3
Background Concepts in Stroke Rehabilitation

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Abstract

Evidence shows 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, although recovery of stroke-related impairments is still possible even years later. Stroke recovery is influenced by a variety of intrinsic and extrinsic factors that influence the likelihood and degree of neurological reorganization. The effects of early initiated rehabilitation, increased therapy intensity, and enriched environments on stroke recovery are of particular interest.

Key Points

- Neurological recovery refers to the intrinsic recovery of impairment.
- Functional recovery refers to regaining independence in activities of daily living.
- Neurological recovery can be divided into early local processes and later reorganization.
- Neurological recovery peaks within the first three months of stroke, while functional recovery can continue for a longer period of time.
- Functional recovery primarily occurs within 3 months and may be influenced by age and lesion size.
- Functional recovery can continue between 6 months to 3 years post stroke.
- Brain capacity is dependent on the number of functional connections (i.e. synapses).
- Learning and experience may result in an expansion of cortical representation.
- Sensory stimulation may facilitate motor recovery.
- Stroke recovery is primarily associated with brain plasticity in the adjacent cortex.
- Motor recovery is primarily associated with brain plasticity involving pathways of the affected hemisphere.
- Ipsilateral motor pathways involving the unaffected hemisphere are recruited when infarcts are so large that the affected hemisphere cannot recover.
- Aphasia recovery is associated with bilateral hemispheric activation.
- More intensive rehabilitation therapies may result in improved functional outcomes.
- Earlier rehabilitation therapy may result in improved functional outcomes.
- Greater lesion volume may be associated with poorer outcomes.
- It is unclear whether and to what extent age impacts stroke recovery.

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3.1 Impact of Stroke

Stroke is a common life-altering event that often has a dramatic effect on stroke survivors, their families, health care resources, and society in general. In Canada, approximately 62,000 individuals suffer a stroke annually and about 405,000 are currently living with the consequences of a stroke. Moreover, with an aging population and improved acute care it is anticipated that this number will increase by 80% over the next two decades. Caregivers also experience an increase in physical demands (Sit et al. 2004; Wikstrom et al. 2000) along with a decrease in health-related quality of life (Godwin et al. 2013) and a greater risk of psychological distress (Simon et al. 2009).

3.2 Classifying Outcomes Post Stroke

The WHO International Classification of Functioning, Disability and Health (ICF) (WHO 2001) provides a multi-dimensional framework which was revised from the previous classification. The ICF framework (2001) identifies three primary levels of human functioning: the body or body part, the whole person, and the whole person in relation to their social context.

Outcomes may be measured at any of these three levels: **body functions/structure** (impairment), **activity** (formerly referred to as disability), **participation** (formerly referred to as handicap). Activity and participation are affected by **environmental** and **personal** factors (formerly referred to as contextual factors). The ICF terms are described in Table 3.2.1 and illustrated in Figure 3.2.1.

Table 3.2.1 ICF Terms and Descriptions

ICF Term	Descriptions	Examples
Body Functions	Physiological functions of body systems (including psychological functions)	Conscious functions Orientation functions Muscle power functions 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 extremities
Activity	Execution of a task or action by an individual Limitations are difficulties an individual may have in executing activities	Walking Speaking Eating Washing Dressing Toileting
Participation	Involvement in life situation	Driving Return to work
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	Age Gender Ethnicity Lifestyle Education Occupation Socioeconomic status

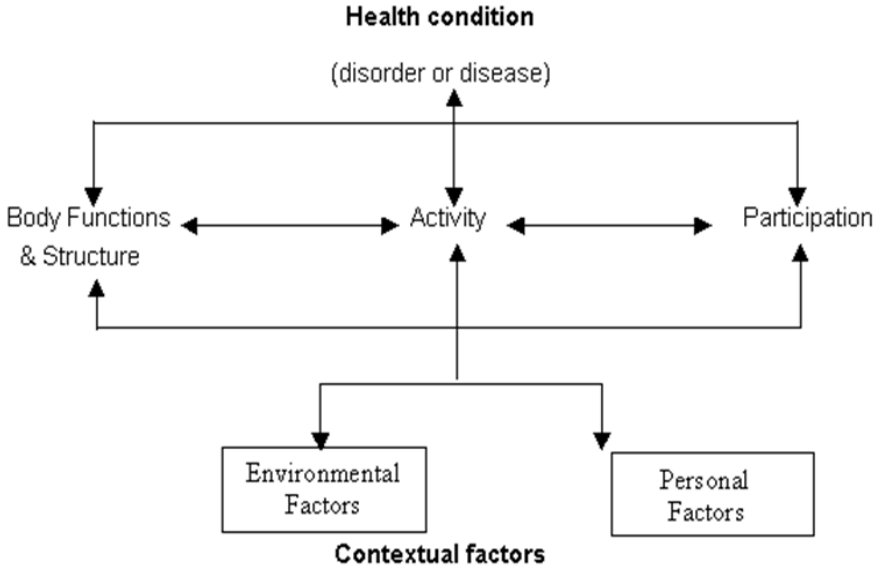

Figure 3.2.1 Classifying Outcomes Post Stroke

The ICF Core Set for stroke includes a comprehensive list of components including body functions, body structures, activities, participation, and environmental factors. 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. These domains account for the most fundamental aspects of stroke-related functioning (see Table 3.2.2). 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.

