 stroke survivors with a mean age of 67.5 years (range= 36-89) at final assessment, either 2 or 3 years after stroke. The majority of recovery was reported within the first 6 months, with continued but non-statistically significant recovery after 6 months. This type of recovery

has, until recently, been regarded as largely inaccessible to medical intervention or manipulation. Neurological deficits resulting from a stroke are often referred to as impairments. These are determined primarily by the site and extent of the stroke.

Functional or Adaptive Recovery

Table 3.3 Mechanisms of Recovery from Stroke (Adapted from Dombrov 1991)

Mechanism	Time Frame of Occurrence
Local Processes Resolution of edema Resolution of ischemic penumbra Resolution of remote functional depression (diaschisis)	Weeks to 2 months Hours to weeks Days to months
CNS Reorganization Neurotransmitter alterations Unmasking (release from inhibition) of ipsilateral and alternate pathways Synaptogenesis	Weeks to years Immediate to a few months Weeks to months

Functional recovery refers to improvement of independence in areas such as self care and mobility. Recovery depends on the patient's motivation, ability to learn and family supports as well as the quality and intensity of therapy. This type of recovery is modifiable by interventions and is influenced by, but may occur independently of neurological recovery. Functional deficits are often referred to as disabilities and are measured in terms of functions such as activities of daily living.

Conclusions: Recovery can be defined as either neurological or functional. Neurological recovery is a result of brain repair/reorganization. Functional recovery is more multi-functional and influenced by rehabilitation.

3.3.2 Mechanisms of Neurological Recovery

While a number of processes have been identified as playing a role in neurological recovery following stroke, the role each plays is not completely understood. Recovery from stroke is often attributed to resolution of edema and return of circulation within the ischemic penumbra (Dombrov 1991). However, spontaneous recovery can be prolonged well past the resolution period of acute structural changes caused by the stroke, with recovery occurring 4-6 weeks post stroke (Brodal 1973). 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 6 months in more severe strokes (Green 2003). Recovery can be grouped into two categories: 1) local CNS processes (early recovery)
2) CNS reorganization (later recovery) (see Table 3.3)

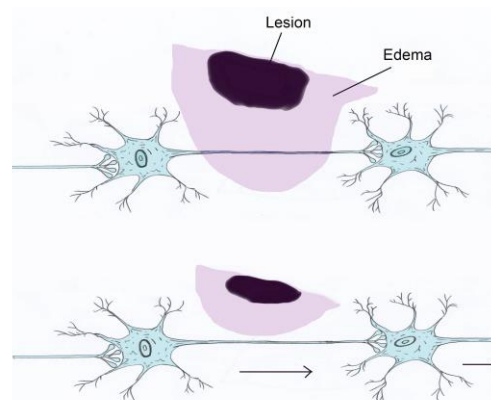
Local Processes (Early Recovery)

Local processes leading to initial clinical improvement occur independent of behaviour or stimuli.

a) Post-Stroke Edema

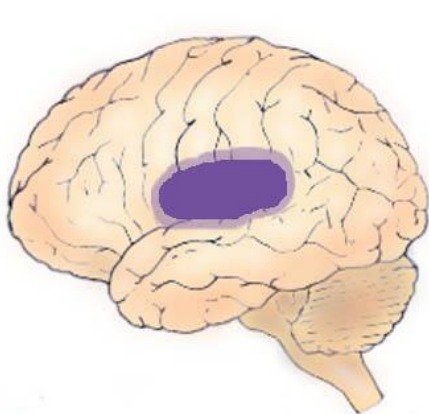
Edema surrounding the lesion may disrupt nearby neuronal functioning. Some of the early recovery may be due to resolution of edema surrounding the infarcted area (Lo 1986) and as the edema subsides, these neurons may regain function. This process may continue for up to 8 weeks but is generally completed much earlier (Inoue et al. 1980). Cerebral hemorrhages tend to be associated with more

edema, which take longer to subside, but which may in turn be associated with a more dramatic recovery.

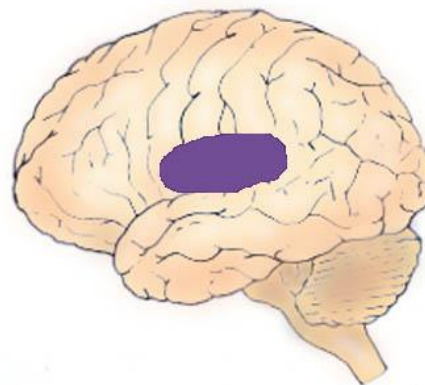


b) Reperfusion of the Ischemic Penumbra

Reperfusion of the ischemic penumbra is another local process which can facilitate early recovery. A focal ischemic injury consists of a core of low blood flow which eventually infarcts (Astrup et al 1981, Lyden and Zivin 2000), surrounded by a region of moderate blood flow, known as the ischemic penumbra (Astrup et al 1981, Lyden and Zivin 2000), which is at risk of infarction but is still salvageable. Reperfusion of this area causes affected and previously non-functioning neurons to resume functioning with subsequent clinical improvement.



Lesion with Ischemic Penumbra



Reperfusion of Ischemic Penumbra

c) Resolution of Diaschisis

Diaschisis is a state of low reactivity or depressed function as a result of a sudden interruption of major input to a part of the brain remote from the site of brain damage. With injury to one area of the brain, other areas of brain tissue are suddenly deprived of a major source of stimulation. Nudo et al. (2001) noted that diaschisis occurs early after injury and is an inhibition or suppression of surrounding cortical tissue or of cortical regions at a distance that are interconnected with the injury core. The reversibility may be partially due to the resolution of edema, which may account for a portion of spontaneous recovery (Nudo et al 2001). Neuronal function may return following the resolution of diaschisis, particularly if the connected area of the brain is left intact. This is particularly true of noncortical structures after cortical injury (Lo 1986).

CNS Reorganization (Later Recovery)

Neurological reorganization plays an important role in the restoration of function. It can extend for a much longer period of time than local processes, such as the resolution of edema or reperfusion of the penumbra, and is of particular interest because it can be influenced by rehabilitation training. Nudo (2003a), based on animal research, has suggested that changes occurring during motor learning, i.e. synaptogenesis and increases in synaptic strength, are likely the same type of changes that occur during this part of recovery from stroke. This has been well shown after small, focal lesions in the motor cortex where the same principles of motor learning and development of functional connections are occurring in adjacent, undamaged tissue.

Nudo (2003a) reports that neuroplasticity post-stroke (with damage to the motor cortex as an example) is based on three main concepts: 1) In normal (non-stroke) brains, acquisition of skilled movements is associated with predictable functional changes within the motor cortex; 2) Injury to the motor cortex post-stroke results in functional changes in the remaining cortical tissue; 3) After a cortical stroke, these two observations interact so that reacquiring motor skills is associated with functional neurological reorganization occurring in the undamaged cortex (Nudo 2003a). This neuroplasticity or cortical reorganization is an important underlying rationale for rehabilitation and a major neurophysiological underpinning of neurological recovery post-stroke.

Conclusions: Reorganization is dependent not only on the lesion site, but also on the surrounding environment, and on remote locations that have structural connections with the injured area.

Cortical plasticity depends both on the damaged area and areas connected to the damaged site

3.3.3 Time Course of Recovery

Peak neurological recovery from stroke occurs within the first one to three months. A number of studies have shown that recovery may continue at a slower pace for at least 6 months; with up to 5% of patients continuing to recover for up to one-year. This is especially true with patients who are severely disabled at the time of initial examination (Bonita and Beaglehole 1998, Duncan et al. 1992, Ferucci et al. 1993, Kelley-Hayes et al. 1989, Wade et al. 1983, Wade et al. 1987)(see discussion below). Progress towards recovery may plateau at any stage of recovery with only a very small percentage of those with moderate to severe strokes (about 10%) achieving “full recovery”.

The return of motor power is not synonymous with recovery of function; function may be hampered by the inability to perform skilled co-ordinated movements, apraxias, sensory deficits, communication disorders as well as cognitive impairment. Functional improvements may occur in the absence of neurological recovery (Duncan and Lai 1997, Nakayama et al. 1994). Functional recovery (the ability to do activities despite limitations) and improvement in communication may continue for months after neurological recovery is complete.

Time Course for Recovery Depends on Initial Severity of Impairments

Jorgensen et al. (1995a, 1995b) studied 1,197 acute stroke patients in the Copenhagen Stroke Study which consisted of a large unselected community-based population admitted to a 63 bed stroke unit. Impairments were classified using the Scandinavian Neurological Stroke Scale (SSS) and functional disability was defined according to the Barthel Index (BI). Typically, recovery for impairment and functional disability meant the highest recorded score in SSS and BI, respectively, with no further improvement.

