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The role of early sensory relearning following nerve injury

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The role of early sensory relearning following nerve injury

The role of early sensory relearning following nerve injury

Pernilla Vikström



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DOCTORAL DISSERTATION

By permission of the Faculty of Medicine, Lund University, Sweden.

To be defended at Lilla Aulan, Medicinskt Forskningscentrum,

Skåne University Hospital, Malmö, Sweden

on 30 November 2018 at 1 p.m.

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<p>Abstract</p> <p>A peripheral nerve injury in the hand or arm has an extensive impact on the individual's function, activities and quality of life. Sensory function, discriminative touch/tactile gnosis specifically, is one of the most affected functions remaining over time. The functional outcome is influenced by mechanisms in the peripheral as well as in the central nervous system.</p> <p>The overall aim of this thesis was to evaluate short- and long- term objective results and subjective experiences of early sensory relearning where the plastic capacity of the brain is used for therapeutic purpose, i.e. guided plasticity. An additional aim was to evaluate the sensory processing patterns following a median or ulnar nerve injury.</p> <p>A randomized controlled multi-centre trial comprising 37 adult patients with median or ulnar nerve injuries at wrist or distal forearm was conducted. The intervention group started early sensory relearning using guided plasticity techniques within one week after the nerve repair. The used methods were observation of touch and mirror visual feedback which were performed 4-5 times per day. The control group did not receive any sensory relearning until the nerve regeneration was re-established in the palm. Discriminative touch was significantly better in the intervention group at 6 months.</p> <p>In a long term follow-up (median 7 years) of 20 participants of the RCT, the benefits in discriminative touch remained, as well as significantly better dexterity and self-reported grip function, fine motor skills and less clumsiness in the group who had early sensory relearning. No differences were seen in the self-reported questionnaires DASH (Disability of the Arm, Shoulder and Hand) or CISS (i.e. questionnaire: Cold Intolerance Symptom Severity).</p> <p>To investigate patient's experiences of early sensory relearning a Q-methodology study including 37 patients was conducted. Q-methodology combines a qualitative and a quantitative approach. Three viewpoints emerged indicating meaningfulness as a key factor. Further it was found that some patients have difficulties to experience the illusions of touch that is a vital part of early sensory relearning and aims at an alternative activation of somatosensory areas in the brain with use of guided plasticity. Patients who have difficulties to experience the illusion of touch need extra support in their training and motivational factors should also be considered.</p> <p>The last study comprised 49 patients operated due to a complete or partial (at least 50 %) transection of the median or ulnar nerve injury. The patients were evaluated with the Adult/Adolescent Sensory Profile™ which examines sensory processing pattern in relation to neurological threshold and self-regulation continuum. The study showed increased proportion of low registration in sensory processing compared to an age and gender matched control group. These findings support that cross-modal rehabilitation techniques, with multiple sensory stimulation, would be beneficial also for people scoring high in the Low registration Quadrant, since this type of rehabilitation increase the intensity of stimulation.</p> <p>The thesis shows that early sensory relearning has a potential to improve both objective and subjective outcome in sensory function and dexterity. Further, viewpoints of experiences of the early sensory relearning has been identified and classified as well as an atypical sensory processing pattern following a major nerve trauma. Timing as well as personal and environmental factors play roles in early sensory relearning, and the findings are of importance for future development of early sensory relearning following nerve repair.</p>			
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The role of early sensory relearning following nerve injury

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Abstract

A peripheral nerve injury in the hand or arm has an extensive impact on the individual's function, activities and quality of life. Sensory function, discriminative touch/tactile gnosis specifically, is one of the most affected functions remaining over time. The functional outcome is influenced by mechanisms in the peripheral as well as in the central nervous system.

The overall aim of this thesis was to evaluate short- and long- term objective results and subjective experiences of early sensory relearning where the plastic capacity of the brain is used for therapeutic purpose, i.e. guided plasticity. An additional aim was to evaluate the sensory processing patterns following a median or ulnar nerve injury.

A randomized controlled multi-centre trial comprising 37 adult patients with median or ulnar nerve injuries at wrist or distal forearm was conducted. The intervention group started early sensory relearning using guided plasticity techniques within one week after the nerve repair . The used methods were observation of touch and mirror visual feedback which were performed 4-5 times per day. The control group did not receive any sensory relearning until the nerve regeneration was re-established in the palm. Discriminative touch was significantly better in the intervention group at 6 months.

In a long term follow-up (median 7 years) of 20 participants of the RCT, the benefits in discriminative touch remained, as well as significantly better dexterity and self-reported grip function, fine motor skills and less clumsiness in the group who had early sensory relearning. No differences were seen in the self-reported questionnaires DASH (Disability of the Arm, Shoulder and Hand) or CISS (i.e. questionnaire: Cold Intolerance Symptom Severity).

To investigate patient's experiences of early sensory relearning a Q-methodology study including 37 patients was conducted. Q-methodology combines a qualitative and a quantitative approach. Three viewpoints emerged indicating meaningfulness as a key factor. Further it was found that some patients have difficulties to experience the illusions of touch that is a vital part of early sensory relearning and aims at an alternative activation of somatosensory areas in the brain with use of guided plasticity. Patients who have difficulties to experience the illusion of touch need extra support in their training and motivational factors should also be considered.

The last study comprised 49 patients operated due to a complete or partial (at least 50 %) transection of the median or ulnar nerve injury. The patients were evaluated with the Adult/Adolescent Sensory Profile™ which examines sensory processing pattern in relation to neurological threshold and self-regulation continuum. The study showed increased proportion of low registration in sensory processing compared to an age and gender matched control group. These findings support that cross-modal rehabilitation techniques, with multiple sensory stimulation, would be beneficial also for people scoring high in the Low registration Quadrant, since this type of rehabilitation increase the intensity of stimulation.

The thesis shows that early sensory relearning has a potential to improve both objective and subjective outcome in sensory function and dexterity. Further, viewpoints of experiences of the early sensory relearning has been identified and classified as well as an atypical sensory processing pattern following a major nerve trauma. Timing as well as personal and environmental factors play roles in early sensory relearning, and the findings are of importance for future development of early sensory relearning following nerve repair.

List of papers

Enhanced early sensory outcome after nerve repair as a result of immediate post-operative re-learning: a randomized controlled trial

Rosén B, Vikström P, Turner S, McGrouther DA, Selles RW, Schreuders TA and Björkman A.

Journal of Hand Surgery, European Volume. 2015; 40 (6), 598-606.

Patients' views on early sensory relearning following nerve repair – a Q-methodology study

Vikström P, Carlsson I, Rosén B and Björkman A.

Journal Of Hand Therapy. 2017 Sep 26. pii: S0894-1130(17)30047-9. doi: 10.1016/j.jht.2017.07.003. Published online ahead of print.

The effect of early relearning on sensory recovery 4 to 9 years after nerve repair: a report of a randomized controlled study.

Vikström P, Rosén B, Carlsson IK and Björkman A.

Journal of Hand Surgery, European Volume. 2018; 43 (6), 626-630.

Atypical sensory processing pattern following median or ulnar nerve injury – A case-control study

Vikström P, Björkman A, Carlsson IK, Olsson A-K and Rosén B.

BMC Neurology. 2018; 18, 146-151.