Table 3.2.2 ICF Core Sets for Stroke

Category	Comprehensive Set	Brief Set
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. Almost all spontaneous recovery occurs during the first three to six months post 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 at final assessment, either two or three years after stroke. The majority of recovery was reported within the first six months, with continued but non-statistically significant recovery after six months.

Recovery post stroke has been best studied with motor recovery. Spontaneous recovery as defined by measuring motor impairment has been found to resolve by fixed proportion. For instance, within six months of stroke, motor recovery of the upper extremity occurs by fixed proportion. Approximately 70% of each patient's maximum possible improvement occurs regardless of the initial impairment (Fugl-Meyer score), but only for those with relatively intact corticospinal (motor) tract function (Prabhakaran et al. 2008). Fixed proportionality has been shown to hold true for patients across all ages and countries with different rehabilitation services (Byblow et al. 2015).

Irreversible structural damage to the corticospinal tract severely limits recovery of the upper limb movement (Stinear et al. 2012; Stinear et al. 2007). Proportional resolution of upper extremity motor impairment post stroke is associated with recovery outcomes (Stinear 2010). This spontaneous recovery of impairment is minimally affected by rehabilitation therapy. Krakauer et al. (2012) has speculated that low therapy intensity may be responsible for rehabilitation not influencing spontaneous recovery. 3D kinematics in individuals with subacute and chronic stroke have shown that motor recovery associated with rehabilitation is driven more by adaptive or compensatory learning strategies, which propel brain reorganization. However, most clinical tests only assess a patient's ability to accomplish a certain task or function and do not measure impairment.

Functional or Adaptive Recovery

Functional recovery refers to improvement of independence in areas such as self-care and mobility. Recovery depends on the patient's motivation, learning ability, and family support 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 (ADL).

Conclusions Regarding the Definition of Recovery

Neurological recovery of impairment is a natural, spontaneous, intrinsic process. Functional recovery of independence is influenced by compensatory/adaptive learning strategies (i.e. rehabilitation) and other extrinsic factors (e.g. family support).

Neurological recovery refers to the intrinsic recovery of impairment.

Functional recovery refers to regaining independence in activities of daily living.

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 process plays is not completely understood. Recovery from stroke is often attributed to resolution of edema and return of circulation within the ischemic penumbra (Dombovy 1991).

However, spontaneous recovery can be prolonged well past the resolution period of acute structural changes caused by the stroke, with recovery occurring four to six weeks post stroke (Brodal 1973). Furthermore, clinical trials have indicated that the cerebral cortex undergoes functional and structural reorganization for weeks to months following injury. with compensatory changes extending up to six

months in more severe strokes (Green 2003). Recovery can be grouped into two categories (see Table 3.3.2.1): 1) Local CNS processes (early recovery); and 2) CNS reorganization (later recovery).

Table 3.3.2.1 Mechanisms of Recovery from Stroke (Adapted from Dombovy 1991)

Mechanism	Time Frame of Occurrence
Local CNS Processes	
Resolution of edema	Weeks to months
Resolution of ischemic penumbra	Hours to weeks
Resolution of remote diaschisis	Days to months
CNS Reorganization	
Neurotransmitter alterations	Weeks to years
Unmasking of pathways	Immediate to months
Synaptogenesis	Weeks to months

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 eight 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 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 that eventually infarcts (Astrup et al. 1981; Lyden & Zivin 2000). It is surrounded by a region of moderate blood flow, known as the ischemic penumbra (Astrup et al. 1981; Lyden & Zivin 2000), which is at risk of infarction but still salvageable. Reperfusion of this area causes previously non-functioning neurons to resume functioning with subsequent clinical improvement.

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 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 non-cortical structures after cortical injury (Lo 1986).

CNS Reorganization (Later Recovery)
Neurological reorganization plays an important role in the restoration of function which is a combination of spontaneous recovery, improvement of impairment, and relearning through rehabilitation. 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 as it can be influenced by rehabilitation training. Based on animal research, Nudo (2003a) suggested that changes occurring during motor learning (e.g. synaptogenesis) are likely the same type of changes that occur during later recovery from stroke. This relationship has been well shown following 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) also reported that neuroplasticity post stroke is based on three main concepts (with the motor cortex as an example): 1) In 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 in the undamaged cortex. Neuroplasticity or cortical reorganization is an important underlying rationale for rehabilitation and a major neurophysiological underpinning of neurological recovery post stroke.

Conclusions Regarding the Mechanism of Neurological Recovery

Local processes of neurological recovery occur early on and include resolution of edema, resolution of diaschisis, and reperfusion of the penumbral region.

Cortical reorganization occurs later in the neurological recovery process. It is dependent on not only the lesion site but on the surrounding environment and remote locations that have structural connections with the injured area.

Neurological recovery can be divided into early local processes and later reorganization.

3.3.3 Time Course of Recovery

Peak neurological recovery from stroke occurs within the first three months. A number of studies have shown that recovery may continue at a slower pace for at least six months. Up to 5% of patients continue to recover for up to one year, which is especially true for patients who are severely disabled at the time of initial examination (Bonita & Beaglehole 1988; Duncan et al. 1992; Ferrucci et al. 1993; Kelly-Hayes et al. 1989; Wade et al. 1983; Wade et al. 1987). 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 ataxia, apraxia, sensory deficits, communication disorders, and cognitive impairment. Functional improvements may occur in the absence of neurological recovery and may continue for months after neurological recovery is complete (Duncan & Sue Min 1997; Nakayama et al. 1994).