At the time of the initial assessment, 41% of patients had mild strokes, 26% moderate and 19% severe, reflecting the severity of their neurological impairment as measured by the SSS. As a group, 95% of all patients reached their best neurological level within 11 weeks, on average. 95% of patients with mild strokes had reached their maximal neurological recovery within six weeks; for patients with moderate, severe and very severe strokes, 95% of the group had achieved their maximal recovery within 10, 15 and 13 weeks respectively. Neurological recovery occurred on average two weeks earlier than functional recovery. The specific timeline for neurological and functional disability recovery is presented in Tables 3.4 and 3.5. In surviving patients, the best neurological recovery occurred within 4.5 weeks in 80% of the patients, while best ADL function was achieved by 6 weeks. For 95% of the patients, best neurological recovery was reached by 11 weeks and best ADL function within 12.5 weeks.

In another study, Jorgensen and associates (1995c) reported that best walking function was reached within four weeks for patients with mild paresis of the affected lower extremity, six weeks for those with moderate paresis and 11 weeks for severe paralysis. Consequently, the time course of both neurological and functional recovery was strongly related to both initial stroke severity and functional disability. Jorgensen et al. (1995a, 1995b, 1995c), noted that two-thirds of all stroke survivors have mild to moderate strokes and are able to achieve independence in ADL.

Table 3.4 Impairment and Neurological Recovery of Stroke Patients in the Copenhagen Stroke Study

Category (SSS)	Admission ¹	Discharge ²	Survival (%)	Weeks to 80% Best Recovery ³	Weeks to 95% Best Recovery ³
Very Severe (0-14)	19%	4%	38	10	13 (11.6-14.4)
Severe (15-29)	14%	7%	67	9	15 (13-17)
Moderate (30-44)	26%	11%	89	5.5	10.5 (9.5-11.5)
Mild/No (45-58)	41%	78%	97	2.5	6.5 (5.4-7.6)

¹Percentage patient distribution on admission, grouped by stroke severity sub groups, as measured by SSS (scores range from 0-58 points).

²Percentage distribution of survivors (79% of initial group) after completion of stroke rehabilitation.

³Neurological recovery as measured by SSS.

Table 3.5 Disability and Outcome of Stroke Patients in the Copenhagen Stroke Study

Category (BI)	Discharge ¹	Survival (%)	Weeks to 80% Best Recovery ²	Weeks to 95% Best Recovery ²
Very Severe (0-20)	14%	50	11	17 (15-19)
Severe (25-45)	6%	92	15	16 (13.5-18.5)
Moderate (50-70)	8%	97	6	9 (7.5-10.5)
Mild (75-95)	26%	98	2.5	5 (4-6)
No (100)	46%			

¹Percentage patient distribution on discharge, grouped by stroke severity sub groups, measured by BI.

²Functional recovery as measured by BI.

Based on these observations one can safely conclude that the initial severity of the stroke is inversely proportional to the final functional outcome, with the majority of patients who suffer mild strokes demonstrating no or only mild disabilities, while the majority of patients who suffer very severe strokes still experience severe or very severe deficits even upon completion of rehabilitation.

Conclusions: Neurological recovery peaks within the first 1-3 months post-stroke and may continue at a slower pace for a couple of months. Nevertheless, functional recovery can continue for sometime after neurological recovery is complete. Recovery occurs more quickly in milder strokes.

Post-stroke neurological recovery peaks within the first 3 months.

3.3.4 Recovery of Specific Functions

In a longitudinal study by Hier et al. (1983), arm and leg weakness recovered in approximately 40% by week 16, sensory extinction recovered in 80% by week 46, hemianopsia in 65% by week 33, unilateral spatial neglect on drawing in 70% by week 13, anosognosia and neglect in nearly all by week 20, motor impersistence in all by week 55, and prosopagnosia and constructional apraxia in 80% by week 20. Hier et al. (1983) found that earlier recovery was associated with:

- lesions measuring less than 6% of the right hemisphere volume
- a parenchymatous hemorrhage
- younger patients.

a) Ambulation

Dobkin (1997) noted that a community-based population study done by Jorgensen et al. (1995c) in Copenhagen followed 800 acute stroke survivors. At baseline, the authors found that 51% were unable to walk, 12% walked with assistance, and 37% were independent ambulators. At discharge, 22% could not walk, 14% walked with assistance, and 64% of survivors walked independently. Approximately 80% of those who were initially non-walkers reached their best walking function within 6 weeks and 95% within 11 weeks. In patients who walked with assistance, 95% reached best function within 5 weeks. Independent walking was achieved by 34% of the patients who had been dependent at baseline and by 60% of those who initially required assistance. However, many initially dependent walkers never achieved walking speeds that are considered to be sufficient for independent community ambulators.

b) Upper Extremity Function

Dobkin (1997) noted that a community-based study by Nakayama et al. (1994) reported that the best upper extremity function, as assessed by the Barthel Index sub-scores for grooming and feeding, was achieved by 95% of patients within 9 weeks. The authors also found that patients with mild paresis improved by 6 weeks, and patients with severe paresis reached best function by 11 weeks. Full function was achieved by 79% of those with mild paresis, but only by 18% with severe paresis. These and other studies suggest that arm and hand function for most patients tends to improve for up to 12 weeks (Dobkin 1997).

Furthermore, Dobkin (1997) reports that patients who can flex and extend the affected fingers and wrist by 3 month's can improve for more than a year in specifically practiced tasks. Along the same lines, Dobkin (1997) also reported that a community-based British study assessed 680 patients at onset of acute stroke. Hemiparesis was found in 88%, with equal amounts of patients in each severity category; mild (functionally insignificant), moderate, and severe (little or no movement). At 1 month, 26% had no impairment, and 39% were graded as mild. Motor impairment at 6 months was rated as none for 39%

of survivors, mild for 36%, moderate for 10%, and severe for 14%. According to Dobkin (1997), patients presenting with a mild instead of a severe motor impairment were 10 times more likely to achieve full recovery.

c) Higher Cerebral Functions

According to Dobkin (1997), approximately 35% of acute stroke patients will be admitted to an acute hospital with aphasia and approximately 18% will still have aphasia upon discharge from the acute and rehabilitation stay (Wade et al. 1986, Pedersen et al. 1995). For aphasia, most improvement occurs within 12 weeks, although gains that are important for social functioning may continue for a year (Dobkin 1997). Other higher cerebral functions, such as dementia are also apparent in stroke patients (Tatemichi et al. 1994). Kokmen et al. (1996) found that dementia was nine times more frequent in the first year after stroke than expected.

Conclusions: Vast majority of recovery for ambulation, upper extremity function and higher cerebral functions such as aphasia and neglect post-stroke occurs within 12 weeks. Faster recovery may be related to smaller lesions and younger age.

Most recovery occurs early on and is influenced by age and lesion size.

3.3.5 Maintenance of Stroke Recovery

Once functional status plateaus, it remains relatively stable (Stineman and Granger 1991). Between 6 months and 3 years post stroke the average level of functional ability is maintained (Dombovy et al. 1986). Beyond five years, slight increases in institutionalization rates and deterioration in function are noted, most likely related to the effects of increasing age and co-morbidity (Stineman and Granger 1991). Although overall function remains stable, there are differential shifts in performance of specific functions following stroke rehabilitation. Mobility and bowel incontinence continue to improve long-term (Heinemann et al. 1987, Lehman et al. 1975). However, activities of daily function tend to decline, which has been related to caregivers providing increasing assistance once patients are discharged home. Socialization within and outside the home, as well as hobby activities decline significantly. This decreased socialization extends beyond the effect of the physical deficits; in other words the stroke impairment itself cannot fully account for the decrease in socialization.

Duncan and Lai (1997) reported that the most dramatic recovery occurred in ADL function within the first 30 days post-stroke for 100 patients with mild to moderate strokes. However, even individuals with mild and moderate strokes exhibited limitations in higher physical functions, physical and social role functioning and return to work. Patients with severe strokes had a much more protracted recovery, with most recovery occurring between one and three months post stroke. This group also had the greatest degree of variability in ADL recovery. A very strong correlation was noted between motor recovery and ADL recovery, although the percentage of ADL recovery was always greater than the percentage of motor recovery. The authors felt that this suggested that stroke patients might achieve independence in basic ADLs in the presence of significant residual motor impairment (Duncan and Lai 1997).

Generally, survivors of brainstem strokes have reported good prognosis for recovery and long-term survival in comparison with hemispheric infarctions (Garrison and Rolak 1993). Chua and Kong (1996) retrospectively studied 53 consecutive brainstem strokes admitted to an inpatient rehabilitation unit. They found 96% of the patients were discharged home and patients with a lower Modified Barthel Index

(MBI) score on admission had a worse functional outcome. The total MBI was the only significant factor to influence outcome while nonsignificant factors studied included age, pattern of motor weakness, presence or absence of ataxia and urinary incontinence.