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Thesis at a glance

Paper I

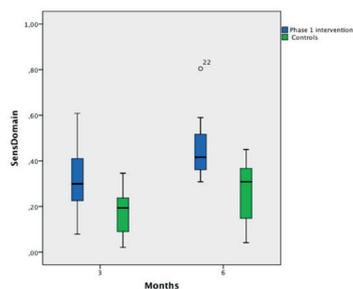
Enhanced early sensory outcome after nerve repair as a result of immediate postoperative relearning: a randomized controlled trial

Introduction: Persistent impaired sensory function after nerve repair at wrist/forearm level causes long-term disabilities. We investigated the use of guided plasticity training to improve the outcome in the first 6 months after nerve repair.

Methods: In a multicentre randomized controlled trial, 37 adults with median or ulnar nerve repair at the distal forearm were randomized either to intervention, starting the first week after surgery with sensory and motor relearning using mirror visual feedback and observation of touch, or to a control group with relearning starting when re-innervation could be detected. The primary outcome at 3 and 6 months postoperatively was discriminative touch (by Shape-Texture Identification test), part of the SensoryDomain of the RosenScore.

Results: At 6 months, discriminative touch was significantly better in the early intervention group. Improvement in discriminative touch between 3 and 6 months was also significantly greater in this group. The favourable outcome for early relearning was also seen in the composite outcome in the Sensory Domain. There were no significant differences in motor function, in pain, or in the total score.

Conclusion: Early relearning using guided plasticity may have the potential to improve outcomes after nerve repair.



Differences in SensoryDomain between groups at 3 and 6 months follow-up.

Paper II

Patients' views on early sensory relearning following nerve repair – a Q-methodology study

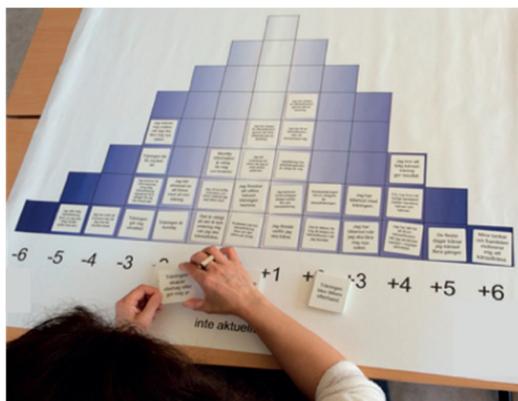
Introduction: Early sensory relearning where the dynamic capacity of the brain is used has been shown to improve sensory outcome after nerve repair. However, no previous studies have examined how patients experience early sensory relearning. The purpose of the study was to describe patients' views on early sensory relearning.

Methods: Thirty-seven consecutive adult patients with median and/or ulnar nerve repair who had completed early sensory relearning were included.

Q-methodology was used, involving 56 statements under 4 topics: (1) understanding, (2) ability to experience an illusion of touch, (3) completion of training, and (4) the impact of the therapist, personal factors, and the environment. Factor analysis was used for data processing.

Results: Three factors were identified, explaining 45% of the variance: (1) “Believe sensory relearning is meaningful; manage to get an illusion of touch and complete the sensory relearning”; (2) “Do not get an illusion of touch easily and need support in the sensory relearning”; and (3) “Are not motivated; manage to get an illusion of touch but do not complete the sensory relearning”.

Conclusion: Many patients succeed in implementing their sensory relearning but a substantial proportion of the patient population need more support, have difficulties in creating an illusion of touch, and lack motivation to complete the sensory relearning. The three unique factors indicate that motivation and a sense of meaningfulness are key components that should be taken into consideration in developing programmes for person-centred early sensory relearning.



Participant undertake the Q-sort into the cell grid.

Paper III

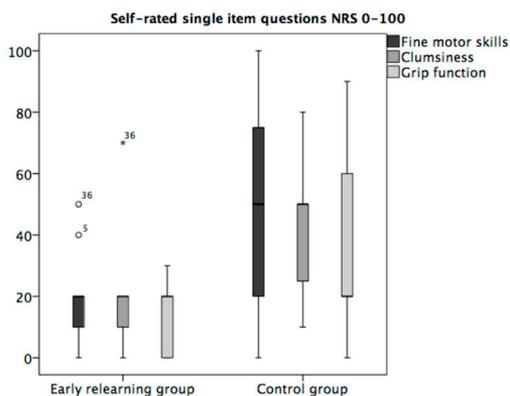
The effect of early relearning on sensory recovery 4 to 9 years after nerve repair: a report of a randomized controlled study

Introduction: Persistent impaired sensory function after nerve repair at wrist/forearm level causes long-term disabilities. Early sensory relearning using guided plasticity has shown advantages for sensory function 6 months after nerve repair. This randomized controlled trial was designed to evaluate sensory recovery 4 to 9 years after median or ulnar nerve repair, with the specific aim of investigating whether the benefits of early sensory relearning using guided plasticity persist.

Methods: Twenty patients randomized to either early sensory relearning (nine patients) or traditional relearning (11 patients) were assessed 4 to 9 years after the nerve repair. Outcomes were assessed with the RosenScore, DASH and CISS questionnaires, and self-reported single-item questions regarding function and activity.

Results: The patients who had early sensory relearning had significantly better recovery in the Sensory Domain of the RosenScore, specifically tactile gnosis/discriminative touch and dexterity. The patients with early sensory relearning also had significantly less self-reported problems regarding grip, clumsiness, and fine motor skills. No differences in DASH or CISS scores were found between the two groups.

Conclusion: Early sensory relearning improves sensory recovery following nerve repair in the long term.



Self-reported problems regarding grip, clumsiness, and fine motor skills. 0 = no problem 100 = worst possible problem.

Paper IV

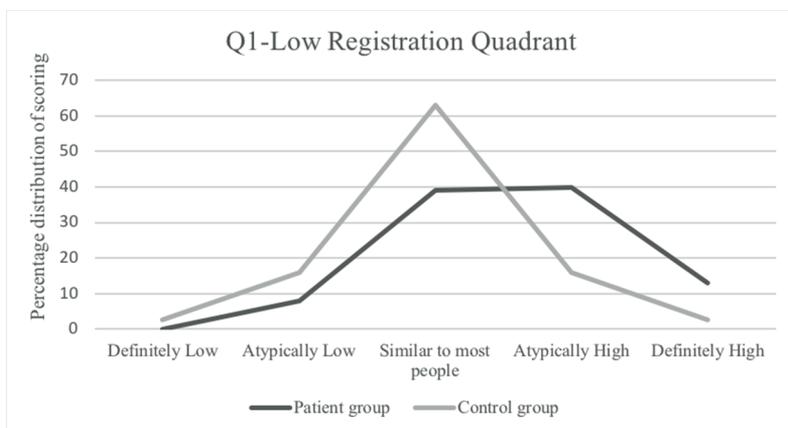
Atypical sensory processing pattern following median or ulnar nerve injury – A case-control study

Introduction: Due to brain plasticity, a transection of a median or ulnar nerve results in profound changes to the somatosensory areas in the brain. The permanent sensory deprivation after a peripheral nerve injury might influence the interaction between all the senses. The aim was to investigate whether a median and/or ulnar nerve injury gives rise to a changed sensory processing pattern.

Methods: Fifty patients who were operated due to a median and/or ulnar nerve injury were included. The patients completed the Adolescent/Adult Sensory Profile questionnaire (AASP). This includes a comprehensive characterization of how sensory information is processed and how a person responds to multiple sensory modalities. AASP categorizes the results in four possible quadrants of behavioural profiles (“Low registration”, “Sensory seeking”, “Sensory sensitivity”, and “Sensory avoiding”). The results from the median and/or ulnar nerve-injured patients were compared to those from 209 healthy age- and gender-matched controls.