In the Copenhagen Stroke Study, Jorgensen et al. (1995; 1995) studied 1,197 acute patients from a large community-based population consecutively admitted to a 63-bed stroke unit. Neurological impairment was classified using the Scandinavian 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 a group, 95% of all patients reached their best neurological level within an average of 11 weeks. For patients with mild stroke, 95% reached their maximal neurological recovery within six weeks; 95% of those with moderate, severe, and very severe strokes achieved their maximal recovery within 10, 15, and 13 weeks respectively.

Neurological recovery occurred on average two weeks earlier than functional recovery. 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. 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. (1995; 1995) also noted that two-thirds of all stroke survivors have mild to moderate strokes and are able to achieve independence in ADL. The findings of the Copenhagen Stroke Study are summarized in tables 3.3.3.1 and 3.3.3.2.

Table 3.3.3.1 Impairment and Recovery of 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 (45-58)	41%	78%	97	2.5	6.5 (5.4-7.6)

[1] Percentage of patient distribution on admission, grouped by stroke severity subgroups, as measured by SSS
[2] Percentage of survivors (79% of initial group) after completion of stroke rehabilitation
[3] Neurological recovery as measured by SSS

Table 3.3.3.2 Disability and Outcome of 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)
None (100)	46%			

[1] Percentage of patients upon discharge, grouped by stroke severity subgroups, as measured by BI
[2] Functional recovery as measured by BI

Based on observations of the Copenhagen Stroke Study, it can be concluded that the initial severity of stroke is inversely proportional to the final functional outcome, with the majority of patients who suffer mild strokes demonstrating only mild or no disabilities, while the majority of patients who suffer very severe strokes experience severe or very severe deficits even upon completion of rehabilitation.

Conclusions Regarding the Time Course of Recovery

Neurological recovery peaks within the first three months post stroke and may continue at a slower pace in the following months. Functional recovery can continue for an extended period time after the completion of neurological recovery. Overall, recovery is generally greater and quicker in milder strokes.

Neurological recovery peaks within the first three months of stroke, while functional recovery can continue for a longer period of time.

3.3.4 Recovery of Specific Functions

In a longitudinal study by Hier et al. (1983), arm and leg weakness recovered in approximately 40% of patients by week 16, sensory extinction in 80% by week 46, hemianopsia in 65% by week 33, unilateral spatial neglect 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: a) younger age; b) parenchymatous hemorrhage; and c) lesion size less than 6% of the right hemisphere volume.

a) Ambulation

Dobkin (1997) performed an analysis of 800 patients from the Copenhagen Stroke Study (Jorgensen, Nakayama, Raaschou, Vive-Larsen, et al. 1995). At baseline, 51% were unable to walk, 12% walked with assistance, and 37% were independent ambulators. At discharge, 22% were unable to walk, 14% walked with assistance, and 64% 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

In another analysis of the Copenhagen Stroke Study (Nakayama et al. 1994), Dobkin (1997) noted that a that the best upper extremity function was achieved by 95% of patients within 9 weeks, as assessed by the Barthel Index sub-scores for grooming and feeding. Patients with mild paresis showed improvement by 6 weeks, while 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. Patients who could flex and extend affected fingers and wrist by three months showed improvement for more than a year in specifically practiced tasks. These findings, and those from other studies, suggest that arm and hand function for most patients tends to improve for up to 12 weeks (Dobkin 1997).

Dobkin (1997) also analyzed the Framingham Study, a community-based study of 680 patients with acute stroke. At baseline, hemiparesis was found in 88% of patients, with equal amounts in each category of severity: mild, moderate, and severe). At 1 month, 26% had no impairment and 39% were graded as mild. Motor impairment at 6 months was rated as non-existent for 39%, mild for 36%, moderate for 10%, and severe for 14%. In fact, patients presenting with a mild motor impairment were ten times more likely to achieve full recovery than those with severe impairment.

c) Higher Cerebral Functions

According to Dobkin (1997), approximately 35% of patients with acute stroke will be admitted to an acute hospital with aphasia and approximately 18% will still have aphasia upon discharge from rehabilitation (Pedersen et al. 1995; Wade et al. 1986). 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 Regarding the Recovery of Specific Functions

> ***The vast majority of recovery for ambulation, upper extremity function, and higher cerebral functions occurs within 12 weeks.***

Faster recovery may be influenced by younger age, smaller lesions, and parenchymatous hemorrhages.

Functional recovery primarily occurs within three months and may be influenced by age and lesion size.

3.3.5 Maintenance of Stroke Recovery

Functional status remains relatively stable once it plateaus (Stineman & Granger 1991). Between six months and three 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 comorbidity (Stineman & 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; Lehmann et al. 1975). However, ADL tend to decline, which has been related to caregivers providing increasing assistance once patients are discharged home. Socialization within and outside of the home, as well as leisure activities decline significantly; decreased socialization extends beyond the effects of the physical deficits.

In a study of 100 patients with mild to moderate strokes, the most dramatic recovery of ADL function occurred within the first 30 days post stroke (Duncan & Sue Min 1997). 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. Thus the authors postulated that stroke patients might achieve independence in basic ADL in the presence of significant residual motor impairment (Duncan & Sue Min 1997).

Conclusions Regarding the Maintenance of Stroke Recovery

Overall function remains relatively stable between six months and three years post stroke. However, differential shifts exist in performance of specific functions (e.g. mobility, socialization) following stroke rehabilitation.