Conclusions: Although overall function remains relatively stable between 6 months and 3 years after a stroke, differential shifts exist in performance of specific functions (i.e. mobility, incontinence, and socialization) following stroke rehabilitation.

Some improvement in function can occur between 6 months to 3 years post-stroke.

3.4 Plasticity of the Cortex

3.4.1 Human Brains Have More Functional Connections

While humans have larger brains than mammals of similar size and are thereby capable of more complex brain functions (Turkstra et al. 2003), this does not necessarily mean that humans have more neurons per kilogram compared to other animals (Turkstra et al. 2003). Rockel et al. (1980) compared the number and density of cortical neurons in human, macaque, cat, rat, and mouse brains. With the exception of the visual cortex, the number of neurons per area was similar despite the fact that the total cortical surface area was greatest in humans (Turkstra et al. 2003). Rockel et al. (1980) speculated that the greater thickness of cortex in humans was primarily caused by the increased number and complexity of dendritic and axonal branches compared to other species.

Therefore, brain capacity appears to be dependent on the number of functional connections rather than the number of neurons present. Thus, for new learning to occur after stroke the spared connections need to be adjusted so that new functional connections are developed. However, since functional connections develop over a lifetime of genetic programming and experience, they are likely to be somewhat resistant to change post-stroke (Turkstra et al. 2003).

Conclusions: Brain capacity is dependent on the number of functional connections and not the number of neurons present. Functional connections develop over a lifetime of genetic programming and experience. Functional substitutions after injury requires the development of new connections.

Brain capacity is dependent on the number of functional connections, i.e. synapses.

3.4.2 Learning, Experience and Motor Reorganization

Cortical Motor Maps

As described by He et al. (1993), and Stepniewska et al. (1993), the motor cortex is composed of several interconnected cortical areas including: the primary motor cortex located in the precentral gyrus; the premotor cortex (including ventral premotor cortex and dorsal premotor cortex), the supplementary motor area; and the cingulate motor areas (Frost et al. 2003). With the use of functional MRI, researchers have been able to identify which parts of the human brain are activated during specific tasks. For example, Kim et al. (1993) has shown that in right-handed persons, right-handed unilateral

motor tasks are associated with brain activation confined primarily to the contralateral (left) hemisphere, with ipsilateral (right) brain activation being relatively small in comparison. In contrast, the authors found more ipsilateral brain activation for movements involving the left hand.

Animal Studies

a) Enriched Environments Increase Brain Functional Connections

Hebb (1949) first discovered that rats placed in a stimulating environment improved problem-solving skills when compared to rats raised in standard laboratory cages. Researchers have since discovered that motor learning results in morphologic changes to the motor cortex (Diamond et al. 1964, Greenough et al. 1985b, Kleim et al. 1996, Rosenzweig et al. 1964). 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, more perforated synapses, and more synapses per neuron (Bennett et al. 1964, Diamond et al. 1967, Diamond et al. 1964, Globus et al. 1973, Rosenzweig et al. 1962, Turner and Greenough 1985, Volkmar and Greenough 1972, West and Greenough 1972). Short-term changes include the immediate expression of early genes, alterations in synaptic efficacy, and long-term potentiation (Kleim et al. 1996, Rioult et al. 2000, Rioult-Pedotti et al. 2000), whereas long-term changes include an increase in dendritic arborization, spine density, axonal sprouting, and the number of synapses per neuron (Calverley and Jones 1990, Greenough et al. 1985b, Jones et al. 1997, Withers and Greenough 1989). These modifications are likely due to the availability of greater sensory stimuli and more learning experiences, which in turn are expressed as structural changes within the brain.

Janssen et al (2010) performed a systematic review and meta-analysis to determine the efficacy of enriched environment on neurobehavioral scores, learning, infarct size and mortality in animal models of ischemic stroke. Results showed that animals recovering in an enriched environment post-stroke had mean neuro-behavioural scores of 0.9 SD (95% CI=0.5 to 1.3, $p < 0.001$) above the mean scores of animals recovering in standard conditions and showed a trend towards improvement in learning (25.1 % improvement; 95% CI=3.7 to 46.6, $p=0.02$). There was no significant increase in death although animals exposed to enriched environment had 8% (95% CI=1.8 to 14.1, $p=0.015$) larger infarcts than control animals . The results indicate significant improvements in sensorimotor function with enriched environment post-stroke but suggest a small increase in infarct volume. The authors emphasize that clarification of the underlying mechanisms requires further study but should not overshadow the observed functional improvements and their application to clinical trials during stroke rehabilitation (Janssen et al, 2010).

Conclusions: In animal studies, enriched and complex environments result in a greater number of synapses and an increase in dendritic branching, specific to the area of cortex being stimulated. Enriched environment also result in improvement of sensorimotor function in animal s with animal models of ischemic stroke.

In animal studies, enriched and complex environments result in a greater number of synapses and improvement in sensorimotor function.

b) Effect of Learning on Cortical Motor Reorganization

In animal studies it has been shown that newly learned movements are represented over larger cortical territories (Karni et al. 1998, Kleim et al. 1998, Nudo et al. 1996b, Pascual-Leone et al. 1995); however, the associated increase in the number of synapses per neuron appears to be specific to the cortical area

being stimulated (Greenough et al. 1985b, Kolb 1995, Withers and Greenough 1989). Hence, brain reorganization with training may generalize to new but related tasks (Turkstra et al. 2003). Repetitive unskilled movements that do not require motor learning do not produce changes in the rat or monkey motor cortex (Kleim et al. 1998, Plautz et al. 2000). As well, failure to maintain training will result in a contraction of cortical representation (Castro-Alamancos and Borrel 1995, Nudo et al. 1996b, Nudo et al. 1996a).

Nudo et al. (2001) looked at changes to the motor cortex in monkeys by training the animals to grasp food from either a narrow (more difficult) or wide (less difficult) wells (Kolb 2003). In the case of the narrow wells, animals had to manipulate their digits in finer movements; with the wider wells animals were able to use gross movements of the wrist and hand to obtain food. For the narrow-well tested animals the cortical area representing the digits expanded while in the wide-well animals the motor cortex representing the wrists was increased (Kolb 2003).

Conclusions: In animal studies, motor learning results in changes to the motor cortex, which are specific to the area of cortex involved. Lack of training can result in further reduction of cortical representations. Repetitive unskilled movements that do not require motor learning do not result in motor cortex changes. Experience results in significant brain reorganization improving motor performance and also increasing future learning potential.

In animal studies, motor learning results in changes to the motor cortex.

Clinical Studies

a) Enriched environment

In a non-randomized trial by Janssen et al (2013), the difference in change of physical cognitive and social or any other activity were directly observed in stroke patients located in a mixed rehabilitation unit exposed to an enriched environment, EE (n=15) versus non-enriched environment(n=14). The stroke patients in the EE were 1.2 (95% CI 1.0 to 1.5) times more likely to engage in social activities, 0.7 (95% CI 0.6 to 0.9) times as likely to be inactive and alone and 0.5 (95% CI 0.4 to 0.7) times as likely to be asleep than patients without enrichment. The preliminary trial suggest that the comprehensive model of enrichment developed for use in a rehabilitation unit was effective in increasing activity in stroke patients and reducing time spent inactive and alone.

b) Motor Learning Results in Reorganization of the Motor Cortex

With the use of functional MRI, researchers are now able to identify which parts of the human brain are being activated during specific tasks. Similar to motor learning in animals, motor learning in humans results in the associated movements being represented across large cortical areas (Karni et al. 1998, Pascual-Leone et al. 1995). Grafton et al. (1992) reported that subjects learning to track a moving target with their dominant right hand showed parallel and progressive activation increases in the left primary motor cortex as accuracy and smooth pursuit movements improved. Similarly, people learning to play a new piano piece demonstrated that the size (or excitability) of the motor representation of the hand increased as the individuals improved (Hallett 2001, Pascual-Leone et al. 1995).

Learning vs. Recovery

Both neurological recovery and motor learning occur post stroke. There is no data to contradict the supposition that individuals post stroke can “learn” new motor skills using their involved limbs in a fashion similar (although attenuated) to healthy individuals. The ability to learn new motor skills likely

represents a continuum based on the severity of neurological deficits. Several studies have shown the ability of individuals post stroke with chronic, stable motor deficits to improve their motor functioning after specialized intensive training (Werner 1996, Taub et al. 1993, Tangeman et al. 1990, Wolf 1989, Lehman et al. 1975). Also the amount of improvement correlates with the intensity of rehabilitation (Nugent 1994, Smith et al. 1981, Langhorne et al. 1996). Is this neurological recovery or is it learning? Can the two phenomena truly be distinguished? Cortical mapping has demonstrated changes in the organization of the cerebral cortex associated with learning motor tasks in the intact brain (Nudo et al. 1996b, Pascual-Leone et al. 1994), as well as in the injured brain (Nudo and Milliken 1996).

