Brain plasticity and hand function

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Abstract

The aim of this thesis was to investigate the effects of cortical reorganisational changes following experimental deafferentation and peripheral nerve injury and apply the concept of brain plasticity to enhance sensory re-education following peripheral nerve injury and repair in the hand.
In the first two papers the effects on hand function of contralateral deafferentation was investigated. Tourniquet induced anaesthesia (paper I) resulted in significant improvement in perception of touch, tactile discrimination, and grip strength in the opposite hand during anaesthesia. In order to investigate the effects of contralateral deafferentation with the pain factor eliminated, 100 patients, operated on in axillary plexus anaesthesia, were investigated (paper II). Axillary plexus anaesthesia also resulted in rapid, significant improvement in sensibility in the contralateral hand.
In paper III selective ipsilateral cutaneous anaesthesia of the forearm resulted in rapid significant improvement in ipsilateral hand function.
In the last two studies previous findings were applied on patients with median or ulnar nerve injuries. Tourniquet induced anaesthesia (paper IV) of the healthy hand results in significant rapid improvement in sensibility in nerve-injured hands. Repeated ipsilateral cutaneous anaesthesia (paper V) in combination with intensive sensory re-education resulted in improved hand function in nerve injured hands lasting at least 4 weeks after the last episode of anaesthesia.
In conclusion, hand function in both healthy persons and patients with median or ulnar nerve injuries can be improved by using the concept of brain plasticity. These findings have a potential clinical application in sensory re-education following nerve repair in the hand.

Key words: nerve injury, brain plasticity, hand function, sensibility, deafferentation, sensory re-education

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To my family

Contents

List of publications

This thesis is based on the following papers, which will be referred to by their Roman numerals:

I. **Acute improvement of contralateral hand function after deafferentation.** Björkman A, Rosén B, van Westen D, Larsson E-M, Lundborg G. NeuroReport 2004;15(12):1861-1865.

II. **Anaesthesia of the axillary plexus induces rapid improvement of sensory function in the contralateral hand: an effect of interhemispheric plasticity.** Björkman A, Rosén B, Lundborg G. Scand J Plast Reconstr Surg Hand Surg 2005;39:234-237.

III. **Acute improvement of hand sensibility after selective ipsilateral cutaneous forearm anaesthesia.** Björkman A, Rosén B, Lundborg G. Eur J Neurosci 2004;20:2733-2736.

IV. **Enhanced function in nerve-injured hands after contralateral deafferentation.** Björkman A, Rosén B, Lundborg G. NeuroReport 2005;16(5):517-519.

V. **Improved sensory relearning after nerve repair induced by selective temporary anaesthesia – a new concept in hand rehabilitation.** Rosén B, Björkman A, Lundborg G. Submitted J Hand Surg (Br.) 2005.

Thesis at a glance

Aim

The aim of this thesis was to investigate the effects of cortical reorganisational changes following experimental deafferentation and peripheral nerve injury in the hand and apply the concept of brain plasticity to enhance sensory re-education following peripheral nerve injury and repair in the hand.

Paper I

Acute improvement of contralateral hand function after deafferentation

Question: Does acute hand deafferentation improve contralateral hand function?

Method: 10 study persons and 10 controls were randomised and examined for left hand function before, during and after tourniquet-induced anaesthesia of the right hand. Functional magnetic resonance (fMRI) analysis was performed on three study persons.

Results: Tourniquet induced anaesthesia of the right hand resulted in rapid and significantly improved perception of touch, tactile discrimination and grip strength in the left hand. The improvement in tactile discrimination and grip strength remained at least 15 minutes after anaesthesia. fMRI showed increased activation in the right primary motor cortex after anaesthesia.

Paper II

Anaesthesia of the axillary plexus induces rapid improvement of sensory function in the contralateral hand: an effect of interhemispheric plasticity

Question: Does deafferentation with the pain factor eliminated, as in axillary plexus anaesthesia, induce improvement in contralateral hand sensibility?

Method: 100 patients operated on in axillary plexus anaesthesia were examined for sensory function in the non-anaesthetised hand before, during and after plexus anaesthesia.

Result: Plexus anaesthesia resulted in rapid, significant improvement in contralateral hand sensibility. The improvement lasted as long as the contralateral arm was anaesthetised.

Paper III

Acute improvement of hand sensibility after selective ipsilateral cutaneous forearm anaesthesia

Question: Does anaesthesia of the volar aspect of the forearm improve function in the same, ipsilateral, hand?

Method: Ipsilateral hand function was evaluated in a single blind randomised study of 20 persons receiving either a local anaesthetic cream (EMLA®) or placebo.

Results: EMLA® induced anaesthesia resulted in rapid and significant improvement in ipsilateral perception of touch and tactile discrimination. The improvement in tactile discrimination remained 24 hours after anaesthesia. Grip strength did not change.

Paper IV

Enhanced function in nerve-injured hands after contralateral deafferentation

Question: Can tourniquet induced anaesthesia induce contralateral improvement in hand function in nerve injured patients.

Material: 14 patients with median or ulnar nerve injuries at wrist level (minimum 6 months old injuries) were evaluated for hand function in their nerve injured hand before, during and after tourniquet induced anaesthesia of their healthy hand.

Results: Tourniquet induced anaesthesia of the contralateral, healthy, hand significantly improved hand function in nerve-injured hands both in the area corresponding to the intact nerve and the injured nerve. The improvement lasted at least 15 minutes after anaesthesia.

Paper V

Improved sensory relearning after nerve repair induced by selective temporary anaesthesia – a new concept in hand rehabilitation

Question: Can selective ipsilateral cutaneous anaesthesia enhance the effects of sensory re-education after peripheral nerve injury in the hand?

Material: 13 patients with median or ulnar nerve injuries (minimum 11 months old) at wrist level were evaluated for hand function. The study design was prospective, randomised and double blind. During a two-week period a local anaesthetic cream (EMLA®) or placebo was applied repeatedly to the volar aspect of the forearm of the injured arm in combination with a sensory re-education program.

Results: Repeated selective ipsilateral cutaneous anaesthesia of the forearm in combination with sensory re-education in nerve-injured patients resulted in significant improvement in perception of touch/pressure, tactile gnosis and in the summarised outcome four weeks after last EMLA®/placebo session.

Conclusion

Hand function in both healthy persons and patients with median or ulnar nerve injuries can be improved by using the concept of brain plasticity. These findings have a potential clinical application in sensory re-education following nerve repair in the hand.

Introduction

The hand and the brain are functionally intimately linked together and hand sensibility is very much a central nervous experience. Hand activity and the inflow of sensory signals from the hand influence the functional organisation of the brain cortex - the hand moulds the brain and the brain moulds the hand.

The human hand possesses unique features; it is a sense organ transmitting information from the surrounding world to the brain. It is also the most important tool for the brains ability to execute different tasks. Much of this is due to the well-developed sensory and motor functions in the hand that make possible strong power grips as well as delicate fine motor functions. The hands are also, together with the face, the body parts that most often are exposed to the surrounding world. Hereby the hand can be seen as a symbol for identity reflecting our state of mind and personality (1).

A peripheral nerve injury affecting a major nerve trunk has profound effects on the individuals' ability to experience and interact with the surrounding world. Today, despite refined surgical repair technique using microscope and special surgical instruments, there is no repair technique ensuring the recovery of normal sensory function in the hand of an adult patient after nerve repair in the hand (1, 2). The outcome is permanently impaired hand function with decreased quality of life, pain problems and also large costs for the individual and society (3, 4).

The focus of research on peripheral nerve injury has shifted from solely surgical repair techniques to include also basic neurobiological mechanisms such as factors affecting post-traumatic neuronal cell death (1, 2, 5, 6) and neurotrophic factors affecting axonal growth and orientation (7, 8). Cortical reorganisation following nerve injury (1, 2, 9-12) and environmental factors and motivation (13) have also gained increasing interest to explain the usually poor outcome after nerve injury and also as potential targets for specific therapies to promote the outcome after peripheral nerve repair.