Functional recovery can continue between six months to three years post stroke.

3.4 Plasticity of the Cortex

3.4.1 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), it 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). The authors 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. 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 Regarding Functional Connections

Brain capacity is dependent on the number of functional connections, and not the number of neurons.

Functional connections develop over a lifetime of genetic programming. Functional substitutions post stroke 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; the premotor cortex; the supplementary motor area; and the cingulated motor areas (Frost et al. 2003). With the use of functional MRI (fMRI), 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.

Enriched Environments

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. 1964; Diamond et al. 1967; Globus et al. 1973; Rosenzweig et al. 1962; Turner & Greenough 1985; Volkmar & Greenough 1972; West & 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), whereas long-term changes include an increase in dendritic arborization, spine density, axonal sprouting, and the number of synapses per neuron (Calverley & Jones 1990; Jones et al. 1997; Turner & Greenough 1985; Withers & Greenough 1989). Researchers have since discovered that motor learning results in morphologic changes to the motor cortex (Bennett et al. 1964; Diamond et al. 1964; Kleim et al. 1996; Turner & Greenough 1985). These modifications are likely due to the availability of greater sensory stimuli and learning experiences, which are in turn expressed as structural changes within the brain.

In a trial by Janssen et al. (2013), patients located in a mixed stroke rehabilitation unit were observed for changes in physical, cognitive, and social activity. Patients who were exposed to an enriched environment were more likely to engage in social activities and less likely to be inactive, alone, or asleep than patients without enrichment. This preliminary trial suggests that the comprehensive model of enrichment developed for use in a rehabilitation unit was effective in increasing activity in stroke patients.

Motor Learning

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, Wise, et al. 1996; Pascual-Leone et al. 1995). However, repetitive unskilled movements that do not require motor learning will not produce cortical changes (Kleim et al. 1998; Plautz et al. 2000). The increase in synapses per neuron associated with motor learning appears to be specific to the cortical area being stimulated (Kolb 1995; Turner & Greenough 1985; Withers & Greenough 1989). Thus brain reorganization with training may generalize to new but related tasks (Turkstra et al. 2003), while failure to maintain training will result in a contraction of cortical representation (Castro-Alamancos & Borrel 1995; Nudo, Milliken, et al. 1996).

Similar to 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). 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 (Grafton et al. 1992). Similarly, subjects 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 versus 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 with chronic, stable motor deficits post stroke to improve their motor functioning after specialized intensive training (Lehmann et al. 1975; Tangeman et al. 1990; Taub et al. 1993; Werner & Kessler 1996; Wolf et al. 1989), with the amount of improvement correlated to the intensity of rehabilitation (Langhorne et al. 1996; Nugent et al. 1994; Smith et al. 1981). Cortical mapping has demonstrated changes in the organization of the cerebral cortex associated with learning motor tasks in the intact brain (Nudo, Milliken, et al. 1996; Pascual-Leone et al. 1994) as well as in the injured brain (Nudo, Milliken, et al. 1996).

Impact of Experience

Similar to animals, experience can yield 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 their unskilled hand. Similarly, the cortical finger representations of the left hand in string instrument players were larger than untrained players, when compared to the cortical space represented by the right-hand fingers (Elbert et al. 2001). It was also noted that the degree of change was proportional to the age when musical training began. However, even when training began in adulthood, the representation of the relevant fingers was still larger in trained than untrained players (Elbert et al. 2001; Kolb 2003).

Repetitive practice of a known task results in changes to 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 (TMS) 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. Likewise, lack of movement of a specific muscle can 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 can cause a decrease in the affected tibialis anterior motor cortical area compared to the area of the unaffected tibialis anterior, which occurs without changes to the spinal excitability or motor threshold (Liepert et al. 1995). Therefore, it can be surmised that repetitive training yields an expansion of cortical regions subserving the motor function, while failure to maintain training results in a contraction of cortical representation.

Conclusions Regarding Learning, Experience, and Motor Reorganization

Learning and experience can yield an expansion of cortical representation, which may be enhanced by enriched and complex environments.

Repetitive practice of a known task leads to an expansion of cortical representation, while failure to maintain training results in a contraction of cortical representation.

Learning and experience may result in an expansion of cortical representation.

3.4.3 Somatosensory Reorganization and Stimulation

Somatosensory Reorganization

In terms of somatosensory changes post stroke, reorganization has been observed in cortical topography and neuronal receptive fields in various animals (Coq & Xerri 1999; Doetsch et al. 1990; Jenkins & Merzenich 1987; Pons et al. 1988). 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 & Xerri 1999) and days (Doetsch et al. 1990; Jenkins & Merzenich 1987) of the focal cortical injury.

Clinical studies have shown that somatosensory reorganization occurs following a stroke. Wikstrom et al. (2000) examined patients up to 15 days post stroke and again at 3 months, comparing them to healthy controls. Recovery of touch post stroke was paralleled by growth of the P1m somatosensory evoked magnetic field deflection, which may have represented reestablishment of lateral inhibitory functions at the primary somatosensory cortex (Wikstrom et al. 2000). As well, cerebral damage in humans has been correlated with a dissociation between the detection and the localization of tactile stimuli, such that readily detected contralesional stimuli show significantly misperceptions of the locations of the stimuli (Rapp et al. 2002). Post-lesion miss-localization may preserve the relative locations of the pre-lesion topography, resulting in systematically shifted and distorted somatosensory experiences (Rapp et al. 2002). Rapp et al. (2002) suggested that tactile inputs were not merely redirected to intact neural tissue, but were instead reorganized within the remaining neural substrate. This hypothesis is consistent with animal research findings that indicate that remodeling of somatosensory neural substrates subsequent to focal cortical lesions generally preserves the original neural topography.

