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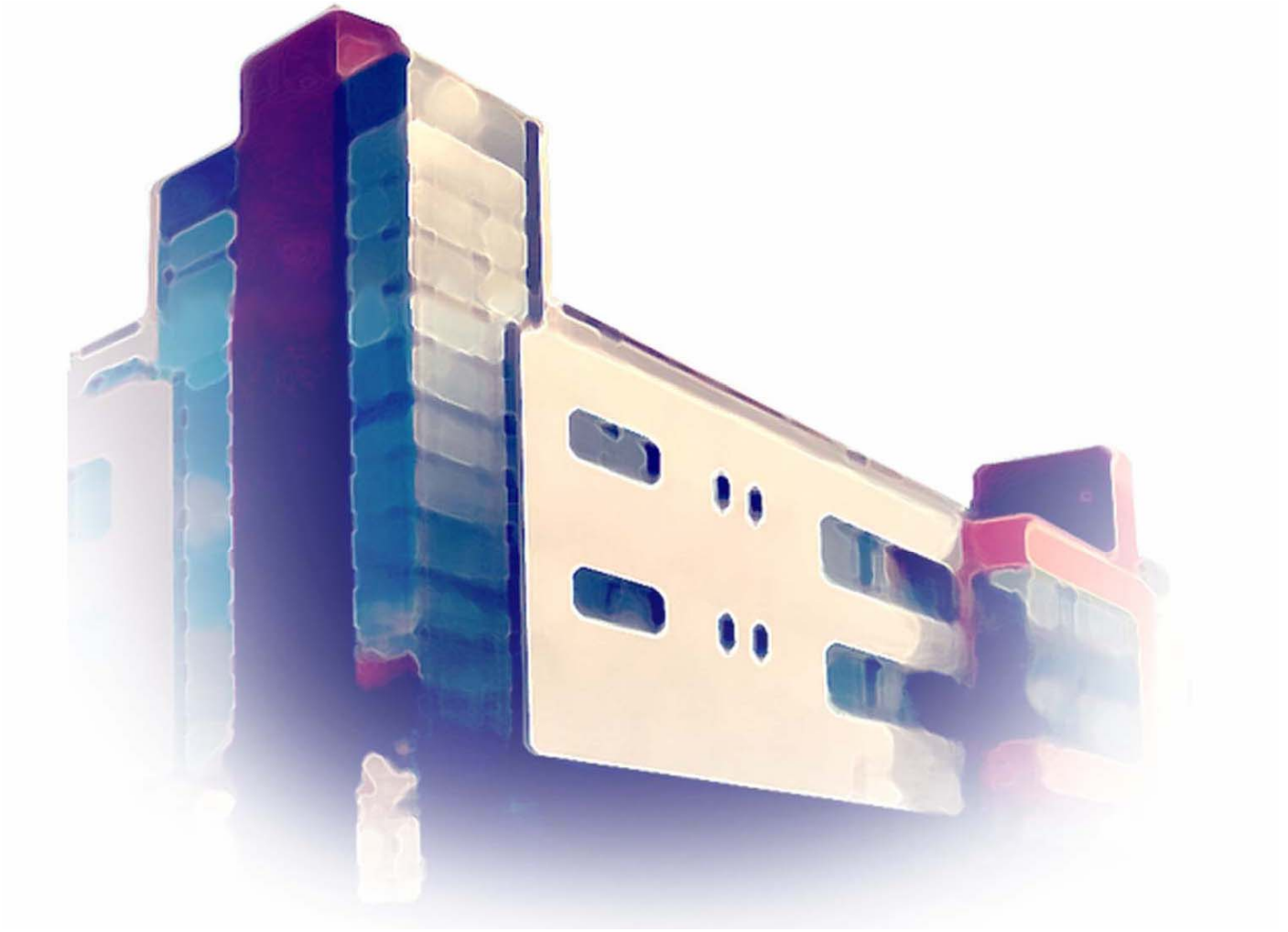

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Plasticity of the adult human brain and motor recovery after stroke

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Abstract

Stroke may cause a major destruction of brain tissue through a loss of blood supply and leads to a functional impairment of the lesioned area. This paper looks at the usefulness of neural networks in providing neuroclinical recovery schemes, with plasticity as seen in the motor cortex following a stroke as the paradigm case. The effects of stroke on the motor cortex of the adult human brain and the possibility of functional recovery through mechanisms of plasticity are reviewed. Plasticity as seen in the uninjured brain, for example during normal motor learning or peripheral deafferentation, provides profound evidence of the mechanisms underlying plastic reorganization and helps to develop an understanding of the neural changes that are involved. Upon this knowledge a definition of the different types of plasticity that come into operation after damage to the motor cortex, such as within-system plasticity, including substitution of parallel pathways, and cross-modal plasticity, is possible. Artificial neural networks that implement these different types of plasticity offer valuable clues on the factors that influence plastic reorganization of the brain. A neural network that has been partly destroyed through lesion strongly depends on guided, targeted input to be able to recover functionally. The evidence that is derived from neural network models then helps to define the factors that influence plasticity. Additionally it aides the development of appropriate neuroclinical recovery schemes for patients affected by a lesion of the motor cortex, such as constraint-induced therapy, leading to a better functional and behavioral outcome after stroke.

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Introduction

The brain is made up of functionally specialized neural networks, which are designed to perform specific tasks individually. Almost always a neural network involved in a specific function is found in the same part of the human brain, as the location is strongly genetically determined. Therefore the brain can be divided into areas like the motor cortex, sensory cortex or visual cortex, brain regions that are anatomically and functionally identical across human brains.

However, if these regions or networks within these regions are partly damaged or even completely destroyed, as can occur after stroke, the specific function they were involved in will be impaired or lost. No other part of the brain 'knows' how to perform the task formerly carried out by the damaged neurons. If for example a certain part of the motor cortex is lesioned this may result in the inability to swallow, paralysis of one arm or paralysis of the contralateral side of the body, known as hemiplegia. In particular, skilled use of the hands and the performance of fine tuned movements are often impaired (Hoffman & Strick, 1995).

Fortunately the brain is 'plastic' and able to reorganize itself up to a certain degree of damage. This is especially true for the motor cortex, which can be modified by sensory input, experience and learning, as well as in response to brain lesions. Thus many people can partly or even totally recover after stroke and regain some or most of the lost function after a period of recovery (Hallett, 2001). The degree to which recovery is possible and the time period involved depend strongly on factors like lesion site and lesion size, as well as individual variations in anatomical and functional connections (Chen, Cohen & Hallett, 2002). Another very important factor is the exogenous application of treatment, either through behavioural therapy or pharmacological treatment. These and other factors strongly influence the brains ability of plasticity and functional reorganization (Robertson & Murre, 1999).

Studying the modulation of cortical representations in response to activity, behaviour and skill acquisition leads to a deeper understanding of the mechanisms involved in plasticity. As these mechanisms are identical to the mechanisms underlying the functional reorganization of the brain after injury through stroke (Donoghue *et al.*, 1996), a thorough understanding is necessary for developing appropriate treatment to improve functional outcome.

With the help of functional imaging techniques it can be actively examined how the brain may compensate for the injuries caused by stroke (Buckner & Petersen, 2000). These non-invasive methods allow the comparison between activity of the undamaged brain during a specific task and post-stroke neural activity in the brains of recovered stroke patients performing an identical task. Differences in intensity and location of activation offer valuable clues to the

reorganizational processes of the motor cortex during recovery (for example Cao *et al.*, 1994; Rossini *et al.*, 1998; Azari & Seitz, 2000; Ward *et al.* 2003).

A more theoretical approach towards the plasticity processes involved in recovery is modelling these with artificial neural networks. Theoretical models help to gain more knowledge about the influence of various factors on successful recovery of a lesioned neural network. Especially, exogenous influences on plasticity can be tested, with the goal of deriving effective neuroclinical recovery schemes.

Several recovery schemes have been proposed, including movement-therapy (Johansen-Berg *et al.*, 2002) and constraint-induced therapy (Liepert *et al.*, 1998), which lead to improved functional outcome after stroke.

How plastic is the brain when recovering from a lesion to the motor cortex after stroke? Which different types of plasticity can be distinguished and what effects do they have on functional performance? What kinds of factors influence the degree of plasticity and therefore the degree of recovery? How can theoretical and practical experimental findings help to develop successful therapeutic approaches for recovery schemes? These questions will be investigated and tried to be answered in this paper.

The overall goal will be to find out how recovery can be positively influenced by neuroclinical recovery schemes, leading to a better functional outcome after stroke, and evaluate how 'plastic' the brain really is. Finding appropriate recovery schemes requires that the mechanisms underlying plasticity of the brain are understood, different forms of plasticity are defined and factors that influence cortical reorganization are determined. To do so practical approaches such as clinical patient studies and animal experiments will be reviewed, as well as looking at theoretical approaches in form of modelling lesions and recovery processes with artificial neural networks. Viewing such practical and theoretical studies, with plasticity in the motor cortex as the paradigm case, will provide the basis for pursuing the above given goal.

To give an overview, in the first part basic facts about plasticity in the uninjured brain will be introduced. In the second part the motor cortex will be described briefly and additionally brain processes during and immediately after stroke will be explained. The third part will present the different types of plasticity involved in recovery of motor function after stroke, including results of functional imaging studies and animal experiments. The forth part will provide examples for modelling plasticity with artificial neural networks, thereby looking at theoretical approaches that help to gain more knowledge about the mechanisms involved in plasticity and provide a basis for possible recovery-schemes.

I. Plasticity

It was long thought that the brain only changed during development and that the adult brain was fixed in its functional organization, with specific areas allocated to specific functions. Today there is no doubt that the brain is reorganizing itself constantly, for example every time new knowledge is stored or a new motor skill learned. The study of mechanisms underlying brain plasticity during 'normal' learning and reorganization provides a good basis for understanding how functional reorganization of the brain takes place after damage through stroke.

Mechanisms of Plasticity

Plastic changes of the brain, either short-term or long-term changes, can be induced by several mechanisms which have proven to be the basis of functional and anatomical reorganization (Hallett, 2000; Hallett, 2001).

One mechanism is a change in the balance of excitatory and inhibitory connections between differential neural networks. The size of a territory of functional influence can be changed if the inhibition (excitation) that defines the region of anatomical connectivity is unmasked. Additionally, previously present but functionally inactive connections can be unmasked. The change of synaptic efficacy follows Hebbian rules and is one of the fundamental principles of cortical plasticity (Hebb, 1949). Synaptic efficacy and the threshold for activation can be influenced by the temporal structure and synchronisation of impulse arrival and neuronal firing. A study by Jacobs and Donoghue (1991) gives a detailed description of the processes involved in unmasking; these include neurotransmitter release, changes in membrane conductance and increased density of postsynaptic receptors.