Results: A significant difference was seen in the “Low registration” quadrant. Forty per cent of the patient group scored atypically in the “Low registration” quadrant, as compared to 16% of the controls. No correlation between atypical sensory processing pattern and age or time since injury was seen.

Conclusion: A peripheral nerve injury causes altered sensory processing pattern with an increased proportion of patients with low registration of sensory stimulus overall.



Nerve-injured patients' scoring distribution in comparison to the normative distributed scoring in the control group.

Abbreviations

2PD	Two-point discrimination
ADL	Activities of daily living
AASP	Adolescent/Adult Sensory Profile™
CISS	Cold Intolerance Symptom Severity
CNS	Central nervous system
DASH	Disabilities of the Arm, Shoulder, and Hand
ICF	International Classification of Functioning, Disability, and Health
MVF	Mirror visual feedback
PNI	Peripheral nerve injury
PNS	Peripheral nervous system
PROM	Patient-rated outcome measure
S1	Primary somatosensory cortex
STI	Shape-texture identification test
SWM	Semmes-Weinstein monofilament

Introduction

In Sweden, about 250 individuals a year suffer from a median or ulnar nerve transection at wrist or forearm level ¹⁰. A peripheral nerve injury has a major impact on the individual. After the nerve suture, a long period of rehabilitation follows but residual symptoms and limitations are to be expected. The disabilities arising from the nerve injury lead to extensive limitations for the individual regarding body functions, activity and participation levels, and also in quality of life ^{8, 37, 38, 74, 107, 155, 180}. In addition to the consequences for the individual, the injury leads to great costs for society ^{28, 150} as many of the nerve-injured patients are of working age ¹⁶⁴.

In the work for this thesis, the aim was to further develop sensory relearning following nerve injury and to improve our understanding of its impact on the individual.

The human nervous system

The human nervous system is made up of the central nervous system (CNS), comprising the brain and spinal cord, and the peripheral nervous system (PNS), comprising the peripheral nerves, receptors, and dorsal root ganglia.

Four modalities of sensibility can be defined: touch, proprioception, nociception, and temperature sensing. Sensory information is detected by receptors in the skin where four types of cutaneous receptors, each sensitive to different tactile stimuli, are engaged in touch: (1) Merkel receptors, (2) Meissner receptors, (3) Pacinian receptors, and (4) Ruffini receptors ⁹⁴. The two most common types of mechanoreceptors (Merkel and Meissner) have small receptive fields and are responsible for detecting form and texture such as edges and corners (Merkel receptors) and for motion detection, which is important for well-functioning grip control (Meissner receptors). The Pacinian receptors detect vibrations, and the Ruffini receptors function in proprioception through stretching of the skin. Both Pacinian receptors and Ruffini receptors have larger receptive fields than Merkel receptors and Meissner receptors. In addition, free nerve endings function in nociception and thermoreceptors detect temperature changes. From the cutaneous receptors, afferent sensory information is carried by the afferent peripheral nerves to the dorsal root ganglia, where the sensory neurons are located. From the dorsal root ganglia, sensory information is sent to the spinal cord,

where it is forwarded in the dorsal columns to the medulla. At the level of the medulla, the axons cross the midline to the contralateral side and the sensory information is sent further through the spinothalamic tracts to the ventral posterolateral nuclei of the thalamus. In the thalamus, afferent, sensory information is processed and sent on to the primary somatosensory area (S1) in the cortex, located in the post central gyrus. Thus, sensory information from the right hand is primarily processed in the left hemisphere^{94, 143}.

Based on the histological appearance, the S1 is divided into four different areas, Brodmann areas 3a, 3b, 1, and 2. Neurons in the S1 are arranged so that they receive and process information from specific areas. This means that neurons processing sensory information from the index finger are located together and so on, and this highly ordered arrangement of neurons is called somatotopy^{94, 143}. Through the pioneering work of Sherrington and Penfield^{140, 166}, we know that a very large number of neurons in the S1 and primary motor cortex (M1) are solely devoted to processing sensory and motor information regarding the hand. Body parts that are especially sensitive to touch, e.g. the hands, are represented in large areas (i.e. more neurons), reflecting the importance of tactile information from those regions. S1 processes the sensory information before sending it on to other areas of the brain such as the secondary somatosensory cortex. S1 is also well connected to the S1 in the ipsilateral hemisphere^{94, 143}.

The motor system has the challenging task of transferring motor information from the brain to the muscles acting in, for example, the hand. The motor system in the brain involves several different areas such as prefrontal areas, premotor cortex, M1, S1, visual cortex, basal ganglia, and cerebellum working together in a network to form a motor signal.

The efferent signal is sent from the brain through the corticospinal tract of the pyramidal tracts, and when the signal passes the medulla oblongata it crosses over to the opposite, contralateral side and travels further in the spinal cord to the lower motor neurons, which are located in the ventral horn of the spinal cord. The axons of the motor neurons extend to the terminal recipients – i.e. the muscles responsible for movement^{94, 143}.

Brain plasticity

The brain has a tremendous capacity to change and adapt, based on the pattern of afferent nerve signalling, environmental demands, learning, and injuries – a phenomenon called brain plasticity^{94, 143}. The cortical representation of body parts and movement is constantly adapted based on afferent signalling and demands/practice, a phenomenon called activity-dependent plasticity¹⁴³. This means that repeated practicing of a specific task or stimulation of a specific area of the skin results in

improved synaptic transmission and recruitment of more neurons, a phenomenon called long-term potentiation. In this way, repeated practice of a task leads to increased speed and accuracy^{40, 75, 143, 181}. An example of this is violin players, where studies using functional magnetic resonance imaging (fMRI) have shown that the neuron representation in the motor areas for the right hand, which handles the bow, is identical to that of non-musicians whereas the representation of the left hand, where the fingers individually handle the strings, is enlarged, i.e. more neurons are recruited to control finger movement^{62, 63}. On the other hand, immobilization or reduced use results in activation of fewer neurons, i.e. long-term deprivation.

An injury to the nervous system, involving the CNS or the PNS, also results in plasticity^{40, 143, 173, 181}. Amputation of a finger is known to result in plasticity, where the neurons in the SI that normally respond to cutaneous stimulation from the amputated finger start to respond within minutes to cutaneous stimulation from the adjacent fingers¹²⁰. Several studies have shown that a peripheral nerve injury involving the median or ulnar nerve in the forearm results in cerebral changes in somatosensory areas in both hemispheres of the brain^{39, 50, 173}. Normally the hand area in the S1 is highly somatotopic, meaning that neurons that respond to cutaneous stimulation of individual fingers are located together in specific areas. From animal studies, it is known that a median nerve injury results in destruction of the normal somatotopy in S1 to a more disorderly pattern whereby the neurons responsible for processing afferent signals are scattered like a mosaic in the S1¹⁴³. In humans with median nerve injury, studies using fMRI have shown that the activation of the hand area in the S1 contralateral to the injury is larger than in healthy subjects^{39, 173}. Interestingly, in a group of adults who had been operated due to a median nerve injury in childhood or adolescence, Chemnitz et al. showed that all had pathological nerve conduction in the formerly injured nerve³⁶. Patients who were injured before the age of 9 years showed an activation pattern similar to that of healthy controls, with extensive contralateral activation in the S1 and deactivation of the ipsilateral S1. However, those patients who were injured in adolescence all had a larger activation in the S1 contralateral to the injury, but in the ipsilateral hemisphere they displayed a completely different pattern where the normal inhibition of neurons was decreased in S1³⁹. Those injured at an age below 12 years had a normal clinical sensory function in the median nerve, while those injured at ages 12–20 years had impaired sensory function similar to what has been described in subjects who were injured as adults^{21, 107, 180}. This demonstrates the superior plasticity in children and that the ipsilateral hemisphere may be more important in recovery than previously thought.