Sensory Stimulation

In animals, Nudo (2003b) 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." Motor deficits can develop when there is a disruption in sensory input to the motor cortex, and such deficits can last for months (Humprey et al. 1994). The responsiveness of the motor area to a loss of somatosensory stimuli begins to return by four months, although it does not return to its pre-stroke ability (Nudo 2003b). It is suspected that compensatory strategies are adopted (i.e. using other sensory modalities to guide motor behaviour), which reduces the need for somatosensory

guidance (Nudo 2003b). Therefore, motor deficits may not simply be an issue of motor output but may also be due to a sensorimotor disconnection.

In clinical studies, it has been noted that prolonged peripheral nerve stimulation increases excitability of related muscle representations in the motor cortex (Hallett 2002), causing the motor map to change in some instances (Ridding et al. 2000). These findings suggest that sensory stimulation may be a useful rehabilitation tool that can be applied in a number of ways, including passive movements, nerve stimulation, and acupuncture (Hallett 2002).

Conclusions Regarding Somatosensory Reorganization and Stimulation

Cerebral damage results in dissociation between the detection and the localization of tactile stimuli.

Tactile inputs are not simply redirected to intact neural tissue post stroke, 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.

Sensory stimulation may facilitate motor recovery.

3.5 Mechanisms of Reorganization Post Stroke

3.5.1 Reorganization of the Affected Hemisphere

Numerous theories and hypotheses have been proposed 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. fMRI, PET, and TMS have all been used to assess motor activation after stroke (Thirumala et al. 2002).

Reorganization in Adjacent Brain Tissue

Animal research has shown evidence that structural changes occur in the uninjured cortical tissue surrounding the stroke. When damage occurs to a portion of the cortex, much of the surrounding undamaged cortex will nevertheless be impacted due to the loss of intracortical projections with the area of injury (Nudo 2003a). Remote areas of the brain that have some connection to the damaged brain region may be impacted as well. Nudo (2003a) 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". Therefore, a process of brain reorganization can be anticipated in the area adjacent to and connected to the damaged area.

In healthy right-handed persons, Cramer (2003) noted that *"performance of a unilateral motor task by the right hand is associated with activation that is largely contralateral…In contrast, there is greater ipsilateral activation for movements by the left hand."* Following a stroke, Cramer (2003) noted that movement of the affected hand resulted in three patterns of cortical reorganization that were not mutually exclusive of each other and may occur concomitantly:

1. Greater degree of bilateral motor cortex activity, with recruitment of the motor network of the ipsilateral (unaffected) hemisphere.
2. Increased recruitment of secondary cortical areas in the contralateral (affected) hemisphere.
3. Recruitment along the cortical rim of the infarct.

The predominate pattern of reorganization, which correlates with therapy-related improvements in upper extremity movements, involves increased fMRI activity in the premotor cortex, supplementary motor area, and secondary somatosensory cortex contralateral to the affected limbs (Johansen-Berg et al. 2002). Similarly, the area of cortical representation of the affected hand increased dramatically with the use of constraint-induced movement therapy (Liepert et al. 2000). 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 an anterior (Weiller et al. 1993) or posterior (Cramer & Bastings 2000; Pineiro et al. 2001; Rossini et al. 1998) shift in the site of activation within the stroke-affected hemisphere.

Plastic Changes in the Penumbra

Frost et al. (2003) 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." These principles imply that some form of connection to the damaged motor area is required for functional reorganization. Larger strokes, which damage primary and secondary motor areas, severely limit the capacity for compensatory reorganization. Thus, greater the damage to reciprocal intracortical pathways is associated with greater the plasticity in secondary intact areas.

Plastic changes in the damaged hemisphere are associated with the best recovery (Hallett 2001). 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." The 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). More recent definitions focus on the potential for rescuing this tissue, which is at risk of infarction using appropriate therapy (Heiss & Graf 1994). According to Read et al. (1998), multiple regions of the brain, especially the peri-infarct area, may play a large role in cortical reorganization and functional recovery after stroke. As such, it is important to determine the extent of the penumbra, how long it persists after stroke, and its salvageability at various time points.

Conclusions Regarding Clinical Studies on Reorganization of the Affected Hemisphere

Motor recovery primarily involves the contralateral pathways of the affected hemisphere rather than the unaffected hemisphere; involvement of adjacent hemispheric regions is indicative of recovery potential.

The predominant pattern in cortical reorganization is increased activation of secondary (surrounding) cortical regions of the affected hemisphere. Axonal sprouting and subsequent synaptogenesis may be associated with recovery.

Stroke recovery is primarily associated with brain plasticity in the adjacent cortex.

Motor recovery is primarily associated with brain plasticity involving pathways of the affected hemisphere.