A second well studied mechanism is the strengthening or weakening of synapses through long-term potentiation (LTP) and long-term depression (LTD). This process, which is typically involved in acquisition of knowledge and memory formation, relies on specific patterns of synaptic activity that lead to a strengthening of connections between the synapses of neighbouring neurons that fire together. LTP requires NMDA-receptor activation and increased intracellular calcium concentration, and has been demonstrated in the motor cortex (Hess & Donoghue, 1994). Changes in strength can occur very fast and can last between hours and weeks.

A third mechanism of plasticity is the anatomical change through sprouting of new fibres, where the formation of new synapses and the growth of new axon terminals lead to an increase in synaptic density (Kleim *et al.*, 1996). Consequently existing connections are strengthened or new connections are developed, either within one neural network or between different neural networks. This is a slow process taking place over weeks or months, since the growth of new connections takes time.

Peripheral deafferentation One typical condition where short-term plasticity of the motor cortex can be viewed is after deafferentation of a limb. Studies with primates (Donoghue, 1995), as well as transcranial magnetic stimulation studies with patients who have lost one arm (for example Hallett *et al.* 1993) show that the deafferented cortex undergoes reorganizational changes.

These changes in cortical representation reflect a functional output reorganization of the involved neural networks. Mostly the now functionally unused part of the cortex, the territory of the amputated limb, is taken over by the expanding motor cortex of the muscles proximal to the amputation. Therefore a change in cortical representation during the use of proximal muscles leads to the conclusion that a functional reorganization of the motor cortex must have taken place.

A study examining the time needed for motor cortical representations to change and the modulation of motor output to occur has been conducted with reversible deafferentation in humans (Brasil-Neto *et al.*, 1992). A blood pressure cuff above the elbow was used to produce ischemia in the lower part of the arm and hand. Additionally, sensory input was inhibited by regional anaesthesia to produce the overall impression of a deafferented limb. This was determined by the absence of movement, the disappearance of motor evoked potentials (MEP's) from the muscle ipsilateral to the cuff and absence of tactile sensation below the cuff. The amplitudes of the MEP's to magnetic stimulation from muscles proximal to the temporarily deafferented limb were then measured.

The results showed an increase in the amplitudes of the MEP's immediately after onset of anaesthesia, and also a quick return to control values after the blood flow was released and anaesthesia subsided (*Fig 1*). This indicates that the process of reorganization of the motor cortex can be very fast and in this case sets in immediately after the input from the muscles subsides. It also shows that plasticity is reversible and a re-reorganization can occur as soon as the input of the temporarily deafferented cortex returns to normal.

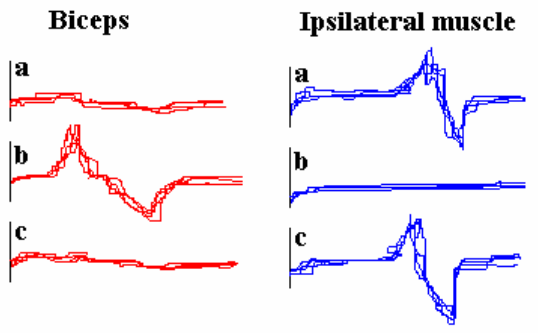


Figure 1: Effect of reversible deafferentation of lower arm on biceps MEP's. MEP's from biceps and ipsilateral muscle before anaesthesia (**a**), during anaesthesia block (**b**) and after anaesthesia (**c**). (Freely adapted from Brasil-Neto *et al*., 1992)

Motor Learning The most common occurrence that induces long-term cortical reorganization is a change in the pattern of behaviour, for example when a new motor skill is acquired. The function of each neuron or network of neurons is determined by the most dominant input it receives and can be altered through certain behaviour.

In order to study motor learning, Pascual-Leone *et al.* (1995) conducted an experiment where the subjects had to learn a skilled task with their hand and therefore practiced a five-finger exercise on a piano for 2h each day. Over a period of five days the motor cortical representation of the hand was observed.

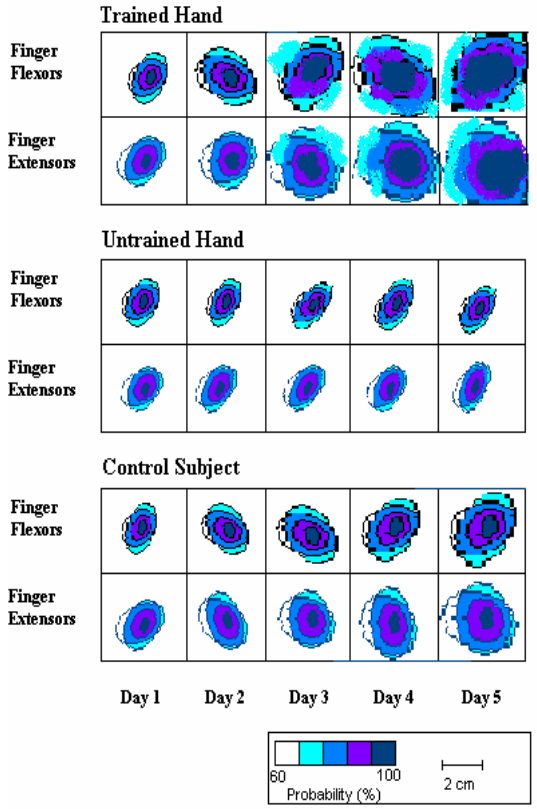


Figure 2: TMS maps, showing the representation of the finger flexor and extensor muscles in the motor cortex; of the trained hand (skilled learning of a five-finger exercise on a piano), untrained hand (contralateral hand of same subject) and control subject (played single notes, but no specific sequence on piano) recorded on five successive days. (Freely adapted from Pascual-Leone *et al.*, 1995)

The results showed a strong correlation between the size of the motor representation and the level of performance. The more skilled the subjects became on the five-finger task, the larger was the size of the corresponding motor representation of the hand (*Fig. 2*). In contrast the motor representation of the untrained hand, in the contralateral hemisphere of the same subject, did not undergo any changes. Compared to the increase in size of the motor representation of the hand of control subjects who played single notes on the piano for 2h each day, but no specific sequence, the increase in size for skilled learning was much larger.

It can be concluded that a certain behavior, like playing the piano for some time, will lead to a change in the motor representation of the used hand. This type of motor learning is called 'adaptation learning' and simply refers to a change in the nature of motor output. An even stronger response of the motor cortex can be seen, if the behavior is not just simple motor output, but a purposeful sequence of actions through which a new motor skill is acquired. This is referred to as 'skilled learning' and implies the development of a new capability.

These two types, adaptation and skilled learning, are two important components of motor learning (Hallett & Grafman, 1997).

Blind Plasticity The so-called blind or cross-modal plasticity is a phenomenon that is often found in blind subjects who read Braille. Sadato *et al.* (1998) studied the brain areas activated during a Braille reading task and found that this task produced consistent activation in the bilateral occipital cortex, including the primary visual areas, in the blind, but not in normal subjects (*Fig. 3*). An experiment they conducted, using repetitive

transcranial magnetic stimulation (rTMS), led to the conclusion that the occipital areas are not only activated casually, but they also are an essential component of the network involved in performing the Braille reading task (Cohen *et al.*, 1999).

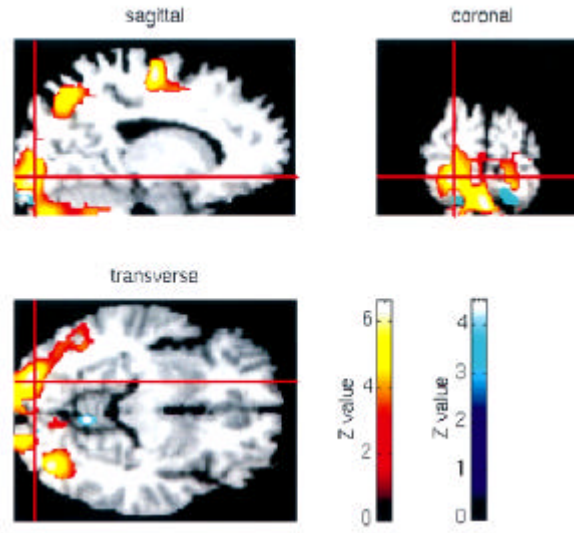


Figure 3: Consistently activated areas during the Braille reading task in blind subjects are shown here. The bilateral occipital cortex, including primary visual areas, is activated in blind but not in normal subjects, indicating a functional reorganization of the visual cortex in the blind. (Reproduced from Sadato *et al.*, 1998)

This result indicates that an unused area of the brain, which is normally reserved for vision, can be stimulated and functionally used by different sensory modalities in the blind. Plasticity of this type, in which a brain area that is normally functionally unrelated to a certain task becomes active and partly or totally takes over the functional representation of this task, is called 'cross-modal plasticity'.

Cohen *et al.* (1999) determined that an important factor of cross-modal plasticity is the age of blindness. In so called 'late blind' subjects (blinded after the age of 14) much less activation of the visual cortex during Braille reading could be detected than in early blind subjects. Thereupon it can be concluded that after a certain amount of time in which the visual cortex has been used for normal vision a reorganisation is only partly possible. Whereas in early blind subjects a more drastic form of cross-modal plasticity can lead to total functional reorganization of the visual cortex.

Summary

The study of plasticity in the uninjured brain sheds light on the mechanisms and possibilities of functional reorganization.

As the above described studies show, either a prevention of input to the motor cortex, as during temporal deafferentation, or an intensification of motor input, as during motor learning and skill acquisition, can both lead to plasticity induced changes in the brain.

These findings suggest that as soon as a change of input occurs, either through behavioural or environmental change, a reorganizational process is initiated in the functionally responsible neural network. Neural networks are strongly input dependent and reorganizations can be as quickly reversed as they originated, if the change of input subsides. This asserts the fact that always the most dominant input determines the function of each neural network, whereby the changes can have short-term or long-term effects.

The example of cross-modal plasticity in the blind shows that not only those parts of the brain that are functionally related, for example

different parts of the motor cortex, are involved in reorganizational changes among each other, but also functionally unrelated brain areas, such as the visual cortex and the sensorymotor cortex, can take over additional tasks which they are normally not connected with.

Accordingly, plasticity can not only occur within the same neural network, but between different neural networks. The pathways usually connected to one network are then re-routed to another network and regions originally reserved for other processes will be functionally invaded. A re-routing of function of this kind is an age dependent process.