Taken together the recovery of sensory and motor function in a hand after peripheral nerve injury and repair is the result of functional, biochemical and cellular events in the peripheral nerve as well as in the central nervous system. Despite the enormous amount of new experimental data on neuroscience that has evolved over the past two decades, nerve injuries are treated much in the same way today as 25 years ago (7, 14). The operating technique, with microscopes and specialized instruments cannot be refined more and the rehabilitation programs used after nerve repair were designed in the 60ies and 70ies and have not changed much since (13). Therefore, there are reasons to search for new strategies for improving functional recovery after nerve injury and repair (15).

An increased understanding of the cortical changes that follow nerve injury and also the cortical changes following rehabilitation is essential for designing new strategies for sensory re-education and sensory relearning following nerve injury and repair in the hand.

Background

The sense of touch – physiology

The human nervous system is divided into the central nervous system (CNS) comprising the brain and spinal cord and the peripheral nervous system (PNS) comprising all neural tissue outside the CNS (16, 17).

The skin can detect a wide range of stimuli through different receptors distributed throughout the body (18). Somatic sensibility has four major modalities: pure and discriminative touch, proprioception, nociception and temperature sense. All of these modalities are being mediated by a distinct system of receptors and pathways to the brain (16, 17).

All somatosensory information from the hand is conveyed by dorsal root ganglion neurons located adjacent to the spinal cord. The larger fibres, mediating touch and proprioception from the hand ascend in ipsilateral dorsal columns and terminate in the nucleus cuneatus. Here, the axons cross to the contralateral side terminating in the ventral posterior lateral (VPL) nucleus of the thalamus. The smaller afferent fibres mediating nociception and temperature ascend contralaterally in the anterolateral system to the thalamus. Like axons mediating proprioception and touch the axons mediating nociception and temperature are arranged somatotopical. The thalamic afferents project primarily to the primary somatosensory cortex, the dorsal anterior insular cortex and the anterior cingulated gyrus.

The thalamus is a complex relay station receiving and processing large amounts of information before sending it on to the cortex. The neurons in the VPL mediating touch and proprioception project their axons to the primary somatosensory cortex (SI) in the postcentral gyrus. The SI contains four cytoarchitecturally different areas: area 3a, 3b, 1 and 2 (19, 20). Area 3b and 1 receive most of their information from receptors in the skin (19, 21), area 3a and 2 receive most of their information from the muscles and joint. Furthermore, it has been shown (22) that the different areas are activated by different forms of stimuli so that area 3b and 1 are activated by discrimination of all types of stimuli, whereas area 3a is activated only when also motor activity occurs. Area 2 is activated by all mechanical stimuli, but has been show to have a preference for surface curvature differences and shape stimuli. Each area in the SI contains a complete map of the body. However, all four areas in the SI are extensively interconnected.

The body surface is represented in an orderly fashion throughout the CNS up to the SI. The somatosensory information terminates in the SI in an orderly fashion forming a map of the body, this is called somatotopy. The body surface is not equally represented in the SI, instead the size of the cortical area processing information from a specific body part is proportional to the degree of innervation of that body part. A separate somatotopical map, a so called homunculus (Figure 1) is seen in every one of the four areas in SI and also in the primary motor cortex (MI) (23, 24). The hand is

very densely innervated with peripheral receptors and thus has a, compared to its size, very large cortical area.

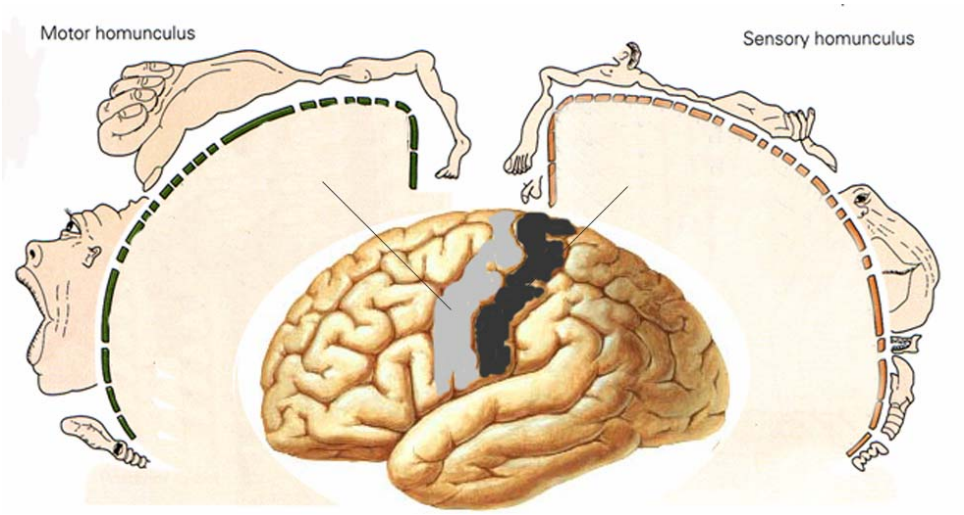

Figure 1 shows the cortical body map, homunculus, illustrating the cortical representation of various body parts in the primary motor and sensory cortex. The primary motor cortex MI is located in the precentral gyrus (light gray) and the primary sensory cortex SI in the postcentral gyrus (dark gray).

The processing of sensory information begins in SI and from there information is sent to the secondary somatosensory area (SII) located on the superior bank of the lateral fissure. This so called unimodal association area project the information to multimodal association areas where an integration of the information from several sensory modalities takes place and plans for action are made. The hemispheres are also linked together so that a cortical functional change due to a changed afferent nerve signal in one hemisphere is immediately mirrored in the opposite hemisphere (25, 26).
Both SI and SII as well as the multimodal association area send information to both pre-motorcortex and motorcortex providing information necessary for motor action (16, 17, 27-29).

Peripheral nerve injury and regeneration
Following a peripheral nerve injury and repair a series of events occurs in both the proximal and distal nerve segment. Distally the cut axons loose contact with their cell bodies leading to Wallerian degeneration of axons distal to the injury (30). Proximally a nerve injury may cause death of up to 35% of the injured neurons (6, 31, 32). Sensoryneurons appear to be more susceptible than motorneurons to die after

peripheral nerve injury (33). After a delay period the surviving neurons start to grow distally to re-innervate peripheral target organs. This is a biologically complex process depending on multiple environmental factors such as occurrence and influence of several types of neurotrophic factors (1). The speed of axonal regeneration is about 1mm per day in the hand (34). Regardless of type of nerve repair a substantial axonal misdirection at the repair site occurs (35, 36) resulting in new and changed innervation of the target organ (37).

The outcome of peripheral nerve repair has been shown to be dependent on various factors. *Age* is one such factor; the functional outcome of nerve repair in adults is mostly disappointing (1, 38), whereas the outcome in children is much better (38). A better adaptability of the young brain to interpret the new afferent nerve impulses sent by the misdirected axons is thought to be a reason for the superior results in children compared to adults (2, 38, 39). *Cognitive capacity* such as verbal learning capacity and visiospatial logic capacity has been shown to explain differences in sensibility in adults after nerve repair (40, 41). *Timing of repair* of the injured nerve is important, and there is a general agreement that injured nerves should be repaired with a minimum of delay (42) minimizing postoperative cell death, loss of neurons (1, 43), and fibrosis of the distal nerve segment. The *type of nerve* is also important; an injury to a pure sensory nerve eliminates the risk for mismatch between sensory and motor nerve fascicles whereas an injury to a mixed nerve has a high risk of motor-sensory mismatch (1). The *type of injury* is also a factor of importance. A crush injury always results in better functional outcome compared to a cut nerve because the axons are more easily guided back to their peripheral targets by the continuous Schwann cell layer. As a result, the functional outcome is always better after a crush injury as compared to a nerve transsection (1). Also the *technique of repair* is a factor of importance. Today microsurgical techniques with magnification or microscope combined with specialized instruments are routinely used in nerve surgery. Different types of repair using epineural sutures, group fascicular suture technique or entubulation are used but no differences in outcome between the different repair techniques have been demonstrated (1).