3.5.2 Role of Ipsilateral Pathways

Animal research has shown that the amount of dendritic growth in the undamaged motor cortex is associated with both the size of the lesion and the distribution of the injury (Biernaskie et al. 2004). Damage to the primary motor cortex leads to compensatory recruitment of the ipsilateral undamaged hemisphere, involving the sensorimotor cortex and premotor area (Feydy et al. 2002; Schallert et al. 2003; Stepniewska et al. 1993). As the size of the damage increases, reorganization in the surrounding affected cortex may no longer be possible, resulting in continued activation of the unaffected hemisphere (Biernaskie et al. 2004).

In clinical research, functional neuroimaging has been influential in suggesting that ipsilateral pathways may be involved in post-stroke recovery. Several studies have demonstrated changes in activation patterns during movement of the affected limb in both the affected and unaffected motor cortex (Cao et al. 1998; Chollet et al. 1991; Cramer et al. 1997; Cuadrado et al. 1999; Feydy et al. 2002; Honda et al. 1997; Johansen-Berg et al. 2002; Kopp et al. 1999; Weiller et al. 1993). Ipsilateral motor evoked potentials (MEP) 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). Compared to contralateral MEP, ipsilateral MEP are associated with poorer functional recovery. Therefore, ipsilateral pathways appear to be inadequate for motor recovery alone, and play a role only when the contralateral pathway is too damaged to be activated.

Conclusions Regarding Ipsilateral Pathways

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 pathways cannot recover.

Ipsilateral motor pathways involving the unaffected hemisphere are recruited when infarcts are so large that the affected hemisphere cannot recover.

3.5.3 Recovery from Aphasia

Functional neuroimaging has also been utilized to explore recovery in patients with aphasia. Although there is predominance of the left hemisphere over the right in language functions, language recovery depends on the restitution of a speech-relevant network that involves both hemispheres (Kuest & Karbe 2002). Cao et al. (1999) found that language recovery was associated with bilateral activation in five patients and right hemispheric activation in two patients, but the former was associated with better recovery than the latter. Similarly, Weiller et al. (1995) and Buckner et al. (1996) reported an increased degree of right hemisphere activation when compared to controls in Wernicke's and Broca's aphasia. However, Heiss et al. (1999) found that the most efficient language recovery was achieved only when the left temporal area was preserved.

Conclusions Regarding Recovery from Aphasia

Aphasia recovery is associated with bilateral hemispheric activation. Right hemispheric activation alone may be associated with a worse outcome, suggesting the need for the left hemisphere in the recovery process.

Aphasia recovery is associated with bilateral hemispheric activation.

3.6 Influence of Rehabilitation on Post-Stroke Reorganization

3.6.1 Intensity of Therapy

Improved post-stroke recovery may be achieved with increased intensity of rehabilitation, which can be defined as greater duration, frequency, and/or exertion of therapy. Several meta-analyses have shown that greater therapy intensity is a strong predictor of overall functional improvement (Cooke et al. 2010; Galvin et al. 2008; Kwakkel 2006; Kwakkel et al. 2004; Lohse et al. 2014; Veerbeek et al. 2011; Veerbeek et al. 2014). Therapies examined in the meta-analyses included physiotherapy, occupational therapy, speech-language therapy, aerobic training, resistance training, and constraint-induced movement therapy. While there have been some notable exceptions, such as the VECTORS, CIRCIT, and ICARE trials (Dromerick et al. 2009; English et al. 2015; Winstein et al. 2016), the dose-response effects of these findings suggest the concept that "more is better" applies to stroke recovery (Gladstone et al. 2002).

One of the challenges with therapeutic intensity is determining the critical threshold needed to obtain a benefit (MacLellan et al. 2011). Research suggests that hundreds of task-specific repetitions may be necessary for optimizing recovery (Lang et al. 2016). Another challenge is providing enough therapy in order to reach a therapeutic threshold. Given limitations of health care systems, the intensity of therapy generally provided during post-stroke rehabilitation is suboptimal (Lang et al. 2009). Incorporation of assistants/volunteers, evening/weekend therapy, group therapy, and technology (e.g. robotic devices, virtual reality) may be required may be necessary to achieve optimal intensity.

Conclusions Regarding Intensity of Therapy

Greater intensity of stroke rehabilitation therapies is generally associated with improved functional outcomes. However, the benefits of therapeutic intensity may not be uniform or proportional.

More intensive rehabilitation therapies may result in improved functional outcomes.

3.6.2 Timing of Therapy

Animal research has demonstrated that the brain has an increased propensity for responding to rehabilitation therapies early after stroke, which is manifested in the reorganization of the adjacent intact cortex (Biernaskie et al. 2004). In early reviews of clinical studies, researchers identified a positive correlation between early rehabilitation and good recovery (Cifu & Stewart 1999; Ottenbacher & Jannell 1993). Several large-scale studies have since reported that early admission to rehabilitation was associated with improved functional outcomes (Maulden et al. 2005; Paolucci et al. 2000; Salter et al. 2006; Wang et al. 2015; Wang et al. 2011; Yagi et al. 2017; Yagura et al. 2003). However, these findings may be misleading, as a variety of confounding factors can result in later admission to rehabilitation (e.g. stroke severity, medical instability, comorbidity index) (Wang et al. 2015; Wang et al. 2011).