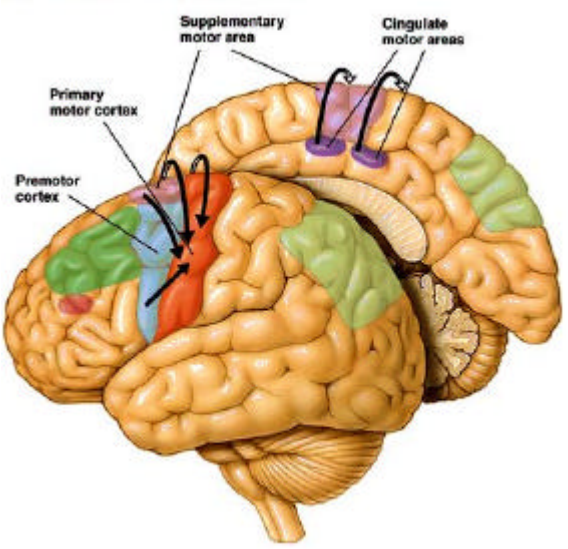
II. Motor Cortex Damage through Stroke

Anatomy of Motor Cortex

The motor cortex is composed of several cortical areas that are reciprocally interconnected (He *et al.*, 1993). Major motor cortical areas are the primary motor cortex (M1) and non-primary areas, including the supplementary motor area (SMA), the premotor area (PMA) and the cingulate motor area (CMA) (*Fig. 4* ***a.)***). Each of these cortical motor areas plays a different role in the control of voluntary movements and since they are interconnected, it is likely that the function of one area will be affected by damage to another area (Luppino & Rizzolatti, 2000).

The motor cortex is easy to identify by the presence of a high density of large pyramidal tract neurons; additionally this area is characterized by a relatively low current threshold for eliciting movements by electrical stimulation.

a.)



b.)

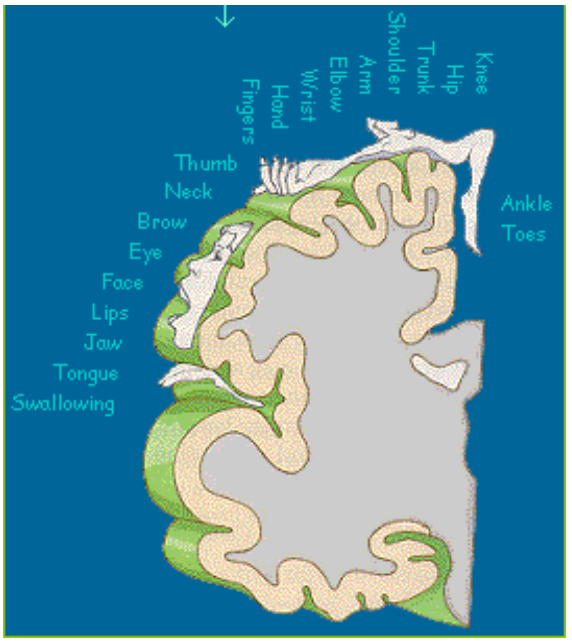


Figure 4: **a.)** Anatomy of the motor cortex showing the locations of the primary motor cortex (M1), the supplementary motor area (SMA), the premotor area (PMA) and the cingulate motor area (CMA). **b.)** The 'motor homunculus' reveals a somatotopic representation of body parts onto the motor cortex.

This was utilised by Penfield and Boldrey (1937) some decades ago to derive maps of the motor cortex using cortical stimulation techniques. Their motor maps created a basis for the somatotopic output organisation of the motor cortex and resembled a body projection, the so called 'motor homunculus' (*Fig. 4* ***b.)***).

Three general functional concepts underlie the 'Penfieldian-scheme': there exists an orderly point-to-point representation of the body parts onto the cortical surface within M1, secondly the M1 motor representations occupy non-overlapping subzones of M1 and thirdly each region occupies a single, separable region of cerebral cortex. It follows that each neural element, consisting of either a single neuron or a group of neurons, is unique and has a single, highly specialized function (*Fig. 5* ***a.)***).

However, today the 'Penfieldian-scheme' and the idea of a static representation pattern within the motor cortex has to be modified, as there is evidence for a highly dynamic and adjustable organization of the primary and non-primary motor cortex. An alternate scheme was presented by Sanes and Donoghue (1997) in form of 'neural networks', which postulates three functional concepts contrary to those of the Penfieldian plan (*Fig. 5* ***b.)***). To begin with they conclude that although major subdivisions exist within motor cortical representations, their internal representation is highly distributed. Secondly the representations of different body parts are said to overlap spatially and temporally. Their third concept assumes the existence of multiple, separable sites for each property of motor cortical functional organization.

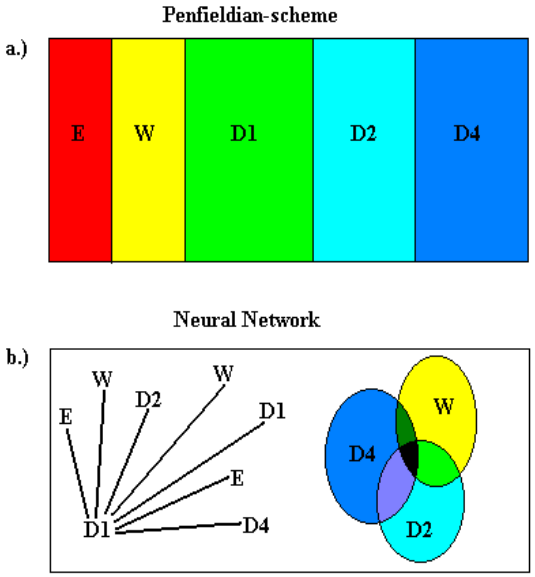


Figure 5: Schematic drawing of motor cortical organization for arm movements (elbow **E**, wrist **W**, digits **D1**, **D2**, **D4**) **a.)** Organization in the 'Penfieldian-scheme' is made up of non-overlapping patches of cerebral cortex, representing movement in a proximal to distal spatial map. **b.)** In the 'Neural Network' intracortical connectivity provides potential coordination of neural elements representing different body parts (left). Multiple neural elements for distal and proximal body parts are distributed throughout the motor cortex and can overlap (right). (Freely adapted from Sanes & Donoghue, 1997)

From this type of arrangement it follows that there is a flexible organization of the motor cortex, with a possible reuse of the neural elements which compose each cortical module. This is advantageous for functional plasticity, as co-operating areas may substitute for a related dysfunctional area. This overlap and flexibility in anatomic organization of motor maps may contribute to the ability of the system to reorganize functionally after injury

and provides the basis for recovery of motor function after stroke.

The recovery after cortical injury through stroke involves an interplay of acute and chronic processes which will be described in the next part.

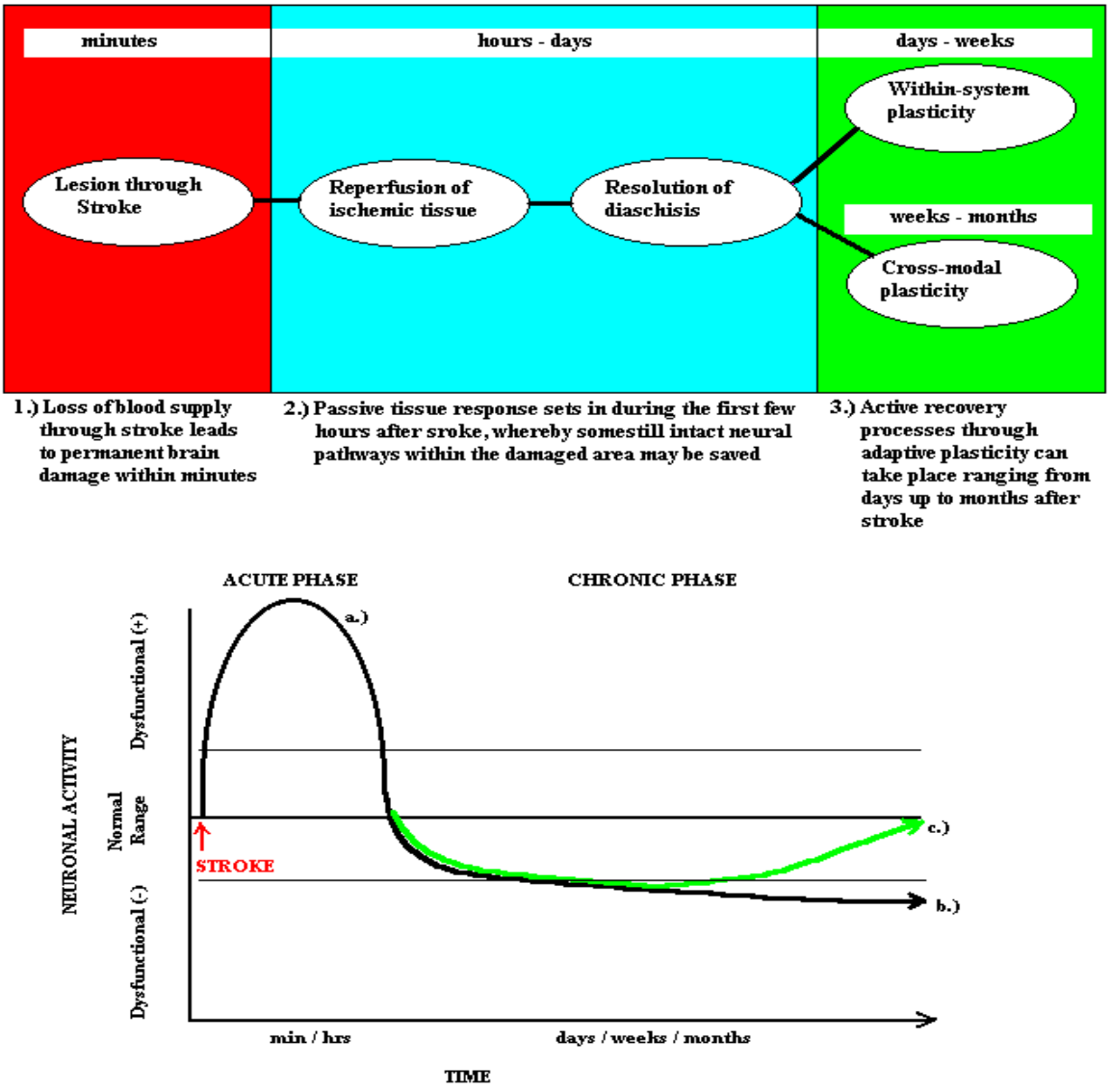


Figure 6: The upper part shows a summary of post-stroke brain processes and their time course. The lower part is adapted from Hamm *et al.* (2000) and shows a biphasic model of the changes in neuronal activity after brain injury. **a.)** Directly after brain injury there is an excessive increase in neuronal function, then the acute activation phase is quickly resolved. **b.)** A period of depressed neuronal activity sets in, leading to chronic dysfunction of the lesioned area if no recovery processes are initiated (black line). **c.)** If recovery through passive tissue response and adaptive plasticity processes is possible there may be an increase of neuronal function back to the normal range (green line).

Pathology of Stroke

The occurrence of stroke is defined as a sudden loss of blood supply to a certain brain region, leading to permanent tissue damage. This may be caused by multiple etiologies such as atherosclerosis, haemorrhage, cerebral embolism, artery occlusion or local thrombosis.