Experience Can Alter Cortical Motor Maps

Similar to animals, experience can also lead to changes to the human motor cortex. Penfield and Boldrey (1937) first showed that the cortical finger representations of the skilled hand in trained badminton players was organized differently than the player's unskilled hand. When compared to those of untrained players, the cortical finger representations of the left hand in string instrument players (the hand which plays the strings) are larger when compared to the cortical space represented by the thumb or fingers of the right hand (Elbert et al. 2001). It was also noted that the degree of change was proportional to the age when musical training began, with the representational area of the left fingers being largest in musicians who began playing before 13 years of age. However, even when training began in adulthood, the representation of the relevant fingers was still larger when compared to persons who did not play stringed instruments (Elbert et al. 2001, Kolb 2003).

Repetitive practice of a known task results in changes in the human motor cortex. Practicing a known sequence of finger movements can produce a progressive expansion of finger representations in the primary motor cortex within 30 minutes (Humphrey 1986) that persists for at least 8 weeks after training (Karni et al. 1998). There is also evidence from transcranial magnetic stimulation that repeated movements of the thumb paired with movements of the shoulder (Cohen et al. 1995), face (Cohen et al. 1996), or foot (Crisostomo et al. 1988) produces a shift in the location of the thumb representational area towards the representation of the paired movement, i.e. paired movements of the thumb and shoulder or the thumb and foot produce a medial shift of the representational areas, while paired movements of the thumb and face produce a lateral shift (Nudo et al. 2001)

Along the same lines, lack of movement of a specific muscle can also result in reorganization of the motor cortex to reflect the lack of use. For example, unilateral immobilization of the ankle joint without a peripheral nerve lesion causes a decrease in the affected tibialis anterior motor cortical area compared to the area of the unaffected tibialis anterior (Liepert et al. 1995), a change that occurs without changes to the spinal excitability or motor threshold (Liepert et al. 1995). Therefore, it seems that while experience or repetitive training results in an expansion of cortical regions subserving the motor function, failure to maintain training results in a contraction of cortical representation.

Conclusions: Clinical research has demonstrated that learning and experience results in an expansion of cortical representation. Repetitive practice of a known task also leads to an expansion of cortical representation while failure to maintain training results in a contraction of cortical representation.

Clinical studies show that learning and experience result in an expansion of cortical representation.

3.4.3 Somatosensory Reorganization and Stimulation

Animal Studies

Altering the Cortical Sensory Maps

In terms of somatosensory changes post-stroke, reorganization has been observed in cortical topography and neuronal receptive fields of monkeys (Jenkins and Merzenich 1987, Pons et al. 1988), raccoons (Doetsch et al. 1990), and rats (Coq and Xerri 1999). Specifically, research in this area has revealed that cortical neurons both adjacent to, and at some distance from the lesion, respond to stimulation of skin regions that were previously represented by neurons in the injured area. These changes have been observed within hours (Coq and Xerri 1999) and days or weeks (Doetsch et al. 1990, Jenkins and Merzenich 1987) of the focal cortical injury.

Sensory Stimulation Enhances Plasticity

Nudo et al. (2003b) have noted that, “The motor cortex receives significant amounts of cutaneous and proprioceptive input that seems to be roughly segregated within the posterior and anterior aspects of the primary hand motor area, respectively.” Nudo et al. (2000) found that a small infarct in the posterior aspect of the primary motor cortex (ie, the region receiving most of the cutaneous input) resulted in a specific type of transient motor deficit whereby monkeys performed “sensory errors”. These errors were observed during a reaching task where the monkey reached into a well to grab a pellet, and would then supinate the forearm and look into the palm, presumably to see if the pellet was there (Nudo 2003b). Often the pellet was not successfully retrieved, normally a rare error. According to Nudo et al. (2003b), this type of error has also been noted after somatosensory cortex lesions and it has been suggested by Xerri et al. (1998) that this is indicative of a form of sensory agnosia. Therefore, motor deficits may not simply be a problem of motor output, but may also be due to a sensorimotor disconnection.

Humphrey et al. (1994) noted that when there is such a disruption in sensory input into the motor cortex, motor deficits subsequently develop which can last for months. According to Nudo et al. (2003b), the motor area’s responsiveness to this loss of somatosensory stimuli begins to return by 4 months; however, it does not return to its pre-stroke ability. It is suspected that the animals adopt compensatory strategies, i.e. using other sensory modalities such as vision to guide motor behaviour, which reduces the need for somatosensory guidance (Nudo 2003b). Even very small infarcts can result in subtle changes in behavioural compensation. For example, following a small infarct, stereotypic movements are abandoned, and the monkey temporarily demonstrates seemingly random patterns of movement (Nudo 2003a).

Conclusions: In animals, somatosensory cortical maps can be altered by changing the afferent input to the motor area. The corollary of ‘use it or lose it’ in the motor system is ‘stimulate it or lose it’ in the somatosensory system of the brain. Post-stroke, reorganization of sensory representation occurs within intact neural tissue.

In animals, somatosensory cortical maps can be changed by changing sensory input to the motor area.

Clinical Studies

Somatosensory Reorganization Post Stroke

Several studies have shown that somatosensory reorganization occurs post-stroke. Wikstrom et al. (2000) examined 14 stroke patients 1 to 15 days post stroke and again 2 to 3 months later and

compared them to 23 normal controls. After a stroke, recovery of touch was paralleled by growth of the P1m somatosensory evoked magnetic field deflection, which may have represented re-establishment of lateral inhibitory functions at the primary somatosensory cortex (Wikstrom et al. 2000). More recently, cerebral damage in humans has been correlated with a dissociation between the detection and the localization of tactile stimuli, such that contralesional stimuli that are readily detected show significantly misperceptions of the locations of the stimuli (Rapp et al. 2002). Moreover, post-lesion mislocalization may preserve the relative locations of the pre-lesion topography, resulting in systematically shifted and distorted somatosensory experiences. The authors suggested that tactile inputs were not merely redirected to intact neural tissue, but were instead reorganized within the remaining neural substrate. This is consistent with animal research findings indicating that the remodeling of somatosensory neural substrates subsequent to focal cortical lesions generally preserves the original neural topography.

Sensory Stimulation May Enhance Plasticity

Hallett (2002) has noted that prolonged peripheral nerve stimulation will increase excitability of related muscle representations in the motor cortex, in some instances even causing the motor map to change (Ridding et al. 2000). This suggests that sensory stimulation could be a useful rehabilitation tool, as it can be applied in a number of ways including passive movements, transcutaneous nerve stimulation, and acupuncture (Hallett 2002). There is however, conflicting evidence based on RCTs regarding the effectiveness of acupuncture or TENS in improving stroke outcomes (see chapter 20).

Conclusions: Clinically, cerebral damage results in dissociation between the detection and the localization of tactile stimuli. After stroke, tactile inputs are not merely redirected to intact neural tissue, but are instead reorganized within available neural substrate. Prolonged peripheral nerve stimulation changes the motor cortical representations, indicating sensory stimulation may be able to facilitate motor recovery.

Clinically, sensory stimulation may facilitate motor recovery.

3.5 Mechanisms of Reorganization Post Stroke

3.5.1 Reorganization of the Affected Hemisphere Post-Stroke

Clinical Studies

Numerous theories and hypothesis have been forwarded to explain neurological recovery following stroke. Functional brain imaging offers an opportunity to evaluate those theories and actually visualize recovery within the brain following a stroke. Functional MRI, PET and transcranial magnetic stimulation have all been used to assess motor activation after stroke (Thirumala et al. 2002).

Normals

Cramer (2003) notes that, *“in normal right-handed persons, performance of a unilateral motor task by the right hand is associated with activation that is largely contralateral, with brain activity ipsilateral to the active hand being small by comparison (Kim et al. 1993). In contrast, there is greater ipsilateral activation for movements by the left hand.”*

Reorganization in Adjacent Brain Tissue

Cramer (2003) noted that after a stroke in humans, movement of the affected hand resulted in three patterns of cortical reorganization that were not mutually exclusive of each other and which may occur concomitantly:

1. A greater degree of bilateral motor cortex activity was seen with recruitment of the motor network of the ipsilateral (unaffected hemisphere) (Bury and Jones 2002, Cramer 2003).
2. There was increased recruitment of secondary cortical areas such as supplementary motor area (SMA) and premotor cortex in the contralateral (affected) hemisphere (Cramer 2003).
3. Recruitment along the cortical rim of the infarct was seen (Cramer 2003).