Recent efforts in research regarding timing of rehabilitation have focused on very early mobilization (VEM). VEM has been defined as any intervention reducing the time from stroke onset to first out of bed episode and increasing the amount of out-of-bed physical activity post stroke (Bernhardt et al. 2008). While several large-scale trials have reported that VEM improves functional outcomes (Bai et al. 2012; Bai et al. 2014; Chippala & Sharma 2016; Liu et al. 2014; Morreale et al. 2016), a number of smaller trials found it to be no more effective than standard care (Langhorne et al. 2010; Poletto et al. 2015; Sundseth et al. 2012, 2014). AVERT was an international, multicentre trial conducted over an eight-year period, and is the largest-scale trial of VEM to date. Early results of AVERT reported that VEM was a feasible and

effective intervention when compared to standard care (Bernhardt et al. 2008; Cumming et al. 2011; van Wijk et al. 2012). However, the final results found that VEM was associated with greater odds of unfavourable outcome at three months (AVERT Collaboration Group 2015). Additional analysis of these results showed that more frequent and shorter VEM improved the chance of regaining independence, while higher doses of long-term VEM worsened outcomes (Bernhardt et al. 2016).

Conclusions Regarding Timing of Therapy

Earlier admission to rehabilitation is associated with improved functional outcomes. However, additional research is required to examine the effect of potential confounders.

Very early mobilization is associated with improved outcomes when sessions are frequent and shorter, but with poorer outcomes when sessions are prolonged and intensive.

Earlier rehabilitation therapy may result in improved functional outcomes.

3.7 Other Factors Influencing Post-Stroke Reorganization

3.7.1 Effect of Lesion Size on Recovery

Early research suggested that lesion size has an impact on post-stroke outcomes, due to the different mechanisms of neurological recovery. Recovery from smaller lesions involve changes in the remaining intact motor cortex, while larger lesions require changes in other cortical regions to facilitate compensatory behavior (Kolb 1995). In a systematic review of the literature before 2005, Schiemanck et al. (2006) identified 13 studies investigating the impact of lesion volume, as assessed by CT or MRI, on a variety of outcomes in individuals with ischemic stroke. A significant correlation between the two variables was found in 12 of the studies, suggesting that larger volume was associated with poorer outcome. However, the authors noted methodological issues in many of the studies, including: results were not clearly presented; impact of lesion location was not analyzed; and appropriate endpoints were not used. Subsequent studies have investigated the relationship between lesion size and post-stroke recovery, which are summarized in Table 3.7.1.1.

Table 3.7.1.1 Effect of Lesion Size on Recovery

Study	Sample Size	Effect
Vagal et al. (2015)	65	+
Kim et al. (2014)	409	+
Page et al. (2013)	139	x
Vogt et al. (2012)	2538	+
Yoo et al. (2010)	54	+
Barrett et al. (2009)	169	+
Hand et al. (2006)	82	-
Pan et al. (2006)	111	+
Schiemanck et al. (2005)	75	+
Schiemanck et al. (2005)	94	+

Note: + = correlation, - = no correlation, x = conflicting results

Most of the selected studies reported that lesion volume was significantly correlated with or an independent predictor of favourable long-term outcomes, often after adjusting for age, stroke severity, and stroke onset. Patients with smaller strokes scored better on the Modified Rankin Scale (mRS), Barthel Index (BI), and/or National Institutes of Health Stroke Scale (NIHSS) than those with larger

strokes. One study found that lesion volume was associated with upper limb function, but not with outcomes on the Fugl Meyer Assessment (Page et al. 2013). In another study, lesion volume was not a predictor of outcome on the mRS (Hand et al. 2006). However, given the positive findings from the eight studies and the results of the previous systematic review, evidence suggests that lesion volume is negatively correlated with functional outcomes.

Conclusions Regarding the Effect of Lesion Size on Recovery

There is evidence that greater lesion volume is associated with poorer functional outcomes post stroke, after adjusting for age, stroke severity, and stroke onset.

Greater lesion volume may be associated with poorer outcomes.

3.7.2 Effect of Age on Recovery

Animal research has explored a potential biological link between age and stroke recovery. The regenerative response of neurons and glial cells, though largely preserved with age, appears to be delayed or occurs at a diminished rate in older animals (Popa-Wagner et al. 1999; Whittemore et al. 1985): reactive neuronal synaptogenesis declines (Scheff et al. 1978), synaptic replacement rates attenuate (Cotman & Anderson 1988), and sprouting responses are less robust (Schauwecker et al. 1995). However, in the absence of clinical research, it is difficult to determine the impact of age on post-rehabilitation outcomes.

In an early systematic review of the literature up to 1986, Jongbloed et al. (1986) reported that 14 studies found a significant negative correlation between age and outcome, while four studies found no such correlation. Considerable heterogeneity between the studies was noted in terms of patient samples, timing of assessments, and outcome measures. In particular, 12 of the former studies measured function at discharge, while three of the latter studies measured change in function. Subsequent studies have investigated the relationship between age and post-stroke recovery, which are summarized in Table 3.7.2.1.