The plastic capacity of the brain leads to new possibilities. Brain plasticity can be guided for therapeutic purposes to improve functions that have been damaged or lost, a phenomenon known as guided plasticity⁵⁷.

Sensorimotor interaction

An outstanding level of hand function is required for fine motor skills, dexterity, precision, grasping etc. Voluntary motor actions integrate several sensory and motor regions in the brain ¹⁴⁸. This sensorimotor integration uses the sensory input to modulate motor output ⁴ and the motor neurons provide ideal feedback control of grip and load forces during manipulation and grasping of an object ¹⁴⁷.

Simultaneous processing in multiple sensory and motor areas is required for all motor actions and the action is continuously controlled for errors and corrected by sensory feedback. Without the integration of sensory feedback, errors arising during movement would not be corrected, i.e. there would only be feedforward control where a motor command is based on a predetermined order ¹⁸⁹. Tactile feedback is particularly essential in dexterity and fine motor functions of the hands, and without the precise sensory feedback extensive problems in ADL would arise ⁴. In collaboration with the sensory feedback and perception, the motor system transforms and integrates all information to a motor action which is needed, for example, for a specific balanced grip ¹⁴⁸.

An example of the great impact of sensibility on well-functioning motor actions has been shown in development of the Sollerman hand function test ¹⁶⁹ and the Model Outcome Measurement following peripheral nerve injuries – RosenScore ¹⁵⁴. In the initial testing in the development of the Sollerman hand function test, major differences were observed between those who had tactile gnosis functioning and those lacking tactile gnosis ¹⁶⁹. Also, the factor analysis of the RosenScore showed that the Sollerman hand function test grouped together with the sensory tests, and not the motor tests, although it is a test for grip function and dexterity with a high proportion of motor actions ¹⁵⁴.

Long-term follow-up studies of peripheral nerve injuries have shown that there is no difference in recovery depending on whether a motor-dominated nerve (ulnar nerve) or a sensory-dominated nerve (median nerve) is injured ^{37, 107, 155}. This is another indication of the important interplay between the sensory and motor systems.

Peripheral nerve injury

A peripheral nerve injury causes long-lasting disabilities due to loss of motor functions and fine motor skills ¹¹⁰, and may have an extensive impact on occupational performance ^{38, 133}.

Directly after a nerve injury, a multitude of events occur both in the PNS and in the CNS ^{49, 167}. The immediate time after the nerve transection and repair is characterized by a complete disconnection between the hand and the brain. The axons in the nerve distal to the injury start to degenerate, a process called Wallerian degeneration ⁵, leading to nerve cell death and atrophy of the denervated muscles ¹⁷⁴ and deteriorative changes to the mechanoreceptors ⁵⁴. Schwann cells in the distal nerve part facilitate regeneration of the axon stumps, but the regeneration is limited and imprecise, which considerably diminishes the recovery of function ¹⁴³. The limited regeneration is dependent on, among other things, decreased diameter of regenerated axons ⁴⁹, death of up to 50% of the neurons in the dorsal root ganglia ¹⁸⁷, and misdirection in the axonal regrowth, resulting in a changed innervation pattern ²⁰.

Within minutes after the injury, neurons in S1 that usually respond to afferent signals from the injured nerve start to respond to afferent signals from receptors in the skin adjacent to the injured nerve ^{20, 49, 121}. Following re-innervation, a new cortical, mosaic-like representation is developed (Figure 1) due to the changed afferent signal pattern from the injured nerve. This new signal pattern has to be relearned and interpreted ¹⁵⁹.

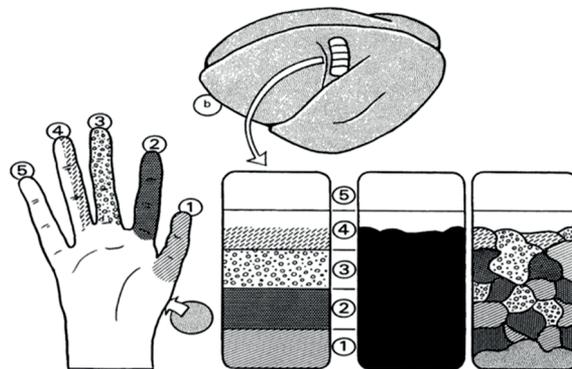


Figure 1. The first grid picture shows the normal somatotopic cortical representation. The next picture illustrates the early period following nerve transection when no afferent input is present. The last picture illustrates the new reorganized mosaic-like cortical representation pattern following axonal regeneration. From: Rosén, B. Sensory re-education. In: Skirven et al. Rehabilitation of the Hand and Upper Extremity. 2011. Mosby Inc. Reprinted with permission from the author.

Tactile gnosis/Discriminative touch

Tactile gnosis is the outcome parameter with the far worst result in the majority of follow-up studies after repair of median or ulnar nerves ^{21, 37, 54, 107, 133, 155, 179, 180}.

Tactile gnosis can be considered to be equivalent to discriminative touch. It is the complex sensibility that gives the hands sight, i.e. makes the hands capable of manipulating and identifying how and what they are holding without visual support

^{123, 124}. Bunnell, the father of hand surgery, described sensation as the eyes of the fingertips, meaning that a hand without sensibility is blind ²⁹. This has been illustrated by Moberg (Figure 2).



Figure 2. Moberg's seeing fingertips. From Moberg, E. Akut Handkirurgi. Lund: Gleerups. 1969.

A hierarchical model of sensory modalities arranges the sensory function by complexity (Figure 3).

The first level includes detection of touch (touch thresholds). Sensory function at this level is dependent of axonal function as well as density and function of peripheral receptors. This level (touch thresholds) cannot improve with relearning.

One level higher in the hierarchy involves spatial discrimination, including localization, spatial discrimination, and spatial orientation. The spatial discrimination and localization – and also the pure detection of touch – are sometimes called passive touch, when objects are placed against the skin. Passive touch is often referred to as a sensation that is experienced in the skin: *“I feel a pricking sensation on my skin”*⁷⁶.

The highest, most complex levels involves identification of shapes, textures, and objects, meaning tactile gnosis/discriminative touch ⁷, and dexterity. Tactile gnosis and identification, sometimes referred to as active touch, is more of a haptic perception that includes both the sensory and motor systems, and also more active participation of the cognitive system. The cognitive system is of course involved in all processing of information provided by the motor and sensory systems, but in tactile gnosis/discriminative touch the level of interpretation is higher than in pure detection of touch. These processes work together and create an experience of active touch which, in contrast to the passive touch, is where we relate the touch to the object being touched: *“I feel a pointed object”*⁷⁶.

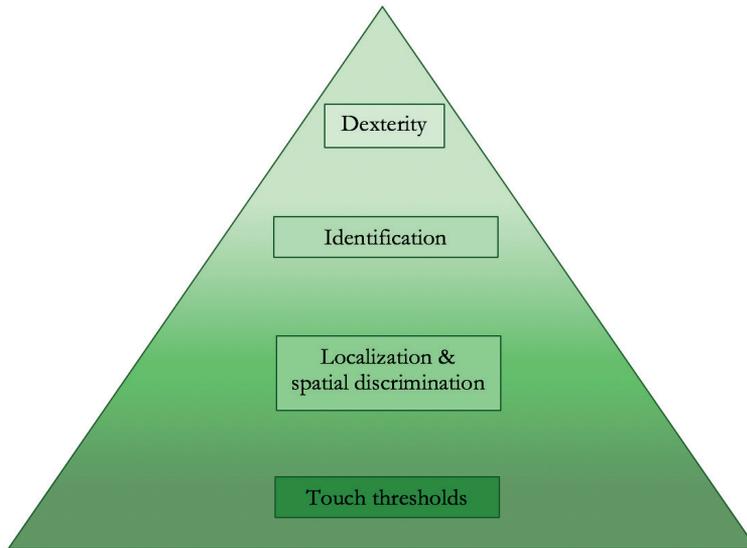


Figure 3. Hierarchical model of sensory modalities. Modified from the American Society of Hand Therapists Clinical Assessment Recommendations⁷.