The predominate pattern of reorganization, which correlates with therapy-related improvements in upper extremity movements, involves increased in fMRI activity in the premotor cortex and supplementary motor area (SMA) and secondary somatosensory cortex contralateral to the affected limbs (Johansen-Berg et al. 2002). Similarly, Liepert et al. (2000) found that the area of cortical representation of the affected hand increased dramatically with the use of constraint-induced movement therapy. It is also known that after a stroke, finger-tapping activates the same motor regions as those activated by the same task in non-stroke controls, but to a larger extent, including involvement of the unaffected hemisphere (Cramer et al. 1997). Most clinical studies examining patterns of cortical reorganization post-stroke have described either an anterior (Weiller et al. 1993) or posterior (Cramer and Bastings 2000, Pineiro et al. 2001, Rossini et al. 1998) shift in the site of activation within the stroke-affected hemisphere.

Conclusions: In humans, following stroke recovery, motor activity in the affected hand results in recruitment of cortical areas along the infarct rim, secondary motor areas in the contralateral hemisphere and ipsilateral hemisphere motor areas. The predominant pattern seen is increased activation of secondary (surrounding) cortical regions of the affected hemisphere.

Clinically, stroke recovery is primarily associated with brain plasticity in the adjacent cortex.

Animal Studies

Increased Synapses in Adjacent Brain Tissue

There is evidence that structural changes occur in the uninjured cortical tissue surrounding the stroke. Nudo (2003a) has suggested that, “the mechanisms that underlie functional changes in the motor cortex of normal animals during motor skill learning are likely the same mechanisms that play a role in recovery after damage to the motor cortex”, and that this is particularly true for small focal lesions in the sensorimotor cortex hand area or the primary motor hand area (Nudo 2003a).

Nudo (2003a) has noted that when damage occurs to a portion of the cortex (as in stroke), much of the surrounding undamaged cortex will nevertheless be impacted because of the loss of intracortical projections both to and from the area of injury. This can be true of even remote areas of the brain when they have some connection to the damaged part of the brain. Hence, a process of brain reorganization can be anticipated in the area adjacent to and connected to the damaged area.

Stroemer et al. (1993) found that after cortical ischemia in rats, in the surrounding intact cortex, GAP-43 immunoreactivity increased, suggesting axonal sprouting, while synaptophysin immunoreactivity was increased, suggesting an increase in the number of synapses (Stroemer et al. 1993). In a later trial, the authors found that the above changes were time dependent, as the GAP-43 increase was significantly elevated only at early survival times (3, 7, and 14 days) while the synaptophysin increase was significant

at later survival times (14, 30, and 60 days), thus suggesting that axonal sprouting was followed by synaptogenesis (Stroemer et al. 1995) in a sequential manner.

Plasticity is Proportional to the Amount of Damage

Frost et al. (2003) have suggested two principles to explain how plasticity is related to the amount of brain damage: “1) reorganization of secondary cortical areas is a general feature of injury-induced plasticity, and 2) remote reorganization is directly related to the reciprocal connectivity of the various motor areas.” The latter concept implies that there needs to be some form of connection to the damaged motor area, i.e. secondary motor areas, for any opportunity for functional reorganization to occur. Thus, larger strokes, which damage primary and secondary motor areas, severely limit the capacity for compensatory reorganization. Hence, the greater the damage to reciprocal intracortical pathways, the greater the plasticity seen in secondary intact areas.

Conclusions: In animals, cortical reorganization is dependent not only on the lesion site, but also on the surrounding cortex where increased axonal sprouting and synapses occur post-stroke and are associated with recovery. Reorganization is dependent not only on the lesion site, but also on remote locations that have structural connections with the injured area. The greater the damage to the primary cortical area, the greater the plasticity seen in intact secondary cortical areas. However, for such reorganization to take place, the secondary cortical area must have structural connections with the area damaged by the stroke.

In animals, the greater the damage to a specific brain area, the greater the brain plasticity in adjacent areas.

Clinical Studies

Plastic Changes in the Penumbra

Hallet (2001) has noted that plastic changes in the damaged hemisphere are associated with the best recovery. For example, according to Cramer et al. (2002), “patients with the greatest recovery from a motor stroke demonstrated a progressive increase in activity in the peri-infarct areas of the supplementary motor area and primary motor cortex contralateral to the affected hand.” This peri-infarct tissue, otherwise known as the penumbra, has been defined as “ischemic peri-infarct tissues that lie between the thresholds of electrical failure and membrane integrity” (Astrup et al. 1981). The penumbra is an important concept in the acute phase of stroke where ischemic tissue lining an area of infarction still hangs in the balance. More recent definitions focus on the potential for rescuing this tissue, which is at risk of infarction using appropriate therapy (Heiss and Graf 1994). According to Read et al. (1998), determining the extent of the penumbra, how long it persists after stroke, and its salvageability at various time points is essential as it is now thought that multiple regions of the brain, especially the peri-infarct area, may play a large role in cortical reorganization and functional recovery after stroke.

Conclusions: Clinically, motor recovery involves primarily the affected hemisphere’s contralateral pathways rather than the unaffected hemisphere’s pathways; involvement of adjacent hemispheric regions is indicative of recovery potential. Axonal sprouting and subsequent synaptogenesis appears to be associated with recovery.

Clinically, greater motor recovery is seen with brain plasticity involving the affected hemisphere.

3.5.2 The Role of Ipsilateral Pathways in Stroke Recovery

Animal Studies

Ipsilateral Pathways are Recruited Proportional to the Size of Stroke

In an animal study of enriched rehabilitation, Biernaskie et al. (2004) found that the amount of dendritic growth in the undamaged motor cortex was associated with both the size of the lesion and the distribution of the injury. Biernaskie et al. (2004) have also noted that if the primary motor cortex was intact, any recruitment of the undamaged hemisphere was short-lived, whereas if the primary motor cortex was damaged, compensatory recruitment of the ipsilateral undamaged hemisphere continued and involved the sensorimotor cortex and premotor area (Feydy et al. 2002, Stepniewska et al. 1993). They demonstrated that small cortical strokes may lead to reorganization of the adjacent cortex, which have similar projection patterns and are more able to efficiently compensate for the impaired function. As the infarct size increases, reorganization in the surrounding affected cortex may no longer be possible, resulting in continuing activation of the unaffected hemisphere (Biernaskie et al. 2004).

Compensation and Heightened Function of the Nonaffected Hemisphere

Schallert et al. (2003) have noted that if the contralateral limb is impaired after injury to the sensorimotor cortex, changes in the ipsilateral or nonaffected hemisphere may give rise to an enhanced ability to compensate for lost motor function. Schallert et al. (2003) noted that after unilateral focal damage to the sensorimotor cortex, rats preferentially use the ipsilateral forelimb for many functions. With persistent or prolonged impairment of one limb, the unaffected limb will be called upon to compensate and repeated need for compensatory skill will result in organization in the unaffected hemisphere (Schallert et al. 2003). As mentioned previously, with damage to the primary motor cortex, compensatory recruitment of the ipsilateral limb involved both the sensorimotor cortex and premotor area (Biernaskie et al. 2004, Feydy et al. 2002, Stepniewska et al. 1993).

Conclusions: Animal studies show that recruitment of ipsilateral (unaffected hemisphere) pathways is directly proportional to infarct size. It may be that ipsilateral pathways work by developing new pathways to the contralateral (affected hemisphere) red nucleus.

Clinical Studies

Activation of Ipsilateral Pathways Post-Stroke

Hallett (2001) has noted that neuroimaging studies, such as that done by Chollet et al. (1991), were influential in suggesting that ipsilateral pathways may be important in recovery from human stroke. Chollet et al. (1991) examined six patients with a subcortical stroke initially causing hemiplegia who had essentially recovered full strength; however, three of the six had a little residual clumsiness and some had mirror movements of the good hand when they moved the recovered hand (Hallett 2001). As Hallett (2001) notes, ipsilateral hemispheric activation was involved in stroke recovery and the recovered hand increased activation of ipsilateral sensorimotor cortex (Cao et al. 1998, Cramer et al. 1997, Honda et al. 1997, Weiller et al. 1993).

Biernaskie et al. (2004) have noted that functional imaging studies in human stroke patients demonstrate changes in activation patterns during movement of the affected limb in both the affected and unaffected motor cortex (Cramer et al. 1997, Cuadrado et al. 1999, Feydy et al. 2002, Johansen-Berg et al. 2002, Kopp et al. 1999). Johansen-Berg et al. (2002) have demonstrated that disruption of ipsilateral motor activation using transcranial motor stimulation reduced reaction times of a finger

movement task. This was regarded as evidence of a role for the unaffected motor system after a severe stroke (Biernaskie et al. 2004).