Table 3.7.2.1 Effect of Age on Recovery

Study	Sample Size	Effect
O'Brien et al. (2016)	71652	+
Radholm et al. (2015)	2839	+
Bentsen et al. (2014)	1437	+
Abanto et al. (2013)	579	+
Knoflach et al. (2012)	14256	+
Denti et al. (2010)	1555	+
Arnold et al. (2008)	1004	-
Saposnik et al. (2008)	26676	+
Luk et al. (2006)	878	x
Black-Schaffer et al. (2004)	979	+
Kugler et al. (2003)	2219	+
Paolucci et al. (2003)	150	+
Bagg et al. (2002)	561	x
Ergeletzis et al. (2002)	223	x
Weimar et al. (2002)	1754	+
Sze et al. (2000)	793	+
Giaquinto et al. (1999)	248	+
Macciocchi et al. (1998)	327	+
Pohjasvaara et al. (1997)	486	+

Alexander et al. (1994)	520	+
Falconer et al. (1994)	260	x
Kalra (1994)	245	+
Nakayama et al. (1994)	515	x
Granger et al. (1992)	7905	+
Heinemann et al. (1987)	163	-

Note: + = correlation, - = no correlation, x = conflicting results

Several of the selected studies reported that age was negatively correlated with favourable outcomes on the Modified Rankin Scale (mRS), Barthel Index (BI), and/or Functional Independence Measure (FIM); some studies found a negative correlation with length of stay and discharge home as well. However, other studies failed to find any association between age and post-stroke outcomes, or reported conflicting results. Old age has been associated with greater rate of comorbidities (Jongbloed 1986), lower quality of care (Luker et al. 2011), and limited tolerance to rehabilitation (Carey et al. 1988). These factors, among many others, could account for a correlation between age and recovery. Conversely, a lack of correlation could be attributed to a ceiling effect of FIM and BI scores in younger patients, who often present with higher scores upon admission (Bagg et al. 2002). In addition, the selected studies showed considerable variation on a number of variables, including division of age groups, use of outcome measures, timing of assessments, and stroke characteristics of patients (i.e. severity, location, size, etiology). Many studies also failed to assess initial neurological impairment and/or report rehabilitation intensity, both of which could influence outcomes. Therefore, given the lack of conclusive evidence, advanced age alone should not be regarded as a limiting factor in providing stroke rehabilitation.

Conclusions Regarding the Effect of Age on Recovery

There is conflicting evidence regarding the impact of age on functional outcomes, length of stay, discharge destination, and mortality post stroke.

It is unclear whether and to what extent age impacts stroke recovery.

Summary

1. ***Neurological recovery of impairment is a natural, spontaneous, intrinsic process. Functional recovery of independence is influenced by compensatory/adaptive learning strategies (i.e. rehabilitation) and other extrinsic factors (e.g. family support).***

2. ***Local processes of neurological recovery occur early on and include resolution of edema, resolution of diaschisis, and reperfusion of the penumbral region.***

3. ***Cortical reorganization occurs later in the neurological recovery process. It is dependent on not only the lesion site but on the surrounding environment and remote locations that have structural connections with the injured area.***

4. ***Neurological recovery peaks within the first three months post stroke and may continue at a slower pace in the following months. Functional recovery can continue for an extended period time after the completion of neurological recovery. Overall, recovery is generally greater and quicker in milder strokes.***

5. ***The vast majority of recovery for ambulation, upper extremity function, and higher cerebral functions occurs within 12 weeks.***

6. ***Faster recovery may be influenced by younger age, smaller lesions, and parenchymatous hemorrhages.***

7. ***Overall function remains relatively stable between six months and three years post stroke. However, differential shifts exist in performance of specific functions (e.g. mobility, socialization) following stroke rehabilitation.***

8. ***Brain capacity is dependent on the number of functional connections, and not the number of neurons.***

9. ***Functional connections develop over a lifetime of genetic programming. Functional substitutions post stroke requires the development of new connections.***

10. ***Learning and experience can yield an expansion of cortical representation, which may be enhanced by enriched and complex environments.***

11. ***Repetitive practice of a known task leads to an expansion of cortical representation, while failure to maintain training results in a contraction of cortical representation.***

12. ***Cerebral damage results in dissociation between the detection and the localization of tactile stimuli.***

13. ***Tactile inputs are not simply redirected to intact neural tissue post stroke, but are instead reorganized within available neural substrate.***

14. ***Prolonged peripheral nerve stimulation changes the motor cortical representations, indicating sensory stimulation may be able to facilitate motor recovery.***

15. ***Motor recovery primarily involves the contralateral pathways of the affected hemisphere rather than the unaffected hemisphere; involvement of adjacent hemispheric regions is indicative of recovery potential.***

16. ***The predominant pattern in cortical reorganization is increased activation of secondary (surrounding) cortical regions of the affected hemisphere. Axonal sprouting and subsequent synaptogenesis may be associated with recovery.***

17. ***Ipsilateral motor pathways from the intact hemisphere contribute to motor recovery, most often in more severe strokes with poor functional recovery.***

18. ***There may be competition between contralateral and ipsilateral connections, with ipsilateral pathways becoming more prominent when functional contralateral pathways cannot recover.***

19. ***Aphasia recovery is associated with bilateral hemispheric activation. Right hemispheric activation alone may be associated with a worse outcome, suggesting the need for the left hemisphere in the recovery process.***

20. ***Greater intensity of stroke rehabilitation therapies is generally associated with improved functional outcomes. However, the benefits of therapeutic intensity may not be uniform or proportional.***

21. ***Earlier admission to rehabilitation is associated with improved functional outcomes. However, additional research is required to examine the effect of potential confounders.***

22. ***Very early mobilization is associated with improved outcomes when sessions are frequent and shorter, but with poorer outcomes when sessions are prolonged and intensive.***

23. ***There is evidence that greater lesion volume is associated with poorer functional outcomes post stroke, after adjusting for age, stroke severity, and stroke onset.***

24. ***There is conflicting evidence regarding the impact of age on functional outcomes, length of stay, discharge destination, and mortality post stroke.***

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