Introduction to brain plasticity

The brain has been seen as a rather static organ, until about 20 years ago, it was widely believed by neuroscientists that no new neural connections could be formed in the adult brain (16, 17). It was assumed that, once connections had been established in fetal life, or early infancy, they hardly changed later in life. This stability of connections in the adult brain has often been used to explain why there is usually very little functional recovery after damage to the nervous system. On the other hand memory and learning require that some changes are possible also in the adult brain (16). It has often been assumed that these phenomena are based on small changes at the synaptic level and do not necessarily involve alterations in the basic circuit of the brain.

The picture has changes radically in the last decades. One of the most interesting questions in neuroscience concerns the manner in which the nervous system can modify its organisation and ultimately its function throughout an individuals lifetime based on sensory input, experience, learning and injury (29, 44) a phenomenon that is often referred to as brain plasticity (16, 17).

Plasticity in the adult somatosensory pathways

There is a complete somatotopic map of the entire body surface in the somatosensory cortex of primates (16, 17). Merzenich et al (45) showed that after amputation of the middle finger of adult primates the area in the cortex corresponding to the amputated digit began, within two months, to respond to touch stimuli presented to the adjacent digits; i.e. this area is "taken over" by sensory input from adjacent digits. Jenkins et al (46) also showed that if a monkey "used" one finger excessively, for an hour and a half a day, then after 3 months the area of cortex corresponding to that finger "expanded" at the expense of adjacent fingers. Furthermore, if a monkey was forced to always use two fingers jointly by suturing two of its fingers together, then after 3 to 7.5 month it was found that single neurons in area 3b had receptive fields that spanned the border separating the two digits (47). Interestingly, if more than one finger was amputated there was no "take over" beyond about 1 mm of cortex. Merzenich et al (45, 48) concluded from this that the expansion is probably mediated by arborisation of thalamo-cortical axons that typically do not extend beyond 1 mm. The figure 1 mm has often been cited as the fixed upper limit of reorganisation of sensory pathways in adult animals (49). Pons et al (50), however, suggested that this view might be incorrect. They found that after long term (12 years) deafferentation of an upper limb the cortical area originally corresponding to the hand was taken over by sensory input from the face. The cells in "the cortical hand area" now started to respond to stimuli applied to the lower face region. Since this patch of cortex is more than 1 cm wide, they concluded that sensory reorganisation could occur over at least this distance, an order of magnitude ten times greater than the original 1 mm limit.

In addition to these long-term changes that are typically seen weeks or months after deprivation or stimulation, Calford and Tweedale (26) reported rapid – within minutes – short term changes that are based, presumably, on the unmasking of pre-existing connections rather than on anatomical "sprouting". Calford and Tweedale (26) also showed that a small unilateral peripheral denervation in adult flying foxes leads to expansion of the cortical receptive field for neighbouring skin areas, as predicted from the work of Merzenich et al (45). Surprisingly, the receptive field of the homotopic region in the other hemisphere mirrored the change. In other words, the second hemisphere learned what the first had done; it copied the revised sensory map. Maintaining symmetric sensory representation of the two sides in the cerebral cortex may be important for the control of symmetric bilateral motor activity.

Experience dependent plasticity refers to the ability of the adult brain to adjust itself to changes in environmental conditions. It relates to the learning of special skills that

requires special training and it often requires motivation and concentration on the task (51).
Another example of brain plasticity is the so called cross-modal plasticity. This phenomenon implies that one sensory modality can substitute for another (52). The most well known example is in blind persons where an improved sensory function is noticed and it has also been shown that when a blind person reads Braille activation in the occipital lobe occurs implying that the somatosensory stimuli from reading activates the cortical area responsible for vision (53).
Another example are persons in whom the lack of sensibility can be substituted with hearing. Trough small microphones on the fingers the persons can, after a short training period, listen to what they feel (54). A crucial element in such cross-modal plasticity seems to be training, in order for a sensory modality to "take over" another sensory modality.

Mechanisms of plasticity
Several cellular mechanisms by which the adult brain can adjust to changes in the environment or in sensory input have been defined, including the following (16, 17);
Decreased inhibition
Many connections between the periphery and the cortex as well as intracortical connections are physiologically "silent" because of inhibitory influences (55). Sensory stimulation of a point on the skin activates neurons in the somatosensory system, near the centre of the area of cortical representation and inhibits activity in neurons near the edges. In this way the receptive field appears smaller than its actual size. The inhibition is due to activation of inhibitory interneurons near the edges of the receptive field. Decreased inhibition would theoretically increase the receptive field size and enable more neurons to be activated by the stimulus; this is sometimes referred to as unmasking of synapses or neural structures. Gamma-aminobutyric acid (GABA) is the most important inhibitory neurotransmittor in the brain (56) and evidence is strong that reduction of GABAergic inhibition is crucial in mediating short term plasticity changes (9).
Increase in synaptic strength
The effectiveness of synaptic connections is continuously adopted in response to functional demands. Synaptic transmission becomes facilitated in a pathway that is frequently used, while those that lay dormant atrophy. In this way, repeated practice of a task leads to increased speed and accuracy of performance. Increased synaptic strength may be a mechanism for learning and also for recovery from brain injury. Repetitive stimulation results in increased excitability and facilitation of transmission in the synapses. These effects persist for some time after the initial stimulus and subsequently show gradual declines (long term potentiation, LTP). Calcium channels in the neuronal membrane appear to be crucial in this process. LTP is probably one of the major mechanism by which learning and memory consolidation takes place in the brain (16).

Axonal and dendritic sprouting

The sprouting and elongation of new dendrites and axons is a common response to injury and cell loss at all levels in the nervous system. Sprouting can also be seen in response to increased functional demand, such as exposure to conditions requiring more complex motor activity (57). Axons at the edges of a lesion send new axonal branches into the damaged area and re-innervate dendrites that have lost their synaptic input. This leads to new synaptic formation at the point of contact of axonal sprouts with these dendritic trees. This mechanism for recovery has been suggested in for example the reaction of the somatosensory cortex to loss of its input from the skin (45, 50).

Formation of new synapses

New synapses are formed and disappear throughout lifetime. Likely there is equilibrium between the formation and the destruction of synapses (16). The formation of new synapses has been demonstrated to occur in animals in response to enriched environment input (57, 58). Synaptic plasticity and number and turnover of synapses have been postulated as important mechanisms underlying cortical map reorganisation (59).

Formation of new neurons

Neural stem cells, which can self-renew and also differentiate to produce progeny cells and neurons have been shown in the sub-ventricular zone and in the hippocampus in the adult human brain (60, 61). The role of these stem cells in humans is not clear. However, in animal studies neurogenesis has been shown in response to enriched environment (62, 63).

fMRI

Functional magnetic resonance imaging (fMRI) was introduced in the early 1990ies (64-66) and has evolved into the dominant technique for investigating sensory, motor and cognitive brain functions in both humans and animals (66, 67). Functional imaging techniques allow assessment of distributed regional brain activity in humans during the performance of specified tasks. fMRI includes many different methods, but the most commonly used is the blood oxygen level dependent imaging (BOLD) technique (66). During an increase in neuronal activation, there is an increase in local cerebral blood flow, but only a small proportion of the oxygen is used. There is therefore a net increase in the tissue concentration of oxyhaemoglobin and a net reduction in the tissue concentration of paramagnetic deoxyhaemoglobin in the local capillary bed, and draining venules. The magnetic property of haemoglobin depends on its level of oxygenation, so that this change results in an increase in signal intensity on T2-weighted magnetic resonance images.

The important question to ask when dealing with fMRI is not only where activity occurs in the brain but what the activity reflects, why the activity is occurring (68). Careful composition of stimuli and tasks for evolving brain activation and their presentation in complex paradigms is essential for inducing distinct BOLD responses.