Activation of Ipsilateral Pathways is a Marker of Poor Recovery

Hallett (2001) has noted that ipsilateral motor evoked potentials, which have a lower threshold and shorter latency, are more likely to be seen in patients with stroke when compared to normal subjects (Caramia et al. 1996, Lammers et al. 1995, Turton et al. 1995, Turton et al. 1996). However, these responses were much more likely to occur in patients with poorer functional recovery (Hallett 2001). Turton et al. (1996) found that the presence of contralateral motor evoked potentials early post-stroke onset was a good indicator of recovery of hand movement while ipsilateral motor evoked potentials were of lower amplitude and generally associated with poorer hand motor recovery. Ipsilateral pathways appear to be inadequate for motor recovery and play a role only when the contralateral pathway is too damaged to be activated, making ipsilateral pathway activation a marker of poor recovery and not having enough of an impact to lead to significant motor recovery.

Conclusions: Clinical studies show that ipsilateral motor pathways from the intact hemisphere contribute to motor recovery, most often in more severe strokes with poor functional recovery. There may be competition between contralateral and ipsilateral connections, with ipsilateral pathways becoming more prominent when functional contralateral (affected hemisphere) pathways cannot recover.

In animal and clinical studies, ipsilateral motor pathways involving the unaffected hemisphere are recruited when infarcts are so large that the affected hemisphere cannot recover.

3.5.3 Aphasia

Functional brain imaging has also been used in aphasic patients and, although there is predominance of the left hemisphere over the right in language functions, language recovery depends on the restitution of the speech-relevant network which involves both hemispheres (Kuest and Karbe 2002). Cao et al. (1999), found that language recovery was associated with bilateral activation in 5 patients and right hemispheric activation in two patients. Bilateral activation was associated with better recovery than right hemisphere alone. However, the importance of bilateral activation during recovery from aphasia may not be entirely clear (Cramer and Bastings 2000). They noted that Weiller et al. (1995) and Buckner et al. (1996) found an increased degree of right hemisphere activation when compared to controls in Wernicke's and Broca's aphasia respectively, similar to that described above. However, Heiss et al. (1999) in PET scan assessment of stroke patients with subcortical, frontal or temporal lobe infarcts found that the most efficient language recovery was achieved only when the left temporal area was preserved.

Conclusions: Aphasia recovery is associated with bilateral hemispheric activation. Right hemispheric activation alone is associated with a worse outcome indicating the need for the left hemisphere in recovery with one study suggesting a special role for the left temporal lobe.

Aphasia recovery is associated with bilateral hemispheric involvement.

3.6 Influence of Rehabilitation on Post Stroke Reorganization

3.6.1 Training and Cortical Representation

Research in monkeys and humans indicates that after a stroke, rehabilitation can shape reorganization in the adjacent intact cortex (Green 2003).

The Role of Therapy Intensity in Animal Studies

Taub (1980) reported that restraining the nonaffected extremity after strokes in monkeys resulted in accelerated recovery of the paretic extremities. Nudo et al. (2001) has noted that monkeys placed in restraint jackets to restrict the use of the unimpaired limb and who also received post-stroke behavioral training demonstrated retention of the unaffected hand representations (Nudo et al. 1996a). More recently, Friel et al. (2000) showed that the retention of the hand area adjacent to a microlesion in the primary motor area requires repetitive behavioral training in addition to restraining, because the use of the restraint jacket alone resulted in no change in hand representations beyond that which was seen with spontaneous recovery. DeBow et al (2003) also showed that in rats subjected to intracerebral hemorrhagic stroke, the combination of daily exercises and CIMT improved functional recovery, while CIMT or daily exercises alone were unable to provide much benefit. The combination group also showed smaller volume of tissue lost than untreated rats (DeBow et al. 2003).

Conclusions: More intensive training of the motor cortex (i.e. constraint-induced movement therapy) increases cortical representation. In animals, at least for smaller strokes, more is better when it comes to the impact of rehabilitation therapies on stroke recovery.

In animal studies, more intensive training increases brain plasticity.

The Role of Therapy Intensity in Clinical Studies

Improved recovery in humans may be achieved with increased intensity of rehabilitation (more hours and greater frequency of therapy) (Kwakkel et al. 1999, Langhorne et al. 1996, Kwakkel et al. 1997, Teasell et al. 2004). For instance, clinical reports indicate that more intensive treadmill training results in improvement in gait outcomes when compared to conventional gait training (Laufer et al. 2001, Richards et al. 1993). Such dose-response effects suggest the concept that “more is better” applies to stroke recovery (Gladstone et al. 2002). Moreover, therapies delivered in a more intensive manner resulted in significantly improved functional outcomes and inevitably reduced hospital stays (Kalra 1994).

Training combined with constraint induced movement therapy also results in benefits in humans (Wolf et al. 1989, Liepert et al. 2000). Moreover, the benefits associated with CIMT can be realized with residual deficits months and years after the acute stroke.

Conclusion: In humans, greater intensity of stroke rehabilitation therapies is generally associated with improved outcomes and maintenance or expansion of cortical representation. The greater the time exposure to various therapies, the better the outcomes, although there is a tendency towards diminishing returns. In other words, doubling therapy times will result in superior outcomes although it will not necessarily result in a doubling in functional improvements. 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.

Clinically, more intensive rehabilitation therapies result in improved functional outcomes.

3.7 Reorganization After Stroke: Other Factors Influencing Recovery

3.7.1 Effect of Time on Brain Activation Post-Stroke

Animal Studies

Very Early Therapy May Be Harmful

It is generally assumed that intense, early targeted therapy should improve function in the impaired forelimb of the rat, and would enhance arborization of dendrites in the pre-injury area. However, some animal studies have reported that forced use of the injured forelimb (by constraining the nonimpaired forelimb) beginning immediately after cortical injury is detrimental to both neural tissue and subsequent functional recovery (Humm et al. 1998, Kozlowski et al. 1996, Schallert et al. 2000a). Risedal et al. (1999) has noted that immobilization the unaffected forelimb immediately following stroke, thus forcing the animal to rely on the affected limb for postural support and movements, may be too stressful for the injured brain. Delayed exaggerated degeneration continuing for several months post-stroke has been reported when intense use of the impaired forelimb is imposed after a focal sensorimotor cortical lesion (Humm et al. 1998, Kozlowski et al. 1996, Schallert et al. 2000a, Schallert and Hernandez 1998, Schallert et al. 2003). By 60 days post-stroke, the size of the lesion had typically doubled (Schallert et al. 2003).

Kozlowski et al. (1996) noted that forced overuse of the impaired forelimb after a unilateral sensorimotor cortex lesions, but not after visual cortex lesions, led to a delayed exaggeration of the infarct (Schallert et al. 2003). This indicated that use-dependent exaggeration of injury was not caused by systemic events and in fact Humm et al. (1999) demonstrated that the damaging impact of early overuse was mediated by NMDA-receptor activity. They speculated that the early high level of activity resulted in release of high levels of the neurotransmitter glutamate in the perilesional area. Glutamate binds and activates the NMDA-receptor; excessive release of glutamate post-stroke can lead to increased cell loss particularly in the sensitive penumbra (Humm et al. 1999).

It is important to recognize that those studies that showed a detrimental effect of therapy in animals were of intense therapy very early on and that these findings were by no means consistent across studies. Turkstra et al. (2003) have suggested that use-dependent mechanisms are transient explaining the apparent inconsistency between the negative effects of forced use in animals early on and the benefits of forced use later in animals and humans post stroke (Taub et al. 1993, 1994, 2002).

During the first week after stroke onset, tissue surrounding the infarct becomes hyperexcitable (Neumann-Haefelin and Witte 2000). Excessive sensorimotor activation too early after the insult may exacerbate injury through a use-dependent, glutamate stimulated NMDA-mediated process (Humm et al. 1999). Biernaskie et al. (2004) note, "The virulence of this process may dissipate over days, explaining why rehabilitative experience (i.e., acrobatic or reach training) beginning 3–5 days after insult does not worsen injury size or behavioral outcome (Jones et al. 1999, Nudo et al. 1996b)." In support of this, a number of studies demonstrated that when forced overuse was delayed until the second week

after brain injury, the injury did not become worse (Humm et al. 1998, Risedal et al. 1999, Schallert et al. 1997).

Conclusions: Animal studies have shown that rehabilitation initiated very early post-stroke may have a detrimental effect on outcomes although study conclusions on this matter have been inconsistent. The damaging effect of early overuse in animals is thought to be mediated by the neurotransmitter glutamate excessively stimulating the NMDA-receptor. This issue has not been studied in humans.

In animal studies, very early and intensive therapy post-stroke may worsen outcomes.

Early Therapy

Although training, particularly more intense training, in the very acute phase of the stroke may be detrimental, Schallert et al. (2003) noted that a period of time exists shortly following the stroke when the brain is primed for neurological recovery in response to rehabilitation training.