The three highest levels of the hierarchical model are dependent on useful touch thresholds, i.e. well-functioning peripheral receptors and afferent signalling, but also on a capacity to interpret the afferent signals^{7, 151}. The three highest levels are addressed in sensory relearning.

There is not a sharp line between spatial discrimination and identification. However, in order to reflect the complexity of nerve regeneration following nerve repair, it is advocated that recovery including not only all levels of the hierarchy of sensory modalities (i.e. touch thresholds, tactile gnosis/discriminative touch), but also dexterity, muscle function, grip strength and pain/discomfort, should be assessed⁷.

Classification of health: ICF

Health is about what we can do or not do and affects how we function in our daily life¹⁸. A framework for describing health and health-related conditions has been provided by World Health Organization: the International Classification of Functioning, Disability, and Health (ICF)¹³⁶. ICF uses the term “functioning” to describe the positive aspect of health, and “disability” as the opposite, negative aspect. ICF has two parts, “Functioning and Disability” and “Contextual factors”. Functioning and Disability includes the components “Body functions” (the physiological functions of

body systems), “Body structures” (anatomical parts of the body), “Activity” (the performance of a task or action), and “Participation” (involvement in a life situation). The Contextual factors are personal and environmental factors where the latter can be facilitators of, or barriers to functioning and health. Health and functioning is seen as a dynamic continuum through the interaction between all body functions, body structures, activities, participation, and environmental factors.

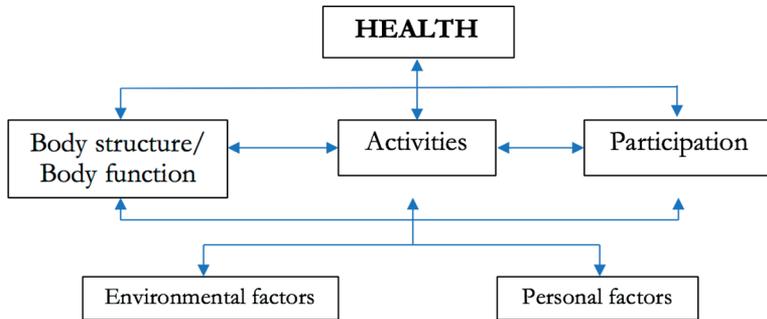


Figure 4. The biopsychosocial model proposed in the International Classification of Functioning, Disability, and Health (ICF) ¹⁸.

This dynamic relationship between the ICF components can illustrate why people with the same injury recover and achieve different levels of functioning. A peripheral nerve injury with limitations in body functions and body structures does not necessarily contribute to reduced functioning itself. It is the extent to which those limitations in body functions and body structures have an impact on activity and participation, with influence from contextual factors, that determines the person’s level of functioning. In order to evaluate functioning, it has been suggested that assessments made should cover different components of the ICF ^{52, 53, 180, 188}.

Peripheral nerve injury: consequences for the individual

A peripheral nerve injury has a major effect on body functions, activity, and participation over a long period of time ^{37, 38, 74, 89, 107, 133, 155, 180}. Several factors influence the outcome following peripheral nerve injury. **Age** at injury is believed to be the strongest influencing factor, and several studies have shown superior outcome in children ^{37, 59, 72, 104, 172}. Chemnitz et al. ³⁷ showed significantly better results in both subjective and objective measures in those injured in childhood than in those injured in adolescence. They suggested that this difference was due to a better cerebral adaptation, i.e. plasticity in the childhood brain. This thesis deals with peripheral nerve injury at wrist/forearm level and **level of injury** influences the outcome ¹⁰⁶ like several

other **neurobiological phenomena** such as Wallerian degeneration, misdirection of regenerating axons, and cortical reorganization all influence the outcome¹⁷³. **Timing of surgery** is another important factor and primary suture as soon as possible is to be preferred^{68, 139} as well as **psychological factors** such as early post-traumatic psychological stress^{90, 178}. **Patient motivation and adherence** to rehabilitation following PNI are also important factors for the final result and outcome⁹⁰. **Cognitive abilities**, such as visuo-spatial logic capacity and verbal/language learning, have also been associated with the degree of recovery after peripheral nerve injury¹⁵¹. Depending on **which nerve is injured** (median or ulnar), different recovery and outcomes have been reported^{129, 155, 180}, especially early outcome. In long-term follow-ups, the differences in outcome between the two nerves are less obvious¹⁰⁷. Additional factors affecting functional outcome following peripheral nerve injury are which **rehabilitation regime** is given¹¹⁵ and (as demonstrated in this thesis) the timing of relearning.

Body functions and Body structure

Both initial and long-term effects following PNI are seen on motor function (mobility and grip strength) and sensory functions including tactile gnosis/discriminative touch and dexterity. As already discussed, tactile gnosis/discriminative touch is strongly affected, leading to persistent disability over time^{37, 107, 115, 122, 155, 180}. Decreased functioning of spatial discrimination, tactile gnosis, localization of touch, and fine motor skills has been reported, which in turn extensively affects grip function and the capacity to use the hands actively.

Pain in different forms is common after peripheral nerve injury, and this in turn is a predictor of increased disability and a decrease in general health¹³³. Hyperaesthesia/allodynia usually occurs as the afferent nerve signalling is re-established¹⁵⁹. Cold intolerance with pain, tingling/numbness, stiffness, and decreased dexterity etc. has been reported in 38–87% of cases after PNI^{45, 134}. Appearance-related concerns over a visibly different “claw hand” deformity and also a feeling of self-consciousness related to scars from the injury have been reported⁸. Emotional reactions such as struggling with anxiety, depression, a sense of bitterness, frustration, and anger may also be present – in addition to grief over the hand and over life as it used to be before the injury^{8, 12, 38, 100}. A PNI can also result in sleep disturbances, which, together with pain, may lead to a reduced quality of life¹⁷⁰.

Activity and Participation

In a study of 84 patients with peripheral nerve injury in the upper extremity, Novak et al.¹³³ described patient-reported outcome at a mean of three years after peripheral nerve injury, using the DASH questionnaire. DASH⁸³ measures the impact of upper

extremity disorders in terms of disability and symptoms. The questionnaire covers a wide range of items including different body functions, the ability to perform specific tasks/activities, and participation in social contexts. A DASH score of between 0 and 100 is possible, where 0 means no disability and 100 means the most severe disability. Novak et al.¹³³ reported a mean DASH score of 52 for the nerve-injured patients, but a mean DASH score of 43 has also been reported recently¹⁷⁰. On the other hand, Vordemvenne et al.¹⁸⁰ reported considerably lower DASH scores, 22–24 depending on which nerve was injured. However, a DASH score of 10 is the mean in the general US population⁸⁵, which clearly shows that ADL is extensively affected following peripheral nerve injury. Inability to open a jar or use a knife to cut food is frequently reported as being problematic¹⁷⁰, common ADL situations that are dependent on well-functioning tactile gnosis, dexterity, and strength. There may also be a correlation between having a higher DASH score and having post-traumatic stress^{84, 178}, and an increased DASH score is a predictor of a reduced level of quality of life¹⁷⁰.