Because fMRI maps are based on secondary activity and not on the electrical activity from the neurons themselves, it remains mostly unclear what the spatial specificity of fMRI is, i.e. how accurate are the maps generated by fMRI as compared with the actual sites of neuronal activity.

Sensory re-education

Recovery of functional sensibility after nerve injury and repair is a learning process. After a nerve injury and repair "the hand speaks a new language to the brain" (69-71). The brain has to learn to interpret this new language, which is achieved be sensory relearning through sensory re-educational programs. The cortical effects of sensory re-education are unknown (72). It is not known whether the functional improvement seen after training is based on a normalization of the distorted hand map created by the initial cortical reorganisation after nerve injury or is caused by adaptations within the brain enabling it to decipher the distorted hand map. In adults it is probably a mixture of both these mechanisms that end up in an improvement in sensory function.

Wynn-Parry published the first sensory re-education program in 1966 (73). The aim in sensory re-education is to take advantage of the cortical reorganisation process following all nerve injuries and to teach the brain "the new language spoken by the hand" (13, 69, 71).

Traditionally sensory re-education is first started when some perception of touch can be demonstrated in the injured area (69, 71) meaning that training starts months after the injury. Lundborg et al. have advocated that one should differentiate between an early post operative phase, before re-innervation has occurred, and a late post-operative phase, when some re-innervation of the hand has occurred, and use different re-educational strategies in the two phases (1, 74). In the early phase sensory by-pass is one alternative using the brains ability for cross modal plasticity, the substitution of one sense with another. The injured nerve is "by-passed" by transmitting friction sound from the hand to the brain (75), in this way the area in the primary somatosensory cortex deprived of its sensory input is activated and theoretically the organization within the primary somatosensory cortex is, to some extent, kept. In the late post-operative phase the multimodal capacity of the brain can be used, the sense of touch is trained by use of vision, smell, taste and hearing (13). Also bilateral tactile training can be used as sensory inputs are processed in both brain hemispheres (2, 76) and the two hemispheres are extensively interconnected. The aim is to maintain cortical sensory input from the hand and thus preserve the cortical organization during the time of peripheral nerve regeneration (1, 2, 13, 74).

Sensory re-education is classically based on vision guiding touch, but other sensory modalities can also be used to guiding touch, thus improving the patients' ability to interpret afferent sensory nerve signals. The exercises are easy to do and can be performed at home by the patient (70). Outcome studies following nerve injury in adults usually show disappointing results as to the recovery of tactile gnosis (77-80). Studies evaluating sensory re-education after repair of the median or ulnar nerve in the forearm and hand are difficult to find in the literature. However, improvement of

functional sensibility after sensory re-education has been reported in a few studies (70, 71, 81-83).
The sensory re-education programs designed in the 1960s and 1970s are still in use today despite the enormous advances in neuroscience and neural plasticity, which have evolved over the last decade.

Clinical assessment of hand function after a nerve injury
Assessing hand function following peripheral nerve injury and repair is not done by one single test, instead different measures are needed to quantify outcome in settings of modalities, such as sensibility, motor function, pain, discomfort and overall functional of the hand (79, 84-88).
The focus of this thesis is primarily on sensibility as a part of the overall outcome from peripheral nerve surgery and cortical reorganisation. The assessments are made on body function and structure level according to "International Classification of Functioning, disability and health" (89).
Different clinical sensibility tests can hierarchically be divided into detection tests, discrimination tests and identification tests (86, 87, 90).
Detection tests, to establish a threshold for perception of touch, require detection of a single stimulus, such as the light pressure from a filament. The most commonly used detection test is the Semmes-Weinstein Monofilament test (SWM) (91) which is similar to von Frey´s hair (92). The principle is that nylon filaments of different thickness mounted on a rod are applied perpendicular to the skin to the point of "buckling" then giving a specific pressure (8mg-450g) depending on thickness. The test is performed in a standardized way and the subject indicates when he or she can feel the touch or not. This establishes the smallest perceivable touch/pressure threshold, which can be detected (91).
Discriminative tests require discrimination between different stimuli and included in the group are also "tactile gnosis" tests (79, 93, 94). To be able to localize touch is maybe the most basic discriminative capacity (86, 90). Another example of the discriminative capacity is the two-point discrimination (2PD) test, which is one of the most widely used tests among surgeons and therapists to assess hand sensibility. The classic static-two-point discrimination test was developed by Weber in 1835 (93-95). One or two points are randomly applied to the tested area and the subject is asked to report whether one or two points were perceived. The limit of 2PD is based on the smallest distance with a certain ratio of correct versus incorrect responses, according to Moberg (96) 7 out of 10 correct answers at just blanching the skin (91). The methodology of 2PD has been questioned as sole test for sensory function and it is important that 2PD results always are accompanied by a detailed description of how the test was performed (84, 90).
The grating orientation test (GOT) was developed as an alternative to the 2PD test (97). The GOT comprise of domes with a fixed grating pattern on a convex surface. The domes are applied to the skin in one of two orthogonal orientations and the subject is asked to state whether the grooves lie along or across the finger. The GOT

has to date not been found sensitive enough for assessing spatial resolution following nerve injury and repair in the hand, and is, as 2PD, based on passive touch (98).
To identify different qualities of objects actively the STI-test (shape / texture identification test) was developed (99). This test along with SWM was one of two sensibility tests to be demonstrated to have good evidence and to be valid and reliable (84). The STI-test is based on active touch with identification of shapes and textures of increasing difficulty, it is standardized and can be used after median as well as ulnar nerve injuries (99). Identifying objects is the most refined aspect of tactile gnosis (69, 79, 93, 94, 99) and this capacity of tactile gnosis is forwarding the test procedure in a direction towards functional sensibility, which sometimes is considered sensory and motor function in "concert" (100) i.e. the hand in use in daily activities. Such integration of sensory and motor function can be expressed in grip function tests (79). A functioning sensibility in the hand gives important feedback to grip function and grip strength, which provides a crude measure on hand function. The Jamar dynamometer is the most widely used tool to evaluate grip strength (91).
The "Model Instrument for Outcome After Nerve Repair" is a new model for routine documentation and quantification of the functional outcome after nerve repair at wrist or distal forearm level (85, 101, 102). The model that has data confirming validity and reliability includes a protocol with a numerical scoring system and comprises assessments reflecting sensory, motor and pain/discomfort aspects. Investigations support the hypothesis that this model of documentation reflects specific impairments and also correlates well with the patient's opinion of the impact of the nerve injury on activities of daily living (ADL) (88).

Aim of the thesis

The general aim of this thesis was to investigate the effects of cortical reorganisational changes following experimental deafferentation and peripheral nerve injury in the hand and apply the concept of brain plasticity to enhance sensory re-education following peripheral nerve injury and repair in the hand.

Specific aims were to:

investigate the effects of contralateral experimental deafferentation on hand function in healthy subjects and patients after median or ulnar nerve repair. (Paper I, II and IV)

investigate the effects of selective ipsilateral deafferentation on hand function in healthy subjects and patients after median or ulnar nerve repair. (Paper III and V)

apply the results from these studies into a clinical training program focusing on the brains ability to reorganise and hereby enhance the functional outcome after nerve injury and repair in the hand. (Paper V)

Material and methods

The local ethics committee approved all studies and written informed consent was obtained from all participants both volunteers and patients.

Tourniquet induced anaesthesia
Transient deafferentation of the hand was induced by an ischemic nerve block using a pneumatic tourniquet on the forearm (25, 103-106) (Figure 2). Tourniquet induced anaesthesia induces not only tactile loss, but also loss of proprioceptive sensation as well as motor paresis.
A conventional tourniquet, 7,5 cm wide, was placed just distal to the cubital fossa. The tourniquet was inflated to 250 mm Hg. The arm was placed comfortably on a soft padding. The tourniquet pressure was kept constant during the experiment. Anaesthesia was defined as the time when touch perception was abolished when tested with Semmes-Weinstein monofilament 6.65. The testing started immediately after onset of anaesthesia. The study subjects were instructed to report when they experienced discomfort in the forearm and hand, at this time the pressure in the tourniquet was released. Sensibility and motor function in the hand returns within minutes to normal after the pressure is released in the tourniquet. No side effects were noticed in any study subject after tourniquet induced anaesthesia.