As soon as the blood flow is disrupted the area affected by ischemia undergoes changes in neural activity and undersupplied neurons or neural networks start to degenerate. The process of destruction happens fast and can only be prevented or reduced in its extent through reperfusion of the ischemic tissue during the first few hours and days after stroke.

After this initial passive tissue response, whereby some still intact neural pathways within the damaged neural system may be saved, the anatomical extent of the damage that has been caused to the brain area is permanent and not reversible any more.

Post-stroke Brain Processes Recovery processes set in immediately and during the first few hours and days after stroke the passive tissue response leads to a reperfusion of ischemic tissue and a cessation of inflammatory processes, which are secondary to brain damage. Thereby the extent and time of initiation of reperfusion ultimately determine the degree of persistent damage and consequently the degree of possible later recovery. Pharmacological treatment within the first hours after stroke may be able to actively support these processes and prevent the loss of neuronal tissue to some extent (Hamm *et al.*, 2000).

Also the initially induced 'shock' of those neurons which are connected to the lesion site is resolved during the first few days after stroke. In these sites, which are connected to the ischemic area, a functional change in neuronal activity may lead to metabolic changes, which cause temporarily and reversible dysfunction. This condition is known as diaschisis and its resolution may explain some motor recovery after stroke (Seitz *et al.*, 1999).

The above described passive recovery mechanisms are initiated in the first few hours and days after the stroke occurred. Then the damage that was caused can not be reduced through passive tissue response any more and the extent of the lesion becomes clear. Subsequently, active recovery through reorganizational processes sets in to provide a basis for functional recovery. These processes involve adaptive plasticity and take place over a much longer time course, ranging from days to months or even years (*Fig. 6* summarises these events). Active recovery through plastic reorganization will be discussed in the next section.

III. Plasticity of Motor Cortex after Stroke

Mechanisms of Recovery

Much of the recovery after the initial days is likely due to active recovery of the injured

motor cortex through mechanisms of adaptive plasticity. The functions previously performed by the damaged regions are now taken over by some areas of the brain that have not been damaged through stroke.

Several different mechanisms of plastic recovery have been proposed by Lee and Van Donkelaar (1995), including redundancy of brain circuitry, where a parallel pathway performing a similar function as the damaged pathway may be able to functionally take over after brain injury. A second mechanism, which they have described, leads to functional recovery after stroke through unmasking of previously existing but functionally inactive pathways, a process defined earlier. A third possibility is the sprouting of new fibres from surviving neurons, leading to the formation of new synapses.

Mechanisms such as unmasking and the substitution of pathways may explain why functional reorganization is possible, although most cortical circuits are local and normally are anatomically restricted in their functionality.

Apart from several possible mechanisms for plastic reorganization the extent of functional recovery also depends on factors such as location and size of the lesion, the age of the patient and individual variations in anatomical and functional connections (Chen, Cohen & Hallett, 2002).

Basically the recovery mechanisms that will be activated after stroke depend on the extent of the injury and have to be distinguished into at least two different types of plastic recovery. 'Within-system plasticity' is possible if some pathways within the lesioned neural system have survived undamaged and can be recruited for recovery processes. If, on the other hand, there is complete damage to a neural system, there may still be the possibility to recruit an alternative system which can compensate for the functional loss through so called 'cross-modal plasticity' (Seitz & Freund, 1997).

Functional imaging makes it possible to investigate the different types of plasticity after stroke in vivo.

Functional Imaging Studies

Studying brain plasticity with non-invasive functional imaging methods has led to a much better insight on anatomical reorganization. Different types of techniques are available, such as fMRI (functional Magnetic Resonance Imaging) and PET (Positron Emission Tomography) or EEG (Electro Encephalo Graphy), MEG (Magneto Encephalo Graphy) and TMS (Transcranial Magnetic Stimulation). Functional imaging is an essential method for studying plasticity of the human brain, as it allows the observation of neural activity in the intact and in the damaged brain. At first a brain area that represents a specific function in the normal brain has to be localized, and then it can be compared to areas that are active in the post-stroke brain during the same functional task. The goal of functional imaging is to obtain direct evidence for a relationship between cortex reorganization, time course of recovery and clinical outcome in patients.

PET and fMRI PET and fMRI allow a valid measurement of local changes of neural activity and provide a detailed view of the relationship between anatomy and function. Both techniques take advantage of the fact that active neural tissue can be identified through changes in blood properties in the relevant brain region (Buckner & Petersen, 2000).

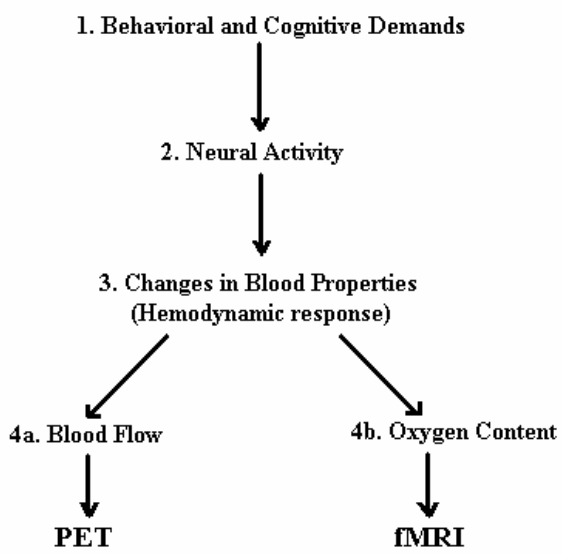


Figure 7: Illustration of PET and fMRI brain imaging techniques. Both methods rely on the fact that changes in behavioural and cognitive task demands (1.) lead to a change in neural activity (2.) and this correlates closely with changes in blood properties (3.). PET measures brain activity through blood property change relating to blood flow (4a.), whereas fMRI relies on blood property change relating to a change in oxygen content (4b.). (Reproduced from Buckner & Petersen, 2000)

PET relies on a change in regional cerebral blood flow (rCBF), which is measured with the help of radioactive tracers. These allow a visualization of blood flow changes related to neural activity. By comparison, fMRI visualizes neural activity indirectly through changes in the oxygen content of the blood. An increase of blood oxygen provides the signal of brain activation, as oxygen enriched blood differs in its response to a magnetic field from blood containing less oxygen (*Fig. 7*).

Both PET and fMRI are able to show the distributed network subtending a given motor task and consequently give evidence for multiple representations, which disagrees with the classical Penfieldian view described in an earlier section (Korvenoja *et al.*, 1999).

However, there are limitations in these blood-flow dependent techniques to investigate temporal sequencing for the activation of different brain areas. These include the inability to differentiate between inhibitory and excitatory effects within the activated neural network and a long examination epoch (1 sec – 1 min) necessary to provide statistically significant activation within which temporal sequences can be discriminated. Another limitation is given by the delay of several 100ms between the onset of electromagnetic brain activity and the following hemodynamic response (Frostig *et al.*, 1990). This indicates that effective resolution for inferring neural plasticity in patients may be limited to some extent and therefore investigating neural plasticity with fMRI has to be based on the assumption that neural plasticity can be observed on a large spatial scale.

Additional difficulties may arise through the comparison between patients and controls. These include the usage of different cognitive strategies to solve a task, performance differences in speed and accuracy during task execution and performing a task at different skill levels (Rickard, 2000). Differences like

these lead to functional imaging results that show differential neural activation patterns, but are not an evidence for plastic changes. To avoid this, a comparison is sometimes made between the damaged and undamaged hemisphere of the same subject during performances of the stroke-affected and unaffected hand, if this is conformable with the task. The best case would be a comparison of brain activity during a certain task before and after the stroke in the same patient, but this is only seldom possible.[1]

To conduct an ideal functional imaging study, three criteria should be fulfilled (Rickard, 2000). First of all the patient must show evidence for significant behavioural recovery of function. Secondly, the task performed should lead to equivalent execution of cognitive or information processing steps in patients and controls. And thirdly there must be statistically significant activation in the plasticity area for the patient, but not for the controls.

Experiments using PET have been conducted by Chollet *et al.* (1991), who found that, compared with movement of the unaffected hand, movement of the recovered stroke-affected hand was associated with increased activation of multiple regions bilaterally, including cerebellum, primary sensory motor cortex and premotor cortex.

In a second PET study, Weiller *et al.* (1993) compared recovered stroke patients with controls and were able to show increased activation, during movement of the recovered hand, in the premotor cortex, sensorymotor cortex and cerebellum of the undamaged hemisphere, as well as in the bilateral anterior inferior parietal cortex and the supplementary motor area.

Both studies give evidence of a role in recovery for bihemispheric activation, recruitment of motor-related networks and cortical map reorganization.

TMS, MEG and EEG The other group of functional imaging techniques are TMS, MEG and EEG, which analyse electromagnetic properties of the brain neurons. TMS allows painless excitation of the neural structures underlying a certain motor output by creating a brief but intense magnetic field. When applied to the scalp regions corresponding to the motor cortex, TMS can trigger transient electromyographic responses in the target muscles, so called MEP's, motor evoked potentials, which allow an examination of the threshold of excitability (Rossini & Rossi, 1998). With the help of TMS individual motor output maps can be generated and maps of the undamaged motor cortex can be compared to motor maps of the lesioned and recovered cortex, to detect plasticity induced changes. These changes show two main characteristics, either an enlargement or restriction of the excitable area due to the recruitment or derecruitment of adjacent neurons, or a migration of the responsive area outside its usual boundaries (Rossini & Pauri, 2000).

[1] This is true for human studies, whereas in animal studies the problems due to using a control group do not exist, as will be described later on.

MEG is able to spatially identify the synchronous firing of neurons in restricted cortical areas in response to an external stimulus and due to its physical properties allows a precise 3D-localisation of the firing neuronal pool (Williamson & Kaufman, 1990). Combining MEG and TMS makes it possible to examine and evaluate the long and short-term effects on cortical motor organization and their interhemispheric differences.

Looking at specific patient studies, where non-invasive functional imaging techniques were used to investigate recovery mechanisms, within-system plasticity and cross-modal plasticity will be further investigated in the following part.

Within-system Plasticity

Following damage to only part of the motor cortex or the pyramidal tract, motor recovery is mediated by reorganization of motor functions immediately around the stroke site (Cao *et al.*, 1994) or by the use of alternative cortical areas somewhere within the motor system, either in the same hemisphere as the lesion or in the opposite hemisphere, if these can access spinal motorneurons (Seitz *et al.*, 1998). Activation to motor tasks can for example occur in the supplementary motor area or the premotor cortex, as these areas have rich interconnections, as well as connections with subcortical structures and the primary motor cortex (Thirumala, Hier & Patel, 2002).

There are three possibilities how within-system plasticity can be realised: Either parallel, redundant pathways take over the function of the damaged pathways or a new region of the contralateral or ipsilateral hemisphere[2] is functionally reorganized to compensate for the lost function of the damaged system.
The third possibility allows a rebuilding of neuronal connections up to a certain degree through neuronal sprouting, if some original connections have survived undamaged.