As previously mentioned, cold intolerance is common in nerve-injured patients, and Carlsson et al.³² stated that cold intolerance could greatly exacerbate problems involving overall hand function. Severe cold intolerance also causes changes in occupational performance and/or occupational pattern, and it may also result in changed life roles and a struggle to maintain one's self-image³².

About 20% of nerve-injured patients state that they have given up their daily activities and hobbies^{12, 119}. Depending on the type of work and employment that the patient has, the nerve injury may influence the ability to work. Inability to return to work is seen in about 20% of patients with peripheral nerve injuries, and about 25% of patients report that they cannot perform their work tasks as they would like¹⁷⁰.

Health-related quality of life

In the study by Novak et al.¹³³, the Short Form (36) Health Survey (SF 36) was used. The SF 36 measures mental and physical health and quality of life, which are grouped into eight domains (bodily pain, physical function, physical role, emotional role, general health, vitality, social functioning, and mental health)¹⁸³. Nerve-injured patients have had significantly reduced scores in all domains compared to normative data, indicating a decreased health-related quality of life in both the physical component and the mental component¹³³. This effect on both the physical and the mental quality of life has been confirmed in a recently published comprehensive study using the shortened version of the SF 36, known as the SF-8¹⁷⁰. Several studies have found symptoms of post-traumatic stress disorder, anxiety, and depression following acute hand trauma with nerve injuries^{12, 100}, which could also affect quality of life.

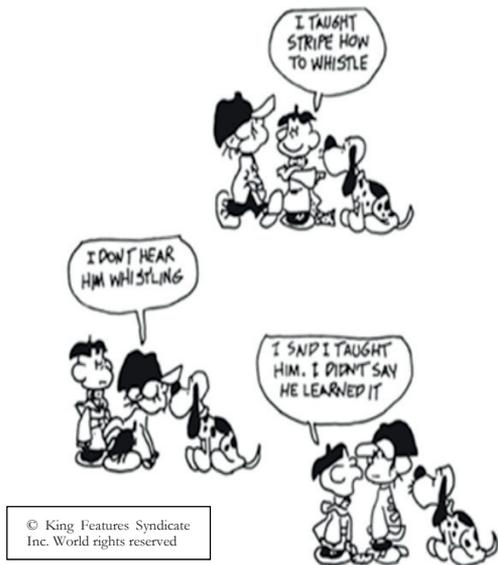
Rehabilitation after peripheral nerve injury

The rehabilitation after a PNI starts directly postoperatively and includes a wide range of interventions not only from the occupational therapist but also from the whole team with physiotherapist, doctor, and social worker. The interventions for the therapist range from covering body functioning such as prevention of contractures, splinting, oedema prevention, desensitization, relieving strategies for cold intolerance, education about how to protect the insensate hand, sensory and motor relearning, and strengthening ⁵⁶. To address limitations in performance of ADL, access to coping strategies and provision of assistive devices and adaptive methods to gradually integrate the hand into ADL again are of importance ^{56, 160}. The use of a holistic approach to rehabilitation and meeting both physical and psycho-social needs are also crucial for patient recovery ⁸. Furthermore, an empathic approach and early psychological support are important for detection of early symptoms of post-traumatic stress, to treat these at an early stage.

A substantial part of rehabilitation after PNI is devoted to sensory relearning. It is said that “*the hand speaks a new language to the brain*” following a PNI. This new language refers to the changed afferent signalling to the brain as a result of misdirection of regenerating axons ^{121, 159, 167, 173}.

Sensory re-education/relearning

The terms relearning and re-education are used parallel in the literature. In *relearning*, there is more emphasis on patient learning and understanding – that the patient is going to learn new skills and how to interpret the new sensibility. *Re-education* focuses more on the therapist as an educator. The different terms can be related to the concepts compliance and adherence. Compliance is described as the extent to which the patients obey and follow instructions, prescriptions, and proscriptions outlined by their treating health practitioner ¹¹⁸. This corresponds well with the underlying meaning of re-education, where the therapist is seen as an educator. Adherence can be described as an active voluntary and collaborative involvement by the patient in a mutually acceptable course of behaviour to produce a preventative or therapeutic result ¹¹⁸. This is more in line with the term relearning, focusing on the patient’s learning and understanding. In this thesis, the term relearning is used throughout.



The purpose of sensory relearning is “to facilitate the acquisition of the new language and to improve the recovery of sensory function in the hand”¹⁵⁹.

Learning is a key factor, and this is described as “the gradual changes in behaviour as a function of training” and is closely related to memory. Learning is a process of encoding experiences that can alter the nervous system by changing the strength and/or number of synaptic connections between neurons. Storage of these neural alterations over time and subsequent access to

these may lead to behavioural change, i.e. learning¹⁴⁴.

Sensory relearning has been defined as “the gradual and progressive process of reprogramming the brain through the use of cognitive learning techniques such as visualization and verbalization, the use of alternate senses such as vision or hearing, and the use of graded tactile stimuli designed to maintain and/or restore sensory areas affected by nerve injury or compression to improve tactile gnosis”⁹¹.

Early versus late sensory relearning

Sensory relearning has been divided into two phases: phase 1 (early relearning) and phase 2. Phase 1 starts immediately postoperatively. During this phase, no afferent nerve signals are sent from the injured nerve to the somatosensory areas in the brain¹⁶⁷. The purpose of relearning in phase 1 is to stimulate the de-afferented neurons in S1 by using the brain’s cross- and multi-modal capacity. This can activate the neurons in S1 until the regenerating axons have re-innervated the skin and afferent signalling is re-established^{110, 159} – a sensory preparation.

Phase 2 relearning starts when detectable touch thresholds are present in the hand, as measured with Semmes-Weinstein monofilaments 6.65 (300 g pressure), and the new axons have re-innervated the muscles. Exercises for tactile gnosis/discriminative touch with localization of touch, identification of shape, textures, and objects are initiated and the complexity and difficulty of the exercises are gradually increased in parallel with regeneration and maturation of the repaired nerve^{110, 159}. The rehabilitation technique

is based on frequent short training sessions with variation between eyes open and eyes closed, and with increasing difficulty ^{54, 159, 191}.

Guided plasticity

The plastic capacity of the brain leads to new possibilities. Plasticity can be guided for therapeutic purposes to improve functions that have been damaged or lost ⁵⁷. There are a large number of different guided plasticity techniques for rehabilitation of nerve injuries in the upper extremity. For example, it has been shown that anaesthetizing the shoulder muscles in patients with impaired hand function due to a stroke can improve the motor function in the hand ¹²⁸. Furthermore, cutaneous anaesthesia of the forearm using an anaesthetic cream can temporarily improve sensory function in the hand in both healthy individuals and in patients with median nerve injuries ¹⁰⁹.

Several techniques for guided plasticity in early sensory relearning have been described ¹⁵⁹ with the aim of stimulating neurons that used to respond to afferent signalling from the injured nerve. In the early stage after a nerve injury, where no nerve signals are being sent in the injured nerve, guided plasticity can use the cross-modal capacity of the brain, i.e. the interaction between different senses ¹³⁸. For example, **observing touch** to someone else's hand or imagining someone touching one's own hand, i.e. **tactile imagery**, is known to activate the hand area of the somatosensory cortex ^{97, 142, 162, 193} (Figure 5).



Figure 5. Tactile imagery.