Cutaneous anaesthesia
A pure sensory cutaneous anaesthesia was achieved by a local anaesthetic cream, containing 2.5% lidocaine and 2.5% prilocaine in an oil and water emulsion, EMLA® (AstraZeneca, Södertälje, Sweden) (Figure 2). Prior to the application of EMLA® a medical history was taken with special emphasis on prior experience with local anaesthetic agents and allergies.
20 grams of EMLA® was applied to the volar aspect of the forearm in an area from the wrist and 15 cm proximally. The EMLA® was placed under an occlusive bandage in order to get a better absorption of the substance. After 1 hour the volar aspect of the forearm is completely anaesthetised and the anaesthesia lasts for a few hours. No study subjects reported any problems or side effects after the EMLA® treatment.

Paper I
Acute improvement of contralateral hand function after deafferentation
The purpose of this paper was to investigate the effect on hand function of contralateral hand deafferentation.
Ten healthy right-handed men, median age 35.5 years (range 27 to 60 years) participated in this study. The controls were 10 men, median age 34 years, (range 24 to 59 years). The study subjects were all recruited from the staff at the Department of Hand Surgery, University Hospital Malmö. The study subjects were matched in pairs based on age. All study subjects received a pneumatic tourniquet on their right

forearm (Figure 2). The tourniquet was inflated to 250 mm Hg in one study subject in each pair and on the other the tourniquet was just applied to the forearm but not inflated. The mean duration of tourniquet inflation before anaesthesia was 25 minutes (range 23 to 30 minutes) and the total inflation time was 40 minutes (range 32 to 45 minutes). Three study subjects also underwent an additional fMRI investigation before, during and after tourniquet-induced anaesthesia.

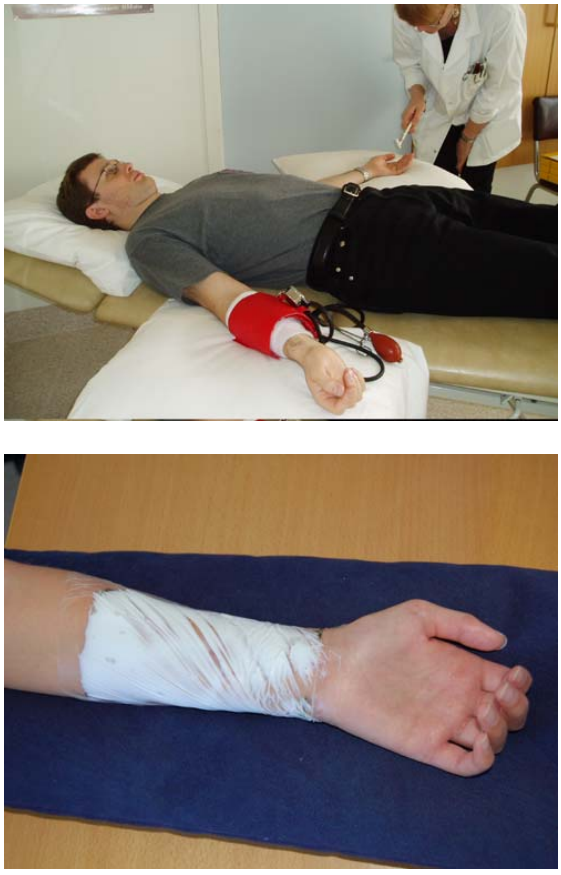

Figure 2
Experimental setup for tourniquet induced anaesthesia (top). The study subject rests comfortably with the tourniquet on the right forearm while sensory tests are performed on the left hand.
Experimental setup for cutaneous anaesthesia (bottom) with a local anaesthetic cream (EMLA®). The cream is applied to an area corresponding to the whole width of the forearm and extending 15 cm proximally to the wrist.

Assessments of sensory and motor functions were done using SWM, 2PD, GOT and Jamar (Figure 3) before, during and 15 minutes after the tourniquet was released. The controls were investigated in exactly the same way.

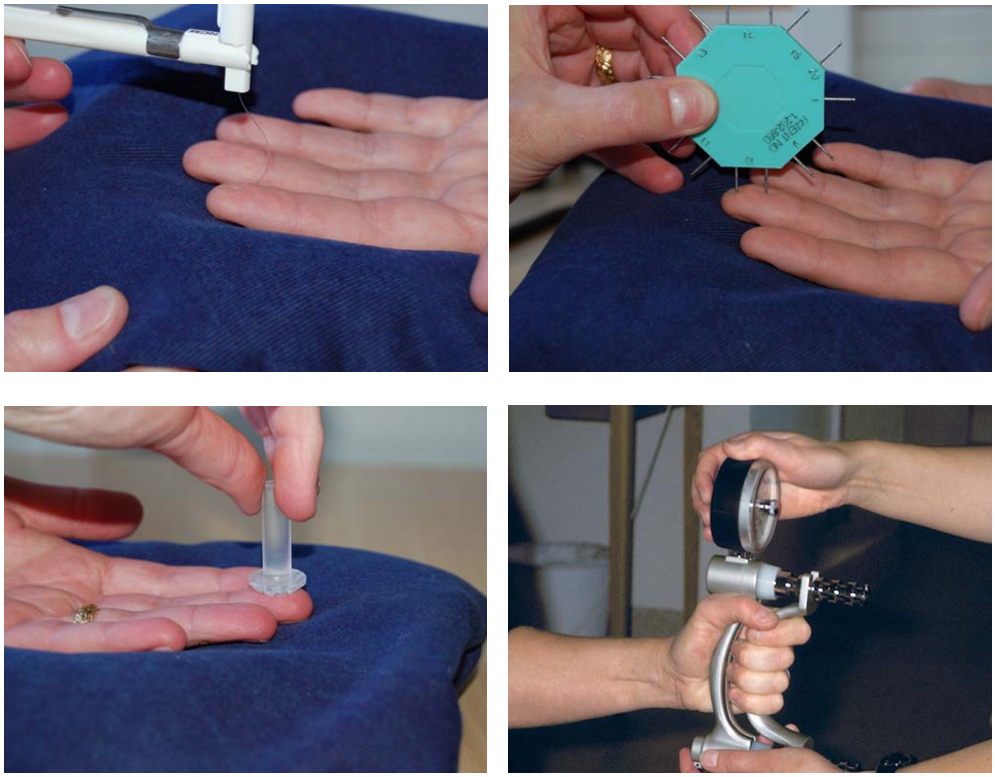

Figure 3 illustrates the experimental setup for the following hand function tests:
Semmes-Weinstein monofilament (SWM) evaluating perception of touch (top left)
Two point discrimination (2PD) evaluating tactile discrimination (top right)
Grating orientation test (GOT) evaluating tactile discrimination (bottom left)
Jamar dynamometer (Jamar) evaluating grip strength (bottom right)

Paper II

Anaesthesia of the axillary plexus induces rapid improvement of sensory function in the contralateral hand: an effect of interhemispheric plasticity

The purpose of this paper was to investigate the effects on hand function of contralateral deafferentation with the pain factor eliminated.

One hundred patients, (56 men and 44 women) mean age 49 years (range 17 to 84 years) being operated on in axillary plexus anaesthesia at the Department of Hand Surgery, University Hospital Malmö participated in this study. Forty-six patients had

their dominant hand operated and 54 their non-dominant hand. All patients listed for operation in axillary plexus anaesthesia and who did not report any subjective nerve symptoms in the hand not to be operated on were asked to participate. The axillary plexus anaesthesia was performed with mepivacaine (Carbocaine®) with or without adrenaline. Sixty patients (35 men and 25 women) were given anaesthesia with mepivacaine and adrenaline and 40 patients (21 men and 19 women) with mepivacaine alone.
Assessments of sensory functions were done with 2PD and SWM before, during and after recovery from anaesthesia. The patients were also asked to describe how they experienced the position of the anaesthetised arm.