In a PET study conducted with stroke patients, Azari and Seitz (2000) tried to find an answer to the question, which neural networks in the brain take over the place of the networks damaged through stroke.

Seven patients had sustained damage to the primary motor cortex after stroke and subsequently showed symptoms of paralysis of the contralateral hand. After a recovery period of six months the patients had regained the ability to use the stroke-affected hand. They then had to perform a sequential finger-manipulation task with the stroke-affected hand and with the unaffected hand. During both tasks the neural activity of the brain was visualised with PET (*Fig. 8*).
The results showed a normal pattern of neural activity while the task was performed with the unaffected hand, engaging the motor cortex, premotor cortex, supplementary motor area, somatosensory cortex and parietal cortex of the unlesioned hemisphere (*Fig 8,* left). This is a

[2] In the course of this paper 'contralateral' will always refer to the undamaged hemisphere, whereas 'ipsilateral' will refer to the hemisphere lesioned through stroke.

normal activation pattern as expected during this type of task.

a.)

b.)

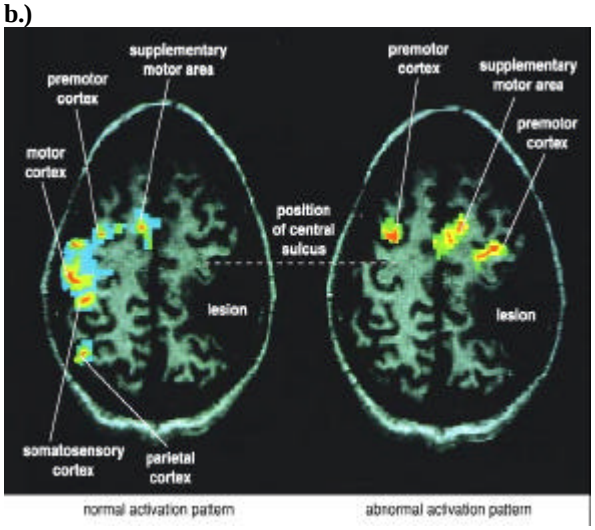


Figure 8*:* a.) A sequential finger-manipulation task was used to assess neural activity of recovering stroke patients. Activity of the brain was measured with PET while the patients performed the task with the stroke-affected hand and the unaffected hand. b.) PET images reveal an abnormal activation pattern during task performance of the stroke-affected hand (right) and a normal pattern of activity during task performance of the unaffected hand (left). (Reproduced from Azari & Seitz, 2000)

In contrast, the performance of the same task with the stroke-affected hand revealed a very different pattern of neural activation, showing activity in regions such as the premotor cortex and the supplementary cortex of both hemispheres and the prefrontal cortex of the lesioned hemisphere. This abnormal pattern of activity leads to the suggestion that the recovery of the stroke-affected hand is based on the recruitment of 'new' cortex, which is part of the same neural system.

Parallel Pathways Within the motor system several parallel motor pathways have been identified. Not only the primary motor area but also premotor cortex, supplementary motor area and the cingulate motor cortex contain somatotopic representations, and all these motor areas contribute to the pyramidal tract. Therefore these parallel pathways can substitute for each other functionally in recovery from stroke (Fries *et al.*, 1993).

In the recovered brains of stroke patients different pathways than in the normal brain are used to control the stroke-affected hand. In the normal brain long projections are sent from neurons in the motor cortex to the pyramidal tract and excite the spinal motor neurons that have an effect on muscle contractions of the hand. However, this normal activation route is compromised through the lesion and a different pathway must be used to achieve recovery.

Azari and Seitz (2000) examined neural activity in patients recovered from paralysis of one hand after stroke. They were able to detect the activation of a compensatory pathway during motor tasks, which led from the supplementary motor area to the spinal cord (*Fig. 9*).

This unusual activation was accompanied by abnormally enhanced connections between the thalamus and the cerebellum. In this case the usage of a strong cerebello-thalamo-cortical pathway serves as a resetting mechanism for the compensatory neural processes and is involved in 'teaching' the supplementary motor area its new role. A 'detour' of motor control allows the brain to function normally,

although the motor pathway formerly involved in control of the hand is disconnected through stroke. Thereby the normal operating mode of the supplementary motor area is reset, making the neural network available for compensatory plasticity.

A 'reset' can occur when for example the level of available NMDA is changed through an alteration in the genetic code of the neurons. Such a change leads to an increase or decrease in the level of excitability of the neurons in a specific area and makes it possible for them to adapt to changes in input (Mu *et al.*, 2003).

Adaptive, as well as skilled learning processes usually call upon several parts of the motor system when a new behaviour is internalized. After the learning process is complete, only one part of the motor system will be functionally active during the performance of this behaviour. If this part is then disconnected through stroke, a substitution of the damaged network through one of the other areas involved in the initial learning process is possible. Therefore the compensatory motor network 'only' has to relearn a function it has been involved in before, namely when this function was learned in the first place. Relearning is a relatively fast process and consequently within-system plasticity can be seen after a short period of recovery.

Cortex Reorganization Anatomical compensation of a damaged brain area or pathway through a shift in cortex organization is a second possibility for within-system plasticity to occur. Thereby the undamaged motor cortex, either adjacent to the lesion or in the contralateral hemisphere, is reorganized and takes over the function of the damaged cortex. This mechanism is similar to changes in the motor cortex induced through peripheral deafferentation, as defined earlier (Weiller *et al.*, 1993).

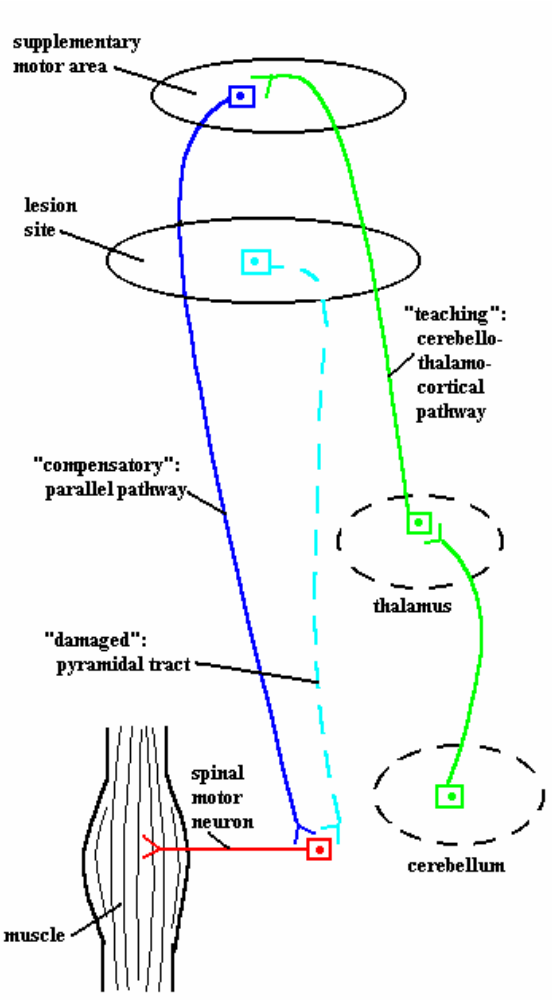


Figure 9: The brain of a recovered stroke patient relies on a compensatory neural pathway (dark blue) as substitution for the damaged neural pathway (blue dashed). The cerebello-thalamo-cortical pathway (green) is "teaching" the supplementary motor area its new function, which is indicated by abnormal activity in the cerebellum and thalamus. (Freely adapted from Azari & Seitz, 2000)

One situation where there is strong evidence for the activation of the motor cortex contralateral to the lesion is in recovery from dysphagia. Swallowing problems affect one in three patients immediately after stroke, but in most cases complete recovery occurs within the first few weeks. A study by Hamdy and Rothwell (1998) relates the qualitative and quantitative very good recovery results to how the area of the motor cortex concerned with swallowing is organized. The bilateral but asymmetric inter-hemisphere representation within the motor and premotor cortex allows for a good compensation of lost function after stroke.

If there is a lesion in the swallowing motor cortex of the hemisphere with the greater swallowing output, dysphagia is likely to occur. However, as additional substrate for swallowing is available in the contralateral undamaged hemisphere, a functional reorganization becomes possible. The contralateral motor cortex is now able to take over the function of the damaged swallowing area and increases the capacity for compensatory reorganization, as well as the chances of good functional recovery.

A comparison between non-dysphagic patients and recovered dysphasic patients shows an increased activation of the proportionally smaller swallowing motor cortex in the undamaged hemisphere of the recovered dysphagic patients. This indicates that the contralateral hemisphere contributes to the recovery process by giving of a functionally identical, formerly unused part of the motor cortex for reorganizational purposes.

Cortical map reorganization within the motor system of the ipsilateral damaged hemisphere, often directly along the lesion rim, is another mechanism which contributes to recovery of motor function after stroke. This theory is supported by the results of Cramer and Bastings (2000), who measured the reorganization of multiple cortical map elements along the lesion rim using fMRI. The intact cortical regions surrounding the lesion were able to take over the function of the damaged region through a shift in cortex representation. Changes that led to this shift include a local increase in dendrites, synapses and levels of proteins related to axonal growth.

A shift in, for example, hand motor representation may be medial, anterolateral, ventral or posterior. A study by Weiller *et al.* (1993) showed that after damage to the hand motor cortex movement of the recovered hand leads to motor cortex activation that extends laterally to the face area, suggesting that the hand representation may shift towards the motor representation of the face. This gives evidence for a relationship between shifts in cortical activation and an improvement of functional performance.

Plastic changes in the ipsilateral damaged hemisphere generally seem to be more efficient in producing good recovery, compared to reorganizational changes involving the contralateral hemisphere. As demonstrated by Rossini *et al.* (1998) the recovering muscles have enlarged and relocated cortical map

representations around the lesion site. These lead to good functional performance and can be viewed after only a short period of recovery, indicating that ipsilateral plasticity is better and faster than contralateral plasticity in producing improvement.

Cross-modal Plasticity

In some cases, if the motor cortex is extensively damaged, patients recruit networks in areas of the brain that are not normally involved in the performance of a particular motor task and which are not part of the original functional system. Often the recruitment of an alternative network outside the damaged system happens in addition to recruitment of cortex within the damaged system. However, after complete destruction of a functional system, substitution by other systems remains the only alternative (Seitz & Freund, 1997). Cross-modal plasticity after stroke is similar to that seen in blind patients, who engage the visual cortex during a tactile Braille reading task.

In the above described study by Azari and Seitz (2000) some recovered stroke patients were observed, who also recruited networks in areas of the brain that are not normally involved in the performance of a sequential finger-manipulation task. When these patients moved the stroke affected hand, neural activity could be viewed in parts of the visual cortex, although they were not receiving any visual input, as they were blindfolded as a control. The visual cortex seemed to subserve a motor function and the active areas within the visual cortex could be functionally associated through PET scan with the motor task that had to be performed. The recruitment of visual cortex happened in the late stages of recovery (after several months) and involved cross-modal adaptive plasticity.