Several studies have shown activation in the motor cortex during **motor imagery** ⁶⁰. Immobilization is known to result in corticomotor depression. In an interesting study

on healthy volunteers who had one arm and hand temporarily immobilized, Bassolino et al. ¹⁴ showed that motor cortex depression could be prevented in subjects who **observed hand actions** performed by another person, but not in subjects who imagined hand movement. The use of **motor imagery** ^{60, 149} and reading **action words** ⁸⁰ has also resulted in activation of the motor cortex. Another method that has been applied in hand therapy is to **substitute senses**. Instead of substituting touch for visual or auditory input, which has been used for centuries by the blind and deaf, hearing can instead substitute for touch. A “sensor glove” can be used, whereby microphones are attached at the fingertips, picking up the sounds created when the hand touches different objects. The patient can learn to associate different sounds with different surface structures and objects ^{101, 108, 157, 171}.

These are all techniques with the potential to be used in early (phase 1) sensory relearning.

The occupational therapy perspective

The term activity in ICF is equivalent to the term occupation in occupational therapy ⁹⁹, and meaningful occupations is the core construct of occupational therapy ^{2, 141}. Occupational therapy interventions need to be based on meaningful occupations, and it is even claimed that if an occupation is not perceived as being meaningful, then it cannot be therapeutic ^{2, 141}. For an occupation to be perceived as being meaningful, it must have some value for the patient ^{19, 99, 141}. The value can be enjoyment in performing the occupation or satisfaction through improved capacity and skills ¹⁴¹, but it can also result from necessity or the need for survival ⁹⁹.

The International Federation of Societies for Hand Therapy defines hand therapy as: *“the art and science of rehabilitation of the upper limb, which includes the hand, wrist, elbow and shoulder girdle. It is a merging of occupational and physical therapy theory and practice that combines comprehensive knowledge of the structure of the upper limb with function and activity. Using specialized skills in assessment, planning and treatment, hand therapists provide therapeutic interventions to prevent dysfunction, restore function and/or reverse the progression of pathology of the upper limb in order to enhance an individual’s ability to execute tasks and to participate fully in life situations”*¹.

This definition highlights the importance of satisfying patient needs regarding body structure, body function, activity, and participation levels.

In hand therapy, the interventions in early sensory relearning can be related to the bottom-up approach and the top-down approach ¹⁸⁶, and also the construct about occupation-based and occupation-focused interventions ⁷⁰.

The top-down approach starts with evaluation of roles, habits, and meaningfulness, and continues with assessment to determine whether the patient can perform a specific task or activity. Body functions are considered later. The self-rewarded value and enjoyment may come directly in the top-down approach and are based on activities and occupations with self-rewarding value.

In the bottom-up approach, body functions and performance skills are considered first to obtain an understanding of the patient's limitations. Return of body functions is assumed, in the end leading to successful performance of daily activities. The bottom-up perspective may not be based on activities or occupations that are joyful in themselves, but ones that have a more concrete value, where the product of the activity is of real value to the patient. Patients' needs can be addressed using either the bottom-up approach or the top-down approach, depending on the situation. The bottom-up approach is more in line with occupation-focused interventions.

Occupation-focused interventions are where the focus on the occupation is at the endpoint as a goal, but is not used as a method of getting there⁷⁰. However, it is of the utmost importance that the therapist does not lose contact with the activity perspective¹⁸⁶. An example of occupation-focused intervention from early sensory relearning is mirror visual feedback (MVF). The mirror reflects tactile actions, e.g. touching varying textures or shapes, and motor actions from the unaffected hand while the affected hand is behind a vertically placed mirror (Figure 6).

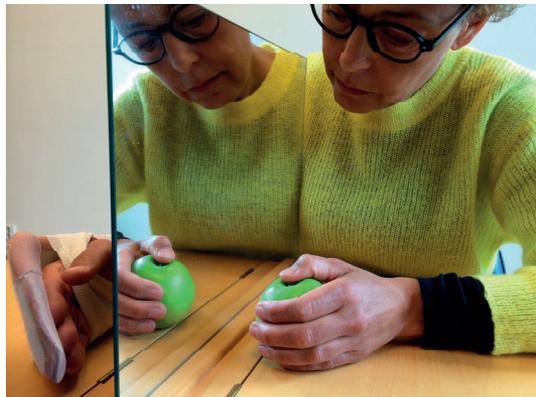


Figure 6. Mirror visual feedback. The mirror reflects the tactile action while the injured hand is behind the mirror.

This contrasts with occupation-based interventions, which use the occupation as both the method and the goal⁷⁰. These have shown effectiveness in stroke rehabilitation, for example, and after hip fractures^{51, 82, 88, 130, 175, 176}. Occupation-based interventions have also been reported to improve motivation and satisfaction^{35, 87, 88}.

Although occupation-based intervention is reported to be uncommon in hand therapy practice ^{6, 77}, it can be used when performing early sensory relearning. An example would be the imagery exercises that use situations and objects selected by the patient, to imagine a tactile sensation. The patient is asked to think about some familiar tactile object/situation and to try to imagine the sensation. To pick a situation or object that is associated with strong emotions is preferable, as it enhances memory ¹¹⁷ and may therefore facilitate the experience of touch. The instruction to the patient can be, for example: *“think of the situation when your dog came and put his head in your lap and looked at you with pious eyes. Imagine that you pet his soft, smooth coat on his head and then you put your hands into the curly fur on his ears”*. A way to accomplish an occupation-focused intervention with MVF is to use familiar objects such as pliers, keys, and cutlery for the patient to handle in the mirror.

In hand therapy following nerve injury, both the bottom-up approach and the top-down approach are valuable and I prefer the use of both from the start of rehabilitation. Due to the acute phase after an injury, when consideration must be given to healing processes, load regimes and hence there are restrictions, the bottom-up approach has to be the first choice. However, a person-centred occupational goal – seen from a top-down perspective – is important already from the first meeting with the patient.

An important role for the therapist during the rehabilitation process is to educate the patient about the injury. This is important in all rehabilitation, but especially following a peripheral nerve injury when so much of the early rehabilitation is focused on the interaction between the hand and the brain, which induces dynamic events in the somatosensory cortical maps.

Adherence is crucial for the implementation of the rehabilitation, i.e. sensory relearning, and it is a challenge for both the therapist and the patient to achieve patient adherence ^{78, 131, 135}. Comprehensive information and education is of great importance to make the patient aware of the concrete value of sensory relearning. Furthermore, meaningfulness leads to motivation ²; because of this, a sense of meaningfulness in the rehabilitation is of utmost importance. This is especially important in early sensory relearning, because sensory relearning does not give immediate results. The axonal re-innervation and dynamic reorganization of the somatosensory cortex during phase 1 of the rehabilitation is not noticed by the patient. This means that there is a gap of more than 3 months between the sensory relearning performed and the benefits gained in terms of ADL performance.

The problem

A peripheral nerve injury has consequences at all ICF levels, in body function (such as sensory loss and clumsiness), in limitation of activities (such as in self-care), and in participation restrictions in both work and recreation ⁸. To limit the impact of nerve injury on an individual's daily life, the methodology in rehabilitation needs to be developed further. There is a lack of research on the topic, and further studies are needed to evaluate the effects of sensory relearning ^{122, 137}. Which rehabilitation method is appropriate for each individual is not known; neither is how sensory relearning is perceived by those who perform it.

Aims

The overall aim of the work for the present thesis was to evaluate objective results and subjective experiences of early sensory relearning, and also sensory processing patterns, in patients after a median and/or ulnar nerve injury.