Biernaskie et al. (2004) did a study where following a small ischemic lesion, rats were placed in social housing or assigned to enriched rehabilitation training for 5 weeks beginning at 5 days, 14 days or 30 days post-stroke. Animals with enriched rehabilitative training at day 5 demonstrated a marked improvement in recovery while those animals exposed at day 30 showed insignificant improvements compared with ischemic animals who were exposed only to social housing. Those in enriched rehabilitation at day 14 achieved an intermediate level of recovery compared to those who received enriched rehabilitation at day 5 and day 30. The author then examined dendritic morphology in the undamaged (contralateral to stroke) motor cortex. Enriched rehabilitation at day 5 increased the number of branches and complexity of layer V neurons compared with both social housing and control animals. Dendritic branching after enriched rehabilitation beginning at day 14 (although it increased) and at day 30 did not vary from those exposed only to social housing. Biernaskie et al. (2004) concluded that the post-stroke brain is more sensitive to rehabilitation early after stroke, and that efficacy declines linearly with time. The authors noted that this was consistent with the notion that the remaining undamaged cortical tissue was most responsive to rehabilitation training early after stroke and that this effect decreases with time.

Conclusions: In animal studies, early therapy results in increased cortical reorganization. The longer the delay, the lesser the impact of therapy. Enriched rehabilitation post-stroke has a positive impact on recovery. Efficacy of enriched rehabilitation decreases proportionally to the time post-stroke when it is provided. In rats there is a significant impact when enriched rehabilitation is delivered within the first week; however, there is little impact if initiated at one month post-stroke. This suggests that there is a window of time when the brain is "primed" for maximal response to rehabilitation training and therapies.

In animal studies, early therapy results in greater brain plasticity; later therapy does not.

Clinical Studies

With animal studies, earlier onset of rehabilitation-type treatments produce better outcomes compared with delayed treatments. Ethically, this is a difficult study to reproduce in a randomized controlled study of humans and so we are left only with association drawn from comparative studies.

Early Onset Rehabilitation

Non-randomized studies suggest that stroke rehabilitation is most effective if initiated early (Feigenson et al. 1977, Hayes and Carroll 1986). Reviews by both Cifu and Stewart (1999) and Ottenbacher and Jannell (1993) have found a positive correlation between early intervention of rehabilitation and improved functional outcome. Unfortunately, these associations can be potentially misleading since more severe strokes i.e. those more prone to a poorer prognosis, are less likely to be admitted early on. However, one uncontrolled study by Paolucci et al. (2000) specifically investigated the outcomes of patients who received rehabilitation at differing times following the stroke and found that those who received rehabilitation early on did better than those who received it at a later date. The results of this single prospective comparative trial provide limited evidence that early admission to stroke rehabilitation directly results in improved functional outcomes.

Conclusions: Clinical studies have indicated that there is an association between earlier admission to rehabilitation and better outcomes which correlates with our understanding of brain recovery/plasticity. An optimal window when rehabilitation therapies should be initiated has yet to be determined.

Clinically, earlier rehabilitation therapy is associated with better outcomes.

Subacute Rehabilitation

Most research regarding the efficacy of stroke rehabilitation examines the subacute phase of rehabilitation. Ronning and Guldvog (1998) have noted that those who are "...most appropriate for subacute rehabilitation are those with moderately severe deficits (Kalra et al. 1993)." In the randomized clinical trial by Ronning and Guldvog (1998), the authors reported that subacute rehabilitation of stroke patients in a hospital-based rehabilitation unit improves outcome, with moderate and severe stroke patients appearing to benefit the most. In addition, Rudd et al. (1997) found that that community rehabilitation following acute treatment is as clinically effective as hospital care.

Conclusions: Clinically, there is strong evidence that rehabilitation, provided in the subacute phase, improves functional outcomes.

3.7.2 Size of the Lesion Influences Recovery

The cerebral cortex undergoes functional and structural reorganization for weeks to months following injury with compensatory changes extending up to 6 months in more severe strokes (Green 2003). Duncan et al. (2000) have noted that there is considerable evidence that both humans and laboratory animals are capable of some spontaneous (independent of rehabilitation therapies) return of lost function after cortical injury, particularly if the lesion is small (Kolb 2003). Clinically, we have already seen that the time course of neurological recovery is highly dependant on the size of the lesion.

Animal Studies

A Smaller Lesion Improves Likelihood of Recovery

It has been shown that while rats with small motor cortex lesions are initially severely impaired in skilled forelimb reaching tasks, they demonstrate significant improvements in reaching, lifting, aiming and advancing the limb to nearly normal levels over a 15-day period (Whishaw 2000). In contrast, rats with

larger lesions show much less return of function and the function that does return may take weeks or months to stabilize (Kolb 1995, 2003). Kolb (1995) noted that rats subjected larger unilateral lesion involving the motor cortex experienced severe long-term loss in the ability to accurately pronate and supinate the forearm to get food. These animals compensated for this disability by indirectly guiding limb movements through whole body maneuvers that enabled them to retrieve some food. However, the ability to retrieve food was still significantly impaired compared with animals with smaller lesions (Kolb 1995).

Nudo and Milliken (1996) studied monkeys undergoing spontaneous recovery (without rehabilitation) following a small stroke affecting the primary motor cortex hand area. They observed that during the first few days post-stroke, there were severe behavioral impairments; the affected hand was not used and the monkey compensated by using the unaffected limb. However, by the end of 3 months following the stroke, motor recovery was complete with little or no evidence of residual deficits (Nudo and Milliken 1996). In contrast, in monkeys who suffered a large stroke affecting the primary motor cortex, motor recovery was shown to plateau by about 3 months (Frost et al. 2003). Hand preference was permanently affected, such that the animal preferred using the less-affected limb. Moreover, even 3 months post-stroke, motor performance was still significantly below normal (Frost et al. 2003).

Kolb (1995) has suggested that the differences between recovery from small and larger strokes is related to the mechanisms of neural recovery. With smaller strokes the mode of recovery is most likely related to changes in the remaining intact motor cortex while with larger lesions changes in other cortical regions occur facilitating compensatory behavior which improves with practice.

Conclusions: Animals with small strokes will experience functional and structural recovery occurring spontaneously (without rehabilitation therapy) for weeks to months post-stroke. The underlying neural changes appear to be related to remaining surrounding brain regions taking over the lost function. Animals with larger lesions show much less return of function and what function that does return may take weeks or months to stabilize. Compensatory movements play an important role here with activation and reorganization occurring in more distant cortical areas.

In animal studies, there is an inverse relationship between stroke size and recovery.

3.7.3 Age Effects Recovery

Animal Studies

The impact of stroke and recovery with age in animals is not entirely clear. In one study examining the effects of age on the development of ischemic injury in rats, the authors discovered that young rats were more affected by the stroke than old rats as exhibited by more pronounced neurological impairments and poorer performance in a water maze task (Shapira et al. 2002). Histological evaluation also revealed more damage in young rats (Shapira et al. 2002). On the other hand, it has been noted that in rats, the duration of motor impairment post brain lesion increases with age (Brown et al. 2003). The regenerative response of neurons and glial cells, though largely preserved with age, appears to be delayed or occurs at a diminished rate the older the animal (Popa-Wagner et al. 1999, Whittemore et al. 1985). Reactive neuronal synaptogenesis declines (Scheff et al. 1978), sprouting responses are less robust (Schauwecker et al. 1995, Whittemore et al. 1985) and synaptic replacement rates diminish (Cotman and Anderson 1988).

In a recent study using older rats subjected to middle cerebral artery occlusions, Linder et al. (2003) showed that although the resulting infarcts were small, rats showed significant functional deficits in forelimb abduction, somatosensory function, fine motor control (staircase reaching test) and motor speed and endurance (bar pressing test). Animal stroke models similar to that presented by Lidner et al (2003), which make use of older animals and stress functional rather than histological outcomes, may more closely mimic the clinical setting and might better evaluate the efficacy of rehabilitative strategies in the recovery of function that could benefit older patients suffering from chronic functional disabilities.

Conclusions: Older animals do exhibit recovery post-stroke, although generally recovery is more rapid and to a greater extent the younger the animal. This correlates with a decline in the rate of formation of new neuronal connections or synaptogenesis. Therefore older animals do improve post-stroke but it takes longer and occurs to a lesser extent. For that reason, age may not be a consistent predictor of functional recovery after stroke.

Younger animals show a more complete and rapid recovery post-stroke.

Clinical Studies

In humans, age is an important risk factor for stroke (Kugler et al. 2003), with people in the general population having a 0.25% risk of stroke per year (Kolominsky-Rabas et al. 1998, Williams et al. 1999), a number which doubles every decade over the age of 50. The incidence of stroke increases to 3.5% at the age of 85 (Jamrozik et al. 1999). In humans, age has long been thought to diminish post-stroke neurological recovery (Nakayama et al. 1994, Pohjasvaara et al. 1997).