A temporal distinction was found between cross-modal and within-system plasticity (Azari & Seitz, 2000). Patients who recruited an alternative network had been recovering for at least six months, while the recovery process of patients using within-system plasticity took only a few weeks. This leads to the suggestion that there must be a distinct time course in recovery processes. Within-systems seem to be easy to access and are recruited fairly early, whereas alternative cross-modal networks are difficult to access and need a longer time to be effective. The alternative network is naïve to the task it is supposed to perform, so that the process of recovery does not only involve a relearning of the task, as during within-system recovery, but the system has to learn what to do in the first place, and this takes more time.

Animal Experiments

In conducting animal experiments for studying the effects of stroke, some of the difficulties which affect patient studies can be avoided. For example it is possible to study brain activity before and after stroke in the same animal, not having to refer to data of unaffected control subjects for comparison. Another advantage is that the lesion can be induced intentionally in exact the area of the animals brain involved in the performance of a

specific task, which has been trained beforehand. The brain area that has been identified to functionally represent this task is lesioned and can then be studied during performance of the same task directly after the lesion and after a period of recovery. Thereby data derived from only one animal provides a good basis for the direct comparison of activity before and after stroke and can reveal information about recovery induced plasticity.

Motor Cortex Lesions in Mice Skilled reaching movements, which are an important aspect of human motor behaviour, are typically impaired after a stroke to the motor cortex. To study the effects underlying the impairment and subsequent functional recovery, Farr & Whishaw (2002) developed a 'mouse- model' of human motor stroke.

A typical task with which mice are trained before lesioning is the 'Whishaw reaching task'. The mouse is trained to retrieve small pieces of food with its forepaws and remains very efficient at this task once trained. Then the motor cortex contralateral to the preferred reaching arm of the mouse is lesioned and tested for functional recovery (*Fig 10*).

After the motor cortex injury the mouse still retrieves the food by reaching with the affected forelimb but is severely impaired in doing so. Both spontaneous and skilled movements are affected and remain strongly impaired until about seven days after lesioning. After two weeks of recovery an improvement can be viewed in reaching accuracy, but recovery remains far from complete. About 70-80 days after lesioning the accuracy of reaching performance reaches prestroke control values.

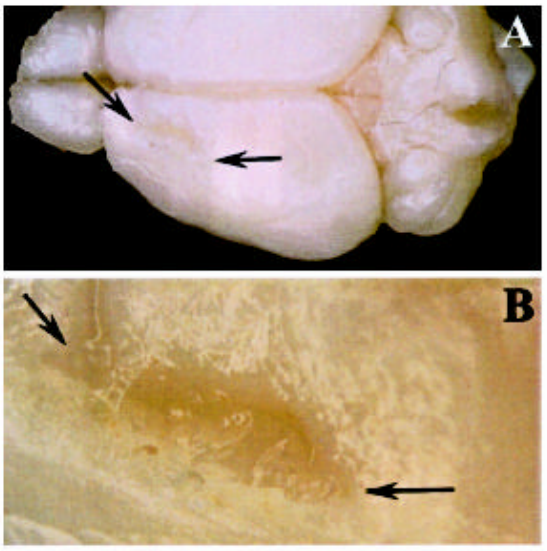


Figure 10: Dorsal view of a typical lesion in the motor cortex of a mouse, after intentionally induced stroke. (Reproduced from Farr & Whishaw, 2002)

Before the lesion the mouse used a distinctive pattern of movement to retrieve the food. A comparison between pre- and postlesional video recordings of reaching success and the movements involved, reveal abnormal movement components after stroke, indicating that some part of the recovery may be the result of behavioural compensation. However, the continuous improvement of performance in the weeks following the lesion, indicate an additional involvement of functional recovery through motor cortex plasticity.

The results of this study suggest that the 'mouse-model' provides a good basis for the analysis of motor skills, plasticity and recovery processes as seen in humans after stroke. Using this type of animal study, recovery-schemes can be developed and their influence on plastic

reorganization can be tested, to help to provide appropriate schemes for human recovery after stroke.

IV. Modelling Plasticity with Artificial Neural Networks

In order to understand how the brain recovers from stroke to the motor cortex and how the mechanisms underlying this recovery work, traditionally either clinical studies with stroke patients or animal models have been pursued, as described above. An alternative approach is the use of computational models, to investigate the reorganizational capacities of the motor cortex following a lesion. As computational models are very useful for the analysis of complex systems in general, they seem to be ideal for examining the complex events occurring in the brain during and after stroke (Reggia *et al.*, 2000).

Hebbian Learning

Although brain functions are strongly genetically determined, not all details of the brain networks and their interactions are specified from the onset. This gives neural networks the opportunity to adapt functionally to changes in input. An important adaptation mechanism is synaptic plasticity, which can be implemented in artificial neural networks using biologically realistic learning rules (Trappenberg, 2002).

'Hebbian learning' is the principle idea behind such rules, based on a theory outlined by Hebb (1949). It provides a framework for investigating the interactions between neural and behavioural levels of analysis and relies on the following assumption: The synaptic strength and therefore the weight between two connected neural elements increases when both elements are active that is there is a correlation between presynaptic and postsynaptic activity, otherwise it decreases.

The ability of networks of neurons to form associations between co-occurrences of stimuli is the basis for many information processing mechanisms in the brain. Implementing these abilities in the brain, by using rules governing synaptic plasticity, enables networks of neurons to efficiently engage in local learning mechanisms through LTP, leading to a change in their response and a reorganization of functional connectivity (Wolters *et al.*, 2003). Local changes between two synapses cause a change in the neural network they are involved in, which in turn may lead to a reorganization of connecting areas, indicating that the basic principle of ordinary learning can lead to functional reorganization on a large scale (Hess & Donoghue, 1994).

Two groups of neurons that have been disconnected by a lesion can reconnect, if they are activated at the same time through an external circuit whose neurons are functionally interconnected. The activation of this neural network leads to simultaneous activation of the disconnected neurons, which may become reconnected through repetition of this process.

Using this knowledge to implement brain functions in artificial neural networks can help to reveal many details of synaptic plasticity and possibilities of manipulation. Therefore

using artificial neural network modelling and the relatively simple mechanisms involved in Hebbian learning is very useful for studying the plastic changes occurring in the brain after stroke.

Computational Models

One goal of developing a computational model of stroke is to understand the changes the lesioned tissue, the connected areas and the undamaged parts of the brain undergo. Upon this knowledge those factors that may lead to a better recovery can be determined and then are used to derive recovery-schemes that can improve functional outcome after stroke.

Several computational models of cortical map self-organization and map refinement have been developed to achieve this goal (Ritter *et al.*, 1992). Typically these models are constructed by using a two-layer network and an unsupervised Hebbian learning method, often involving competitive learning. These studies help to derive some plausible assumptions about network architecture and synaptic modifications due to plastic changes of the brain.

Lesion and Recovery of a Motor Model To be able to demonstrate how brain damage can be modeled computationally, Reggia *et al.* (2000) developed models which were explicitly intended to simulate plasticity following a small stroke to the motor cortex and examine compensatory mechanisms in areas immediately surrounding the lesioned tissue.

Their model consisted of two parts: a simulated arm able to move in three-dimensional space and a closed-loop of neural elements, each representing a group of real neurons, responsible for controlling and sensing the arms position through proprioceptive input and motor output. If the lower motor neuron elements are activated they position the model arm in a specific spatial position and the arm then generates input signals to the cortex via proprioceptive neuron elements.

Four sets of neural elements determine the flow of activation in a closed-loop: M1, lower motor neurons, proprioceptive neurons and proprioceptive cortex (*Fig 11*). Each neural element has an associated activation level, representing the mean firing rate of neurons in that element. The neural activity and synaptic changes are then modelled mathematically, whereby each cortical element excites its immediately adjacent elements, but inhibits more distant surrounding cortical elements in a 'Mexican Hat pattern'.

To simulate map formation an unsupervised, competitive Hebbian synaptic weight change rule is used. The map is then trained and its initial coarse topography changes into a finely tuned topographic motor map. By repeatedly stimulating M1 the map is trained until it is stable and further training does not produce qualitative changes in the trained weights or the cortical feature maps.

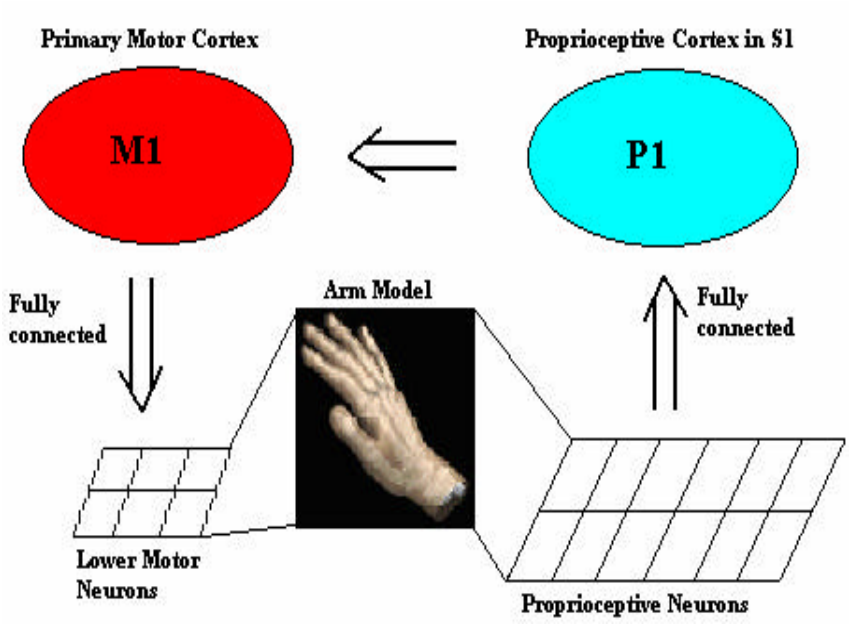


Figure 11: Structure of the closed-loop of neural elements: 12 proprioceptiv neuron elements form the input layer and are fully connected to the proprioceptive cortex (P1). P1 and the primary motor cortex (M1) are two-dimensional arrays of neural elements, with a partial projection from P1 to M1 in a coarse topographic order. M1 is connected to six lower motor neuron elements. The simulated arm model transforms activity in lower motor neurons into proprioceptive input. (Freely adapted from Reggia *et al*., 2000)

After training the M1 motor map develops clusters of elements representing the same muscle group. When this stage is reached the model is lesioned through permanently setting the activation levels of a set of cortical elements at zero and severing the connections to and from the lesioned elements. Then the effect of the lesion on the trained motor cortex is examined directly after lesioning and after a period of continually retraining the lesioned network.