Paper III
Acute improvement of hand sensibility after selective ipsilateral cutaneous forearm anaesthesia
The purpose of this paper was to investigate the effects on hand function of selective cutaneous ipsilateral deafferentation.
Twenty healthy subjects (six men and 14 women), mean age 36 years (range 25 to 52 years) participated in this study. The study subjects were all recruited from the staff at the Department of Hand Surgery, University Hospital Malmö. None of the study subjects reported any subjective nerve symptoms from the hands. The subjects were matched in pairs based on age and randomised to receive a mixture of local anaesthesia containing 2.5% lidocaine and 2.5% prilocaine in an oil and water emulsion (EMLA®) or placebo on the volar side of the right forearm in an area from the wrist and 15 cm proximally under occlusive bandage for one hour (Figure 2). The study design was single blind and all study subjects believed that they received an active substance.
Assessments of motor and sensory functions were done on three separate occasions within a week before the experiment to establish a baseline. Anaesthesia occurred approximately one hour after the EMLA® was applied and at this point motor and sensory functions were assessed as well as 24 hours after anaesthesia. All sensory measures were performed on the left and right index finger. Tactile discrimination was evaluated with 2PD and perception of touch with SWM. Grip strength was evaluated using a Jamar dynamometer.

Paper IV
Enhanced function in nerve-injured hands after contralateral deafferentation
The purpose of this paper was to investigate the effects on hand function of contralateral deafferentation in nerve-injured patients.
Fourteen men, median age 43 years (range 24 to 57 years) participated in this study. Three had median nerve injuries and 11 had ulnar nerve injuries. All injuries were at wrist level and all nerves had been repaired within 24 hours from the injury. The mean time from injury to study start was 20 months (range 6 to 48 months). A tourniquet

was placed on the contralateral, un-injured, forearm. Mean tourniquet time until anaesthesia was 28 minutes (range 22 to 35 minutes).
Assessments of sensory functions in the nerve-injured hand were done on the index and little fingers using 2PD and SWM. Assessment of motor functions in the nerve-injured hand was done using a Jamar dynamometer before, during and 15 minutes after the tourniquet was released.

Paper V
Improved sensory relearning after nerve repair induced by selective temporary anaesthesia – a new concept in hand rehabilitation
The purpose of this paper was to investigate the effects on hand function of selective cutaneous deafferentation and sensory re-education in nerve-injured patients.
Thirteen patients (10 men and 3 women) median age 38.2 years (range 19 to 75 years) with median (n=7) or ulnar (n=6) nerve injuries at wrist level participated in this study. The mean time from injury was 22 months (range 11 to 52 months). The study design was prospective, randomised, double blind. The study subjects were randomised to receive a local anaesthetic cream (EMLA®) (n=7) or placebo (n=6) on the volar aspect of the forearm on the injured side. The participants received EMLA® or placebo at four separate occasions during a two-week period and during the time period when the participant had EMLA® or placebo applied to the forearm they performed a specific training program. They also had an additional home training program, which they performed five times per day.
Assessments of sensory functions in the nerve-injured hand were done according to the Model for Documentation of Outcome after Nerve Repair (102). Tests were performed on the index and little fingers using 2PD and SWM, before the start of training, during training as well as four weeks after the last training episode.

Statistics
Most of the data in this thesis were not normally distributed and on ordinal scales and due to this non-parametric statistics were used. The software StatView® 5.0.1 (SAS Institute Inc, Cary, USA) was used to perform the analysis. A p-value < 0.05 was considered significant.

Results

The following is a summary of the results and for more detailed information the reader is referred to papers I-V.

Paper I

Acute improvement of contralateral hand function after deafferentation

Tourniquet induced anaesthesia of the right hand significantly improved tactile discrimination measured with 2PD, perception of touch, and grip strength in the left hand compared to the results before anaesthesia. The improvement in grip strength and tactile discrimination lasted at least 15 minutes after anaesthesia while perception of touch shifted back to pre-anaesthesia values after 15 minutes. Tactile discrimination measured as GOT did not change in either group during the experiment. The controls were all stable during the test procedure. fMRI in three study subject during tourniquet induced anaesthesia showed increased activation in the right primary motor cortex (MI) after anaesthesia. For sensory stimulation no differences in activation were seen.

Paper II

Anaesthesia of the axillary plexus induces rapid improvement of sensory function in the contralateral hand: an effect of interhemispheric plasticity

60 patients received axillary plexus anaesthesia with mepivacaine and adrenaline and 40 patients with mepivacaine alone. There were no significant differences between the group given adrenaline and those not given adrenaline, so the groups were added to form one group of 100 patients. Axillary plexus anaesthesia resulted in significant improvement in tactile discrimination and perception of touch in the non-anaesthetised hand. Both tactile discrimination and perception of touch shifted back to pre-anaesthesia values after recovery from anaesthesia. Sixty-five percent of the patients felt that the anaesthetised arm had an upright position although it was positioned horizontally.

Paper III

Acute improvement of hand sensibility after selective ipsilateral cutaneous forearm anaesthesia

Selective ipsilateral cutaneous anaesthesia resulted in significantly improved tactile discrimination measured with 2PD compared both to pre-anaesthesia values and compared to the placebo group. The improvement remained at least 24 hours. Perception of touch was significantly improved during anaesthesia compared to pre-anaesthesia values and the improvement lasted at least 24 hours, however no significant group differences were noted in perception of touch. No changes in tactile discrimination or perception of touch were noted in the contralateral hand or in the control group during the experiment. No changes in grip strength were noted in either hand.

Paper IV

Enhanced function in nerve-injured hands after contralateral deafferentation

Tourniquet induced anaesthesia of the un-injured hand in patients with median or ulnar nerve injuries significantly improved tactile discrimination measured with 2PD and perception of touch in the contralateral, nerve injured hand both in the area corresponding to the injured and in the area corresponding to the un-injured nerve. The improvement lasted at least 15 minutes after anaesthesia. Grip strength was also significantly improved in the nerve-injured hands during anaesthesia and the improvement lasted at least 15 minutes.

Paper V

Improved sensory relearning after nerve repair induced by selective temporary anaesthesia – a new concept in hand rehabilitation

Both selective cutaneous forearm anaesthesia with EMLA® and placebo together with intense sensory re-education in nerve-injured hands resulted in improved hand function. However, selective cutaneous forearm anaesthesia with EMLA® together with intense sensory re-education resulted in significant improvement in tactile discrimination, perception of touch and in the summarised outcome in “total score” compared to placebo and sensory re-education. The significant improvement in the EMLA® compared to placebo group lasted at least four weeks after the last application of EMLA® or placebo.

Discussion

This thesis focuses on the reaction of the central nervous system to peripheral nerve injury, the effects of experimental selective deafferentation and, furthermore, addresses the possibilities to manipulate the central nervous system by using its capacity for functional reorganisation to improve hand function after peripheral nerve injuries.

Cortical remodelling following nerve injury

The cortical representation of body parts is constantly changed based on the pattern of afferent nerve input (2, 9, 12, 29). A peripheral nerve injury causes rapid neurochemical, molecular, functional, and structural changes in the peripheral nerve, spinal cord, brain stem and cerebral cortex (1, 2, 9, 12). Consequently the recovery of function following a peripheral nerve injury is the sum of events taking place at all levels in the PNS and CNS.

The focus in the treatment of peripheral nerve injuries has long been on the repair technique using microscope and specialized instruments, even so the clinical outcome after peripheral nerve repair has remained poor (1, 40, 77, 78, 107). Recently, cortical changes following a peripheral nerve injury have been suggested to be the reason for the generally poor outcome (1, 11).