In a cohort study of 2219 patients, Kugler et al. (2003) studied the effect of patient age on early stroke recovery. The authors found that relative improvement decreased with increasing age: patients younger than 55 years achieved 67% of the maximum possible improvement compared with only 50% for patients above 55 years ($p < 0.001$). They also found that age had a significant but relatively small impact on the speed of recovery with younger patients demonstrating a slightly faster functional recovery ($p < 0.001$). The authors concluded that although age had a significant impact it nevertheless was a poor predictor of individual functional recovery after stroke and could not be regarded as a limiting factor in the rehabilitation of stroke patients. However, younger patients did demonstrate a more complete recovery.

A prospective study that included 561 patients admitted to an inpatient stroke rehabilitation program found that age alone was a significant predictor of total FIM score and Motor FIM score at discharge, but not of FIM change (Bagg et al. 2002). For both total FIM score and Motor FIM score at discharge, age alone accounted for only 3% of the variance in outcome. The results from this study suggest that advanced age alone is not a justifiable reason to deny patients access to rehabilitation given the questionable clinical relevance of this factor (Bagg et al. 2002).

Conclusions: In humans, age has a small but significant effect on the speed and completeness of recovery. However, because older stroke patients do recover, albeit at a slower rate, and the overall impact of age is relatively small, age in and of itself is a poor predictor of functional recovery after stroke.

Clinically, age is inversely related to recovery but the impact is small.

3.8 Summary

Impact of Stroke

As the population ages, there will be an increased number of stroke survivors with impairments and disabilities who may benefit from rehabilitation.

Classifying Post-stroke Outcomes

According to ICF, post-stroke outcomes may be measured at any of these levels: body functions/structure (impairment), activities (execution of a task or action by an individual) and participation (involvement in a life situation, formerly referred to as handicap). Activity and participation are affected by environmental and personal factors which are referred to as contextual factors within the ICF. Categories to reflect related post-stroke outcomes are included in the Comprehensive ICF Core Set (130 categories) and Brief ICF Core Set (18 categories).

Defining Recovery and Time Course Post-Stroke

Defining Different Types of Recovery

Recovery can be defined as either neurological or functional. Neurological recovery is a result of brain repair/reorganization. Functional recovery is more multi-functional and more influenced by rehabilitation.

Mechanisms of Neurological Recovery

Reorganization is dependent not only on the lesion site, but also on the surrounding environment, and on remote locations that have structural connections with the injured area.

Time Course of Recovery

Although neurological recovery peaks within the first 1-3 months post-stroke and may continue at a slower pace for a couple of months, functional recovery can continue for sometime after neurological recovery is complete. Recovery occurs more quickly in milder strokes.

Recovery of Specific Functions

For ambulation, upper extremity function and higher cerebral functions such as aphasia and neglect post-stroke, the vast majority of recovery occurs within 12 weeks of even severe strokes. Faster recovery may be related to smaller lesions and less-advanced age.

Maintenance of Stroke Recovery

Although overall function remains relatively stable between 6 months and 3 years after a stroke, differential shifts exist in performance of specific functions (ie. mobility, incontinence, and socialization) following stroke rehabilitation.

Plasticity of the Cortex

Brain capacity is dependent on the number of functional connections and not the number of neurons present. Functional connections develop over a lifetime of genetic programming and experience; functional substitutions after injury requires the development of new connections.

Learning, Experience and Motor Reorganization

In animal studies, complex environments result in a greater number of synapses and an increase in dendritic branching, specific to the area of cortex being stimulated.

In animal studies, motor learning results in changes to the motor cortex, which are specific to the area of cortex involved. Lack of training can result in further reduction of cortical representations. Repetitive unskilled movements that do not require motor learning do not result in motor cortex changes. Experience results in significant brain reorganization improving motor performance and also increasing future learning potential.

Clinical research has demonstrated that learning and experience results in an expansion of cortical representation. Repetitive practice of a known task also leads to an expansion of cortical representation while failure to maintain training results in a contraction of cortical representation.

Somatosensory Reorganization and Stimulation

In animals, somatosensory cortical maps can be altered by changing the afferent input to the brain. The corollary of 'use it or lose it' in the motor system is 'stimulate it or lose it' in the somatosensory system of the brain. Post-stroke, reorganization of sensory representation occurs within intact neural tissue.

Clinically, cerebral damage results in dissociation between the detection and the localization of tactile stimuli. After stroke, tactile inputs are not merely redirected to intact neural tissue, but are instead reorganized within available neural substrate. Prolonged peripheral nerve stimulation changes the motor cortical representations, indicating sensory stimulation may be able to facilitate motor recovery.

Mechanisms of Reorganization Post Stroke

Reorganization of the Affected Hemisphere Post-Stroke

In humans, following stroke recovery, motor activity in the affected hand results in recruitment of cortical areas along the infarct rim, secondary motor areas in the contralateral hemisphere and ipsilateral hemisphere motor areas. The predominant pattern seen is increased activation of secondary (surrounding) cortical regions of the affected hemisphere.

In animals, cortical reorganization is dependent not only on the lesion site, but also on the surrounding cortex where increased axonal sprouting and synapses occur post-stroke and are associated with recovery. Reorganization is dependent not only on the lesion site, but also on remote locations that have structural connections with the injured area. The greater the damage to the primary cortical area, the greater the plasticity seen in intact secondary cortical areas. However, for such reorganization to take place, the secondary cortical area must have structural connections with the area damaged by the stroke.

Clinically, motor recovery involves primarily the affected hemisphere's contralateral pathways rather than the unaffected hemisphere's pathways being indicative of recovery potential. Axonal sprouting and subsequent synaptogenesis appears to be associated with recovery.

The Role of Ipsilateral Pathways in Stroke Recovery

Animal studies show that recruitment of ipsilateral (unaffected hemisphere) pathways occurs with increasing infarct size. It may be that ipsilateral pathways work by developing new pathways to the contralateral (affected hemisphere) red nucleus.

Clinical studies show that ipsilateral motor pathways from the intact hemisphere contribute to motor recovery, most often in more severe strokes with poor functional recovery. There may be competition between contralateral and ipsilateral connections, with ipsilateral pathways becoming more prominent when functional contralateral (affected hemisphere) pathways cannot recover.

Aphasia

Aphasia recovery is associated with bilateral hemisphere activation. Right hemispheric activation alone is associated with a worse outcome indicating the need for the left hemisphere in recovery with one study suggesting a special role for the left temporal lobe.

Influence of Rehabilitation on Post Stroke Reorganization

Training and Cortical Representation

The Role of Intensity of Therapy

More intensive training of the motor cortex, i.e. constraint-induced movement therapy, further increases cortical representation. In animals, at least for smaller strokes, more is better when it comes to the impact of rehabilitation therapies on stroke recovery.

In humans, greater intensity of stroke rehabilitation therapies is generally associated with improved outcomes and maintenance or expansion of cortical representation. The greater the time exposure to various therapies, the better the outcomes, although there is a tendency towards diminishing returns. In other words, doubling therapy times will result in superior outcomes although it will not necessarily result in a doubling in functional improvements. 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.

Reorganization After Stroke: Other Factors Influencing Recovery

Effect of Time on Brain Activation Post-Stroke

Animal studies have shown that rehabilitation initiated very early post-stroke may have a detrimental effect on outcomes although study conclusions on this matter have been inconsistent. The damaging effect of early overuse in animals is thought to be mediated by the neurotransmitter glutamate excessively stimulating the NMDA-receptor. This issue has not been studied in humans.

In animal studies, early therapy results in increased cortical reorganization. The longer the delay, the lesser the impact of therapy. Enriched rehabilitation post-stroke has a positive impact on recovery. Efficacy of enriched rehabilitation decreases proportionally to the time post-stroke when it is provided. In rats there is a significant impact when enriched rehabilitation is delivered within the first week; however, there is little impact if initiated at one month post-stroke. This suggests that there is a window of time when the brain is “primed” for maximal response to rehabilitation training and therapies.

Clinical studies have indicated that there is an association between earlier admission to rehabilitation and better outcomes which correlates with our understanding of brain recovery/plasticity. An optimal window when rehabilitation therapies should be initiated has yet to be determined.

Clinically, there is strong evidence that rehabilitation, provided in the subacute phase, improves functional outcomes.

Size of Lesion Influences Recovery

Animals with small strokes will experience functional and structural recovery occurring spontaneously (without rehabilitation therapy) for weeks to months post-stroke. The underlying neural changes appear to be related to remaining surrounding brain regions taking over the lost function. Animals with larger lesions show much less return of function and what function that does return may take weeks or months to stabilize. Compensatory movements play an important role here with activation and reorganization occurring in more distant cortical areas.

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In humans, age has a small but significant effect on the speed and completeness of recovery. However, because older stroke patients do recover, albeit at a slower rate, and the overall impact of age is relatively small, age in and of itself is a poor predictor of functional recovery after stroke.

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