After a structural lesion to M1, reorganization can be viewed in both the M1 sensory and motor output maps. The results show a two-phase model of recovery. Immediately after the lesion the M1 maps adjusted and the number and excitability of responsive elements in the normal cortex near the lesion edge increased. Additionally, overall rates of responsiveness in the M1 sensory map and relative activity in the M1 motor map increased. These changes in activation dynamics form the first, very rapid phase of recovery, which is then followed by a slow, second phase due to synaptic plasticity.

The increased excitability following the lesion is necessary for map reorganization to be initiated in the cortex surrounding the lesion, which consistently participates in the reorganization process and achieves a higher-density feature map than before the lesion. This can be explained by the synaptic modification rule that underlies map formation. Changes in the receptive field of a cortical element happen through a shift in the receptive field, to become more like the pattern of input elements that activate that cortical element. Therefore low activity following a lesion leads to very slow changes of the receptive fields and only limited reorganization. Whereas high activity induces

quick changes in receptive fields and substantial reorganization can occur. For this reason increased excitability within and effective use of surrounding intact cortex following a lesion can positively influence reorganization and contribute to behavioural recovery following stroke.

This suggests that therapeutic approaches, which intend to actively induce recovery in the post-stroke brain, should foremost try to support the excitability of the cortex surrounding the lesion. One approach would be to inject D-Amphetamine shortly after the stroke, as this has been shown to selectively upregulate neurite growth and excitability within neural circuits, through promoting the expression of specific proteins (Stroemer *et al.*, 1998). Together with the performance of behavioural tasks in the effective time window of D-Amphetamine treatment, this form of therapy can improve behavioural recovery in stroke patients, as it increases excitability within the intact cortex.

Studying reorganizational processes with the help of artificial neural nets can help to suggest mechanisms which underlie functional recovery after stroke, such as increased excitability and effective use of the surrounding cortex. Thereupon recovery schemes which try to support this mechanism, for example pharmacological therapies with D-Amphetamine, can be developed for the treatment of stroke patients.

The added value of modelling stroke and recovery with artificial neural nets means that the proposed effect of a certain therapy can be tested before hand and if the outcome is acceptable, a treatment of the real brain can be developed accordingly.

Theoretical Models of Recovery

The extent of the lesion and the thereupon depending loss of connectivity within the damaged system define the post-lesion state upon which recovery schemes have to operate.

Robertson and Murre (1999) propose three possible post-lesion states and derive appropriate recovery schemes for each through implementing empirical data in neural network models.

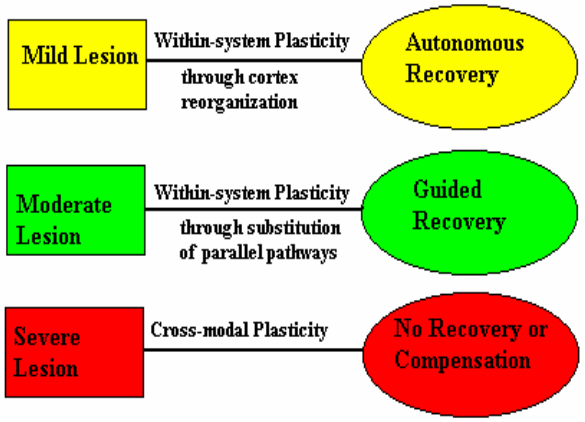


Figure12: Degrees of lesion may vary and result in different forms of plasticity, which in turn influence recovery processes.

Their proposals for recovery schemes are based on the assumption that a small loss of connectivity will lead to autonomous recovery, whereas a major loss of connectivity results in a permanent loss of function and recovery is only possible through compensation. A partly damaged circuit with some still intact

connections may be saved through principles of guided recovery (*Fig. 12*).

Autonomous Recovery One process of plastic reorganization following stroke is the increase in connectivity between surviving neurons in the damaged network. This is possible if the lesion is mild and recovery involves spontaneous reorganization through within-system plasticity. External treatment is not necessary in this case as restitutive reconnection and reorganization occur in an autonomous fashion.

A theoretical model of self-repair helps to investigate the mechanisms involved in autonomous recovery on an abstract level. Robertson and Murre (1999) obtain this by using a biologically informed artificial neural network model and an approach based on Hopfield networks (Hopfield, 1982). They view a neural representation as a set of neural modules with connective tracts between them and model brain lesions by randomly deleting connections within these networks. Repair is then modelled through a mathematical implementation of Hebbian learning in a three-step process: One neural module is activated, its activation spreads to all other connected modules and then new connections are randomly added between the activated modules.

The speed of reconnection depends on the size of the neural circuit, the degree of connectivity within the neural network and the size of the lesion itself. Providing that the number of surviving interconnections within the lesioned circuit is sufficient, the circuit should be able the reconnect autonomously through Hebbian learning (*Fig. 13*).

To aid this process in the real brain a therapy using amphetamine treatment (for example Stroemer *et al.*, 1998; as described above) can be applied to support neurite growth and excitability. A study conducted by Chen *et al.* (2002) has shown that a substance such as inosine, which is synthesised from adenosine, can stimulate neurons to extend new projections to disconnected areas and induces axonal reconnection after stroke. These pharmacological therapies therefore can produce the above described theoretical model effects in the lesioned human brain.

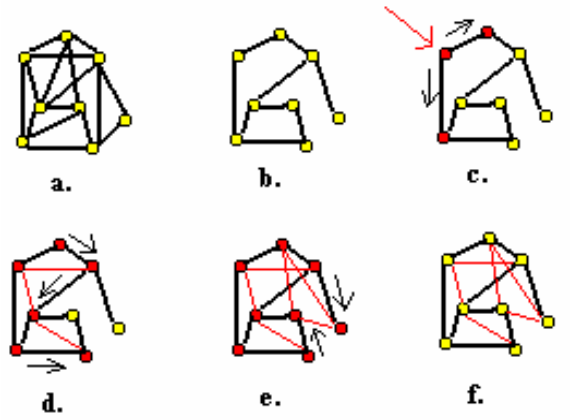


Figure 13: Autonomous reconnection through random stimulation and Hebbian learning. **a.** Neural circuit with intact connections. **b.** After lesion through stroke the connections are partly destroyed. **c.** External random activation of one neural module (arrow). **d.** Activation spreads within the circuit and new connections are formed through Hebbian learning (red). **e.** The process continues until the circuit is well reconnected. **f.** Reconnected circuit with new connections, which will increase in strength through future activation. (Freely adapted from Robertson & Murre, 1999)

However, if the remaining connections are not sufficient for reorganizational processes to

occure due to the extent of the lesion, the reconnection process can be supported by a principle of guided recovery.

Guided Recovery Whereas autonomous recovery is independent of exogenous behavioural influences, guided recovery depends on specific external stimulation. There are various methods available for this purpose, including non-specific stimulation, which can be further classified into bottom-up targeted stimulation and top-down targeted stimulation (Robertson & Murre, 1999).

It has been shown that environmental and behavioural factors have strong elevating effects on synaptic connectivity and dendritic sprouting in animal neural circuits (for example Will & Kelche, 1992). In the above described model of reconnection through Hebbian learning, non-specific environmental stimulation should then facilitate synaptic connectivity through a greater number of coactivations between the disconnected nodes. As a result the reconnection processes of the model should be faster and even more successful in producing good functional recovery.

One example for non-specific environmental stimulation that can be tested in the real brain is multimodal stimulation. In an experimental approach Volpe *et al.* (2000) tested the effect of multidisciplinary rehabilitation activity on functional outcome in stroke patients. They used a novel therapeutic strategy where additional training of the stroke affected limb was delivered by a robotic device, through interacting with the patient in real-time and guiding the affected limb through a stereotyped movement pattern. This robot aided therapy leads to enhanced motor outcome, as it aids reconnectional processes through non-specific stimulation.

One draw back of non-specific stimulation is that it may cause maladaptive connections. This occurs if the stimulation leads to a co-activation of the lesioned circuit with some other neural network, instead of co-activation with disconnected parts of the lesioned network. The other neural network then increases its strength and region of functionality (*Fig.14*). A reconnection of the lesioned network is therefore inhibited or still existing connections are further reduced, as there is a competition for connectivity induced through non-specific stimulation. Consequently, it is important to stimulate the target area, namely the lesioned neural circuit, directly.

For stroke patients needing a stimulative therapy the theoretical principle of maladaptive plasticity indicates that the patients may be deprived of the opportunity for recovery if the rehabilitation inadvertently activates circuits that competitively inhibit the impaired neural network (Fitzsimonds *et al.*, 1997).

Guided, targeted stimulation can either be realized in a bottom-up or top-down fashion. Bottom-up processes should provide a sequence of cued inputs, which are able to precisely boost connections within the lesioned network through repeated stimulation. Such repetitive training would allow a faster

reconnection through Hebbian learning mechanisms, as the same specific set of neurons within the damaged network would be consistently activated.

Top-down stimulation involves deliberate attention, and therefore mental engagement, towards the process that may lead to reconnection of the lesioned neural modules. Attention-mediated plasticity can not easily be implemented in a neural network model, but experimental evidence for this comes from a study by Pascual-Leone *et al.* (1995). They showed that purely mental practice of motor skills, involving intense attention, can enlarge the functionally related neural circuits of the motor cortex.

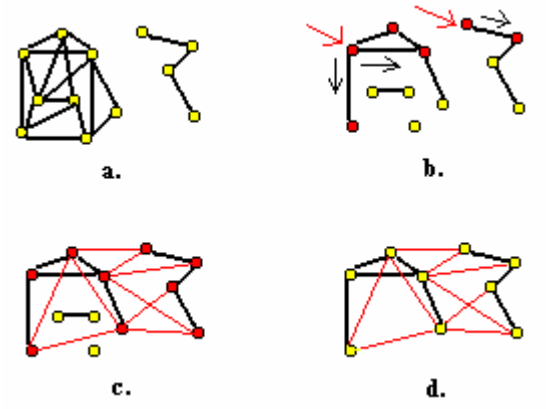


Figure 14: Maladaptive connections that develop between intact parts of the lesioned network and another neural circuit. **a.** Before lesioning. **b.** After the loss of connections through lesion, nonspecific stimulating activates neural modules of the lesioned network and another nearby circuit. **c.** Competition between the networks leads to loss of modules of the lesioned network. **d.** This results in a maladaptive connection that further decreases function of the lesioned network. (Freely adapted from Robertson & Murre, 1999)

Although the neural network models described above are based on realistic concepts of cortical structure, activity dynamics and synaptic plasticity, they still involve substantial simplification of reality. Nevertheless, the principles of recovery that are based on theoretical models can directly lead to neuroclinical recovery schemes for stroke patients, as has been indicated in this section and will be further described in the next.