Contralateral selective deafferentation

Peripheral nerve injury and experimental deafferentation have been shown to induce changes in both brain hemispheres (25, 26). Developing, and to some extent the adult cerebral cortex, deprived of its normal inputs, do not become inactive, but instead seek input from other cortical areas and systems (1, 9). We started by using tourniquet induced anaesthesia, a method that had been shown to induce sensory loss and motor paresis (25, 103-106). Theoretically a large area in the cerebral cortex is deafferentated and this creates a massive cortical reorganisation resulting in a rapid improvement in contralateral hand function (103, 108). Given the possibility that the ischemic pain created by the tourniquet would induce adrenaline release, which in turn could affect the sensory function of the hand, and also that the pain itself would affect the attention of the person being tested, and thus the evaluation, we chose to investigate patients operated on in axillary plexus anaesthesia in order to eliminate the pain factor. A confounding factor is of course that patients being operated on may have difficulties to concentrate on the sensory tests. However, the results are similar in both studies (paper I and II) showing a rapid and significant improvement in perception of touch and tactile discrimination in the contralateral hand (108, 109) and we feel convinced that it is the deafferentation of a cortical area that ultimately leads to a contralateral improvement in hand function.

Rapid and slow cortical remodelling

Two main mechanisms have been proposed to most likely explain the reorganisation after peripheral nerve injury and experimental deafferentation: unmasking of previous present but physiologically inactive connections and growth of new connections (sprouting). Unmasking is a strong candidate as the primary mechanism during the immediate phase following nerve injury. The mechanism behind unmasking is most likely removal of inhibition to excitatory synapses, which in turn may be due to reduction of GABAergic inhibition (1, 9, 25). The improvement in hand function is apparent as soon as the hand is deafferentated; implicating that existing neural substrates are involved and supporting the hypothesis that inactive or inhibited neurons are activated possibly by an decreased inhibition mediated by e.g. the GABA system (25).

fMRI was used to assess the cortical activity in sensory and motor cortex before, during and after tourniquet-induced anaesthesia (108). Even though cortical reorganisation most likely occurred during the deafferentation and the sensory functions of the hand improved, no changes in activity were seen in either sensory cortex with fMRI. An increase was noted in the primary motor cortex 15 minutes after the deafferentation as opposed to before anaesthesia and also compared to the total period before and during anaesthesia. It is not clear whether we could not detect any changes in the primary sensory cortex due to insufficient sensitivity and resolution of the fMRI equipment or due to other factors. These first studies (Paper I-III) (108-110) also showed that it is rather easy to induce cortical reorganisation resulting in improved had function. The improvement lasted at least as long as the hand was deafferentated and in some cases even longer.

Ipsilateral selective deafferentation

Tourniquet induced anaesthesia is not suitable in the clinical situation for several reasons: it is painful, and due to this the time of deafferentation is limited, repeated deafferentation using a tourniquet may induce injuries to the nerves in the forearm with permanently impaired nerve function as a result, and it is difficult for the patient to manage the deafferentation himself. Our main objective was then to look for a method more suitable for patient usage, giving a cortical deafferentation “large” enough to induce changes in peripheral function but not unnecessarily large. The method should also be safe with no side effects, pain free, and easy to us for both patient and therapist. Furthermore, it should be specific for sensory functions not affecting the motor function as this would affect the person’s ability to perform motor tasks. Several studies have shown that a limited peripheral deafferentation results in adjacent cortical areas taking over the deafferentated cortical area (9, 12, 25). Muellbacher (111) showed that temporary deafferentation of the upper brachial plexus in combination with task specific motor practice in patients with stroke resulted in improved motor function in the ipsilateral hand. In analogy with this we wanted to use a limited peripheral deafferentation close to the nerve injured area in order for the cortical representation of the injured nerve area to expand over the deafferentated area.

As the forearm is located next to the hand in the somatosensory cortex we chose to use a local anaesthetic cream, EMLA®, to deafferentate the volar aspect of the forearm. A limited deafferentation using a local anaesthetic cream on the volar aspect of the forearm resulted as expected in rapid and significant improvement in ipsilateral hand function and no changes in the contralateral hand (110). The mechanism behind this is likely expansion of the intact cortical areas over the deafferentated cortical areas resulting in enhanced cortical representation of the hand. The improvement was rapid indicating unmasking of existing neural structures as the mechanism responsible for the expansion of the cortical areas which is possibly based on decreased cortical inhibition. In contrast to the contralateral improvement in hand function seen after hand deafferentation only the ipsilateral hand improved and no changes were seen in the contralateral hand. One explanation to this may be that the limited anaesthetic area (volar part of the forearm) may be too small to induce cortical reorganisational changes in both hemispheres as seen when the whole forearm is anaesthetised by a tourniquet (103, 108). It may also be that adjacent cortical areas connected to the anaesthetised side are even faster in occupying the deafferentated area than cortical areas belonging to the non-anaesthetised side. The improvement in sensory function though was not permanent.

Selective deafferentation and nerve injury

It has been advocated that the reason for the generally poor outcome after peripheral nerve injury and repair is due to cortical changes (1, 2). We identified a cohort of patients with median or ulnar nerve injuries at wrist level and studied the effects of contralateral tourniquet induced anaesthesia on these patients (112). The reason for using tourniquet-induced anaesthesia was that we felt that this method created a larger deafferentated skin area and thus a larger cortical reorganisation thus likely to create a deafferentation large enough to induce functional changes in the nerve injured hand. Tourniquet induced anaesthesia induced improvement in nerve injured hands both in the area corresponding to the injured nerve and to the intact nerve indicating that at least part of the mechanisms for the generally poor functional outcome are located in the CNS. The time window for possible improvement of hand function after nerve repair is likely long, as improvement was seen even in injuries more than 3 years old.

Based on the findings from the first four studies (108-110, 112) a fifth study (113) was designed with the prerequisite that the deafferentation should be limited, pain free, easy to apply and safe, and it should also create a more long lasting effect. Patients with median and ulnar nerve injuries at wrist level were identified and were treated with a local anaesthetic cream or placebo on the volar aspect of the forearm. In order to induce a more lasting effect the cream was applied twice a week for two weeks in a row and combined with sensory re-education. The results showed that both groups improved but the group that had a limited deafferentation using a local anaesthetic cream on the forearm in combination with sensory re-education improved significantly more and the improvement lasted at least 4 weeks. Likely the mechanism behind this is a rapid unmasking of existing neural substrates but through a repeated

deafferentation we may create a more long lasting time window that enables the patient to consolidate the cortical changes better and thus giving a more long lasting improvement.
The frequency and duration of the experimental deafferentation and also the time interval between the deafferentation episodes as well as the design of the sensory relearning are likely of importance in order to achieve an optimal result. Ongoing and future studies will focus on these factors and can hopefully lead to better sensory re-education programs.

Critical time window and learning
Recently the concept of critical periods has been expanded to include periods in brain development during which the effects of environmental stimulation on brain structure and function are maximal. In particular, there has been interest in "time windows of opportunity" during which teaching and enriched environment programs are apt to be most effective (51). At no time in life is the brain so easily shaped by external stimuli and experience than in infancy and early childhood (114). It is during these "critical periods" that neural circuits acquire language with native fluency (38, 115, 116). Discovering the mechanism that limits such plasticity to early life would enhance the possibilities for improved learning in adulthood and also new paradigms or therapeutic agents during rehabilitation and recovery from injury. Essentially two mechanisms have been advocated for (16, 17). According to one view the potential for neural plasticity is never lost, but merely temporarily fixed by an evolving dynamic of neural activity. One would thus need to identify the correct "training" regimen to transfer these neural networks out of one stable state into another. It is indeed easier to do so in a younger brain, but a limited peripheral deafferentation may be one way. Alternatively, among the enormous amount of molecular changes seen in neural development and ageing appears a group of factors that inhibit further plasticity, eventually preventing large scale circuit reorganisation and thereby structurally closing the critical period (16, 17).
So does the critical period permanently hard wire our brains or can we enjoy massive plasticity throughout life by finding the right stimulation and training protocols?

Sensory re-education
The cortical effects of sensory re-education and training have not been well studied but changes in the cerebral cortex analogous to those reported after motor training in animals have recently been found in adult humans using fMRI. Karni and colleagues (117) had subjects undergo daily practice sessions of a complex motor task (rapid sequences of finger movements). The speed and accuracy of performance increased over a period of 4 weeks. At the end of this period, performance of the learned task during fMRI scanning activated a larger area of primary motor cortex (MI) than had been activated prior to the practice sessions. A comparable unpractised task did not produce increased activation, nor was there increased activation of the motor cortex ipsilateral to the trained hand. The effect persisted for several months. The results are

consistent with the establishment of new synaptic circuits, either by utilization of circuits previously dedicated to other motor tasks or by dendritic sprouting, as was found in animal experiments (16, 17). Following a peripheral nerve injury profound cortical reorganisation takes place with adjacent and contralateral cortical areas taking over the injured area. After nerve regeneration the injured nerve tries to recapture its original cortical area usually resulting in a new and changed cortical hand map (80, 118). An understanding of the cortical changes occurring after a nerve injury is essential for designing the sensory re-education following nerve repair. Since conditions for re-education change at different times after a nerve injury, strategies for sensory re-education should be optimised considering time intervals after nerve injury in order to achieve a maximal effect of the training.
However, little is known about the cortical effects of sensory training (72). It is unclear whether sensory re-education reverses cortical changes to a more normal, pre-injury, organisation or whether the hand map remains distorted and peripheral nerve signals are interpreted in a more correct way with help from other cortical regions. Furthermore, the age of the patient might influence results of sensory re-education. Therefore, it might be advantageous to adopt sensory re-education program for different age groups. Much speaks in favour of this, and it is well established that children gain excellent function after a nerve repair (1, 39, 119, 120) whereas older people score lower. As stated previously the ability for plastic changes within the brain is not lost by aging but changed. Furthermore, factors such as motivation and cognitive capacity are important for recovery of function (13, 40, 41, 121) and both factors can also differ for different age groups.

Future

There is still much to be learned about the neural mechanisms underlying spontaneous and rehabilitation induced sensory recovery in patients with peripheral nerve injuries in the hands. A better understanding of the mechanisms behind the cortical changes following peripheral nerve injury and repair and sensory re-education would improve the possibilities of therapeutically regulating cortical changes in order to improve rehabilitation following peripheral nerve injury and repair. Future studies that clarify the changes in brain activity that mediate efficacious sensory and motor rehabilitation will likely lead the way toward brain mapping being used to determine optimal rehabilitation protocols in a nerve injured patients. Ideally a prescription would be made by selecting the rehabilitation approach expected to most effectively promote changed brain activity in the nerve-injured patient. Acquiring a more complete understanding of brain plasticity mediating spontaneous and rehabilitation induced sensory recovery will also open up the possibility of developing new rational post-nerve repair therapies. The therapies might be delivered via the peripheral nervous system, such as modifying somatosensory inputs to elicit specific changes in brain function. The new therapies might also be delivered directly to the CNS for example by means of transcutan magnetic stimulation to modify the excitability of a targeted brain area.

Conclusions

Tourniquet induced anaesthesia of the hand in healthy persons and patients with median and ulnar nerve injuries results in rapid improvement in hand function in the contralateral hand.

Selective deafferentation, with a local anaesthetic agent, of the volar part of the forearm in healthy persons results in rapid improvement in hand function in the ipsilateral hand.

Repeated selective deafferentation, with a local anaesthetic agent, on the volar aspect of the forearm in patients with median and ulnar nerve injuries in combination with sensory re-education results in significantly improved hand function in the ipsilateral, nerve injured, hand compared to placebo and sensory re-education.

These findings may have important implications in sensory re-education following nerve repair in the hand.

Summary in Swedish

Populärvetenskaplig sammanfattning

Nervskador som drabbar händerna orsakar stora problem både för den drabbade i form av försämrad handfunktion och för samhället i form av kostnader på grund av långvarig sjukskrivning. Trots mikrokirurgisk nervreparations teknik med användande av speciella instrument och mikroskop får vuxna patienter ofta bestående besvär med känselbortfall, muskelsvaghet och smärta.
Avsikten med avhandlingen är att beskriva en ny princip för att förbättra utfallet efter nervreparationer med fokus på centrala nervsystemet (CNS).
I **delarbete I** undersöktes hur en bedövning av högra handen, som resulterar i en övergående avstängning av nervsignalerna från denna kroppsdel till CNS – deafferentiering– , påverkar funktionen i den vänstra handen. Studien visade att en högersidig bedövning, inducerad av en uppumpad blodtrycksmanschett, leder till en snabbt förbättrad förmåga att uppfatta beröring och att skilja mellan beröring med en eller två punkter (tvåpunkts diskriminationsförmåga – 2PD). Även greppstyrkan förbättrades, i vänster hand jämfört med kontroll personer som inte bedövades. Funktionell magnetkamera undersökning (fMRI) visade ökad aktivitet i motorcentrum i höger hjärnhalva. Förbättringen i 2PD och greppstyrka kvarstod minst 15 minuter efter bedövningen.
Bedövning med en blodtrycksmanschett framkallar smärta och detta skulle kunna påverka resultaten i delarbete I varför vi valde att undersöka hur en smärtfri bedövning av ena sidans hand påverkar den andra sidans hand. I **delarbete II** undersöktes 100 patienter, som opererades på Handkirurgiska klinken, avseende känsel i den hand som inte opererades och som alltså inte var bedövad. Resultaten visade att bedövning av ena sidans hand medför en snabb och statistiskt säker förbättring av den icke bedövade sidans känsel.
Sammantaget tyder resultaten i de två första delarbetena på att man genom att bedöva den ena handen kan förbättra funktionen i den andra handen. Detta talar för att de båda hjärn-halvorna kommunicerar med varandra avseende registrering och tolkning av känselstimuli och eftersom förbättringen inträffar mycket snabbt så måste redan befintliga nervförbindelser vara inblandade sannolikt så att inaktiva nervceller aktiveras, vilket leder till förbättrad handfunktion.
Efter amputation av ett finger har man tidigare kunnat visa att det område i hjärnan som ansvarar för det amputerat fingret börjar reagera för stimuli av angränsande fingrar. I **delarbete III** tog vi fasta på detta och bedövade underarmens insida på friska försökspersoner med en bedövningssalva (EMLA®). Personerna som fått bedövningssalva förbättrades mer beträffande förmågan att uppfatta beröring liksom i 2PD jämfört med de som fått en vanlig hudkräm. Förbättringen kvarstod minst 24 timmar.

I **delarbete IV** var avsikten att testa våra fynd på patienter som skadat någon av de två stora nerverna som försörjer handen. Patienternas friska hand bedövades med en uppumpad blodtrycksmanschett, detta ledde till förbättrad känsel i den nervskadade handen. Bedövning med en manschett är emellertid inte lämplig att använda i rutin bruk på patienter eftersom den framkallar smärta och är svår att utföra tekniskt.
På grund av detta valde vi att i **delarbete V** behandla patienter med skador i någon av de två stora nerverna i handen med en bedövningskräm (EMLA®) eller en vanlig hudkräm (placebo) på underarmen på samma sida som nervskadan. Behandlingen upprepades två gånger per vecka i två veckor och kombinerades med intensiv känselträning. Alla patienter förbättrades men de patienter som fått bedövning av underarmen fick en statistiskt säkerställd större förbättring i jämförelse med de patienter som inte fått underarmen bedövad. Förbättringen kvarstod minst 4 veckor efter sista behandlingen.
Sammanfattningsvis kan man säga att man genom att manipulera känsel inflödet till hjärnan och genom att utnyttja hjärnans förmåga till anpassning kan få en förbättrad handfunktion i både friska och nervskadade personer. Förbättringen går mycket snabbt och orsakas sannolikt av att nervförbindelser som redan finns aktiveras. Genom att upprepa behandlingen kan man få en mer långvarig effekt. Dessa fynd öppnar möjligheter för att kunna erbjuda bättre rehabilitering för patienter med nervskador i händerna.

Acknowledgement

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