Neuroclinical Recovery Schemes

Neural and behavioural events interact strongly to affect recovery of function after stroke. Therefore designing useful treatments in form of neuroclinical recovery schemes is an important approach to reduce the damage caused by the lesion. In the development of recovery schemes, those factors that influence plastic reorganization of the brain and improve functional performance have to be considered.

The mechanisms of plasticity of the motor cortex can be manipulated by motor learning and motor output, especially voluntary movements, and are aided in their occurrence through guided stimulation. Based on these facts different recovery schemes have been proposed and tested, including use-dependent recovery, constraint-induced therapy and motor re-education.

Following stroke NMDA receptor hyperexcitability, dendritic growth and an increase in synaptic spine density occur, whereby each of these processes is restricted to specific, well-defined intervals. This suggests that the brain is differentially sensitive to use-related manipulations in a time-dependent fashion. Some of the neural events associated with plasticity require motor experience, that is

they are use-dependent. The experience of the appropriate use necessarily has to occur coincidentally with the optimal time-window for the related neural event (Schallert *et al.*, 2000).

Neural events have been shown to be modifiable by disuse, use and overuse. One example for disuse is the 'learned nonuser' that can be viewed in the stroke affected limb after a period of recovery (Taub *et al.*, 1994). In order to compensate for impaired functioning of this limb after stroke, alternative behavioural strategies are often adopted leading to non-use of the affected limb. The reestablishment of normal motor patterns, even if functionally possible, is therefore inhibited.

Liepert *et al.* (1998) studied the effect of constraint-induced movement therapy in the brains of stroke patients. They immobilized the functionally unaffected arm of patients several months after stroke, and in combination with motor re-education in form of physical therapy (such as mechanical stimulation, massage and passive movement) were able to reverse the effect of learned non-use, leading to significant functional improvement in the stroke affected arm. Whereas total disuse of the affected limb over an extended period of time causes the region of the lesion to expand, forced overuse of the affected limb, especially very early after stroke, has the same effect of inhibiting functional improvement (Kozlowski *et al.*, 1996). Consequently it is important to give the right amount of stimuli at the most appropriate time point.

A fMRI study examining the effects of constraint-induced movement therapy on the functionally related areas of the brain (Johansen-Berg *et al.*, 2002), showed an increase in brain activity. Patients took part in a two-week home-based therapy programme, combining restraint of the unaffected limb with progressive exercise of the affected limb. As a result, improvement in hand function after therapy could be viewed, which correlated with increases in fMRI activity in the premotor cortex and secondary somatosensory cortex of the lesioned hemisphere. These changes in activity are associated with successful motor rehabilitation, thus providing evidence for recovery after specific input, as has been predicted above by the neural network model of guided, targeted stimuli.

IV. Conclusion

Several questions were proposed in the introduction and have been thoroughly investigated in the course of this paper with the goal of finding appropriate answers.

The first question was, 'How plastic is the brain when recovering from stroke?'

When the brain recovers from a lesion to the motor cortex after stroke, it nearly always engages in reorganizational processes, which then lead to better functional recovery. Therefore plasticity of the brain during recovery can be seen in most cases. The degree of plasticity and consequently the degree of recovery depend strongly on the extent of the lesion.

The second question asked, 'Which different types of plasticity can be distinguished and what effects do they have on functional performance?'

A very severe lesion may completely destroy a neural network representing a specific function and makes recovery through reorganization of the lesioned area impossible. In this case the only possible plasticity process that can support recovery of function is cross-modal adaptive plasticity. A different area of the cortex that operates independent from the lesioned area is functionally invaded and makes recovery possible through allocating an undamaged neural network towards regaining the functionally impaired behaviour. Recovery in this case is limited in its quality of functional compensation and as the substituted system is extrinsic to the task, it is also a fairly slow process. This type of plasticity is similar to the cross-modal plasticity seen in blind patients during a tactile Braille reading task.

In contrast, if the lesion is moderate to mild, a reorganization of the lesioned area and the surrounding cortex is possible through within-system plasticity and may lead to a fast and very good recovery. Neural modules that have survived the lesion undamaged can be reconnected and neural networks belonging to the same functional system can functionally reorganize. This type of plasticity seems essential for achieving optimal recovery after stroke.

'What kind of factors influence the degree of plasticity and therefore the degree of recovery?' was the third question proposed in the introduction.

A patient who is not able to move his arm after stroke is fairly impaired in daily life, especially as skilled use of the hands and the performance of fine tuned movements are often the most difficult. During rehabilitation two different approaches are possible, either a passive movement therapy is initiated and the patient is encouraged to use the stroke-affected arm, with the goal of providing conditions under which voluntary movement can be obtained. Or the patient must learn to cope with daily challenges without using the stroke-affected arm, therefore engaging in strategies of behavioural compensation.

Changes in the cortex are always experience dependent and plasticity of the brain is a key mechanism underlying both normal learning and recovery of function following brain damage. This is a very important fact with respect to initiating recovery processes, as a variation in experience and motor input to damaged neural circuits is a factor that will strongly shape synaptic interconnections and hence influence recovery. Therefore supporting the brain's capacity for plastic reorganization through stimulative input to the motor cortex has shown to have the same effects as motor learning in general, namely an expansion of the motor cortex representation of the involved body part. This is the main pre-requisite for good functional recovery.

Knowledge of the physiological mechanisms of plasticity can help to develop new therapies for stroke patients. Especially the observation

that disuse, use and overuse can strongly modify neural events is important in this respect.

As the example of peripheral deafferentation of a limb shows, there is a strong competition between adjacent muscles for areas of functional representation in the motor cortex. Immediately after the input from a certain muscle subsides, a reorganizational process sets in. The neighbouring muscles will start to expand their territory of functional representation and invade the now functionally unused part of the cortex. A further tissue loss can be prevented through purposefully retraining the affected muscle and forced non-use of the adjacent muscles. Consequently, when developing a rehabilitative training program, usage of the muscles that are close to the stroke-affected muscle should be prevented, for example through anaesthesia.

Apart from exogenous, therapeutic influences on recovery, other endogenous factors play an important role. The way in which the stroke-affected part of the body is represented in the brain provides the working basis for processes of plasticity.

For example the swallowing motor cortex reorganization shows how plasticity strongly depends on the cortex organization of the lesioned area. The bilateral representation of the swallowing motor cortex allows for a good compensation of the lost function, as additional substrate for network reorganization is available in the undamaged hemisphere.

The fourth question was, ‘How can theoretical and practical experimental findings help to develop successful therapeutical approaches for recovery schemes?’

Analysing the determinants of normal short- and long-term plasticity in the undamaged motor cortex, as in skilled motor learning, provides a useful basis for determining whether and how functional recovery can be guided through the input of appropriate recovery schemes.

It seems that the continual use of a limb is critical for achieving and maintaining an appropriate cortical representation. Improving function of the stroke-affected limb therefore depends on actively using it. Increased excitability and effective use of the cortex surrounding the lesion can be exploited through therapeutic techniques that stimulate movement. Thereby optimal adaptation can be reached through skilled use of the stroke affected limb, rather than just increasing use. To intensify the training effect and to prevent a competition between input of the stroke-affected and the unaffected limb, constraint-induced therapy combined with skilled motor re-education seems to produce the best results in functional recovery.

As has been predicted by the neural network model, the functional input following a lesion has to be a guided, targeted stimulus. Constraining the unaffected limb and in doing so preventing competitive input, as well as intensively training the affected limb, leads to a functionally much better reorganization of the lesioned neural network than could be achieved

through non-specific input. Additionally, the constraint-induced therapy can produce reorganizational effects not only in acute stroke patients, but also in chronic stroke patients, suggesting that the motor cortex retains a capacity for recovery through plasticity over a long period of time after the lesion occurred.

Using neuroimaging techniques provides a basis for bridging the gap between clinical practice and the neural representation of recovery mechanisms in the brain, leading to new physical rehabilitative therapies. In providing information on the excitability, extension, and localisation of motor cortex areas during recovery, functional imaging plays an important role for viewing possibilities of functional reorganization.

Nevertheless, the specificity with which brain reorganization relates to good clinical outcome is still not completely understood. This is due to the fact that most patients that have been studied show good functional recovery. Furthermore, additional factors that may influence recovery, such as age, lesion location and prestroke neurological status make it difficult to generalize experimental findings.

In this paper reorganization capabilities of the brain due to mechanisms of plasticity are looked at referring to relatively low-level functioning of the motor cortex. Many functional imaging studies have been conducted in this area, as the motor circuits in the cortex are well-understood and the precise topographical maps that exist in this area easily reveal any reorganization that takes place.

Nevertheless, there are also several neuroimaging studies that give evidence for the reorganization of circuits that underlie higher-level cognitive functions, such as memory and language, which occurs in a similar fashion to reorganization of the motor cortex (for example Weiller *et al.*, 1995).

Through dealing with and answering the questions that were set out in the beginning, it was possible to fulfil the main goal of the thesis, which was to find out how recovery can be positively influenced by neuroclinical recovery schemes, leading to a better functional outcome after stroke, and evaluate how 'plastic' the brain really is.

Recovery of function after a lesion remains very difficult to predict in individual cases, as many factors that vary in individuals have an effect on the outcome. Therefore a generalisation of post-lesion training effects over time or across patients and their individual situation is not always possible. Individual variations in functional connectivity of the prestroke brain have a large influence on the ability of the affected neural network to recover from the lesion. Strong cortical connectivity between neural modules offers a better basis for reconnection and reorganization than low cortical connectivity. Consequently, the functional outcome is not decided by the number of neurons left, but how they function and which connections they are able to make.

The principle of Hebbian learning implemented in neural networks provides a

model for how partly lesioned neural circuits can regain their original pattern of connectivity and reinvolve in the cortical functions they subserve.

The novel approach of using computational modelling for the study of neuroplasticity can complement traditional studies, such as clinical patient studies and animal experiments, and provides a guide for future studies. One very useful aspect of computational models is their heuristic value in suggesting novel experimental investigations, such as amphetamine therapy or principles of multimodal stimulation, and to shed light on the effectiveness of therapeutic intervention and new recovery schemes for recovery after stroke.

With the help of neural network models the main factors that influence plastic reorganization can be defined as the extent of the lesion, the amount of intact connections between neural modules that have survived the lesion and the availability of specific, targeted input during recovery. These factors determine how plastic the brain is while recovering from lesion through stroke.

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Statement

I, Zoë Rebecca Hunter, hereby confirm that this paper "Plasticity of the adult human brain and motor recovery after stroke" is exclusively my own work, and that I used only the given references and resources.

Erklärung

Hiermit erkläre ich, Zoë Rebecca Hunter, die vorliegende Arbeit „Plasticity of the adult human brain and motor recovery after stroke" selbständig verfasst zu haben und keine anderen Quellen oder Hilfsmittel als die angegebenen verwendet zu haben.

Osnabrück, den 12.08.2004

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