Specific aims

- To investigate whether early relearning, using guided plasticity starting directly after median or ulnar nerve injury, results in better sensory and motor function than traditional relearning alone in the short term (Paper 1) and in the long term (Paper 3).
- To investigate whether the participant's subjective opinion regarding symptoms and level of activity differs between patients who have performed early sensory relearning and patients who have been treated with traditional relearning (Paper 3).
- To determine how patients experience early sensory relearning (Paper 2).
- To investigate whether a median and/or ulnar nerve injury results in an altered sensory processing pattern (Paper 4).

Material and methods

Participants

Participants were mainly recruited at the Department of Hand Surgery, Skåne University Hospital, Malmö. In addition, patients were also recruited in collaboration with (1) Stockholm South General Hospital, Stockholm, Sweden, (2) University Hospital of South Manchester/University of Manchester, Manchester, UK, and (3) Department of Rehabilitation Medicine, Erasmus Medical Centre, Rotterdam, the Netherlands. Most of the patients recruited have participated in more than one study (Table 1).

Study 1. Participants were recruited and training started within one week of surgery, where a complete median and/or ulnar nerve injury had been sutured.

Study 2. Participants who had been operated with nerve repair due to a complete or partial median or ulnar nerve injury were included. In patients with partial nerve transections, it was a requirement that at least 50% of the injured nerve should be transected in order to make sure that the injury had a major impact on hand function. The patients had to have performed and completed early sensory relearning at least three months earlier and not more than three years earlier. The reason for choosing 3 years as an upper time limit was that after more than 3 years, the patients might not remember the details of how they experienced the early sensory relearning.

Study 3. Participants from Study 1 who had data from the six-month follow-up were included in this study.

Study 4. Participants in Study 4 were recruited from Study 2 and Study 3. The aim was to include participants with a large range of time since injury (i.e. some with recent injuries and some with injuries that had occurred several years previously).

Table 1. Participants in the four studies

Pat #	Study 1	Study 2	Study 3	Study 4
1	X			
2	X			
3	X			
4	X			
5	X			
6	X			
7	X			
8	X			
9	X			
10	X			
11	X			
12	X			
13	X			
14	X			
15	X			
16	X			
17	X			
18	X		X	X
19	X		X	X
20	X		X	X
21	X		X	X
22	X		X	X
23	X		X	X
24	X		X	X
25	X		X	X
26	X		X	X
27	X		X	X
28	X		X	X
29	X		X	X
30	X		X	X
31	X		X	X
32	X		X	
33	X		X	
34	X		X	
35	X		X	
36	X		X	
37	X		X	
38		X		X

Pat #	Study 1	Study 2	Study 3	Study 4
39		X		X
40		X		X
41		X		X
42		X		X
43		X		X
44		X		X
45		X		X
46		X		X
47		X		X
48		X		X
50		X		X
51		X		X
52		X		X
53		X		X
54		X		X
55		X		X
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57		X		X
58		X		X
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61		X		X
62		X		X
63		X		X
64		X		X
65		X		X
66		X		X
67		X		X
68		X		X
69		X		X
70		X		X
71		X		X
72		X		X
73		X		X
74		X		X
75		X		
Total	37	37	20	49

List of participants and which studies they were included in.

Outcome measures

The outcome measures are described under the heading of ICF where their main focus is. However, some outcome measures cover more than one level of ICF.

An overview of ICF components covered by the different outcome measures is given in Figure 7.

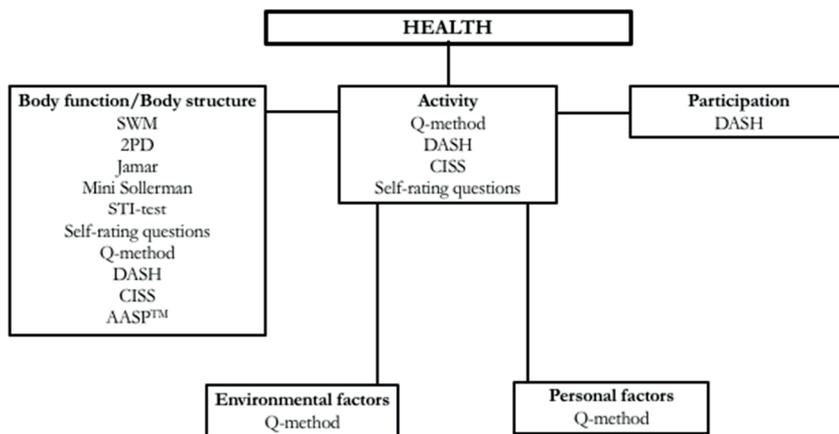


Figure 7. The International Classification of Functioning, Disability, and Health (ICF) including measures and questionnaires used in this thesis.

Body function and Body structure

RosenScore with subtests

RosenScore was used for objective evaluation of hand function in Study 1 and Study 3. RosenScore is a standardized diagnosis-specific outcome measure for evaluation of nerve function following peripheral nerve repair. It is composed of three domains, (Sensory Domain, Motor Domain, and Pain/Discomfort Domain), which are in turn based on two to four subtests. The subtests in each domain are expressed as the quotient between the patient's result obtained and the normal value. This is due to the fact that the subtests included use different measurement scales. An average quotient of the subtests in each domain is calculated where each domain can result in a maximum of 1

point. Adding the three domains together gives a maximum score of 3, which indicates normal sensory and motor function without pain. The summarized results from the subtests at body function/body structure level according to ICF reflect the impact of functional problems on activity level ¹⁵⁴. Instructions for administration of the RosenScore and the subtests are available at www.HAKIR.se ^{79, 154}. A raw data protocol is attached in the Appendix section. The domains and associated subtests of the RosenScore are described below.

Sensory Domain

Touch thresholds

Sensory innervation is assessed in terms of perception of touch/pressure thresholds with **Semmes-Weinstein monofilaments** to determine the capacity to detect a range of stimuli from light touch to deep pressure. The standardized nylon monofilaments provide controlled gradient force to the mechanoreceptors in the skin ^{7, 16}. Each nerve (median/ulnar) is assessed at three critical points (Figure 8) ¹⁵⁴ and the results are interpreted as being normal if the patient perceives ≤ 0.068 grams of pressure (filament number 2.83) ^{7, 16}.

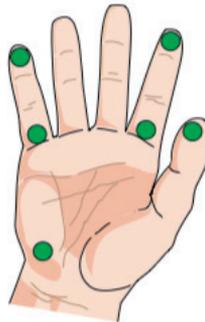


Figure 8. Critical points for median and ulnar nerve to be assessed with Semmes-Weinstein monofilaments in RosenScore. From hakir.se

Tactile gnosis/Discriminative touch

The **Shape Texture Identification test (STI)** is part of the evaluation of tactile gnosis/discriminative touch where the patient has to identify three shapes and textures of increasing difficulty ¹⁵³. It is recommended for discrimination between normal and abnormal tactile gnosis, and also for evaluation of return of tactile gnosis over time ⁷. The maximum (and normal) score is 6 ¹⁵³. For median nerve injuries the tip of the index finger is used for examination, and for ulnar nerve injuries the tip of the little finger is used ¹⁵⁴.

The **static two-point discrimination** test (2PD)^{123, 125} is part of the evaluation of tactile gnosis/discriminative touch where the patient has to determine whether one or two touch points have been applied to the distal phalanx of the index finger (in the case of median nerve injuries) or the little finger (ulnar nerve injuries). A static two-point discrimination is considered to be normal if it is 5 mm or less⁷.

Dexterity

The original version of the standardized Sollerman hand function test includes 20 tasks based on the most common grasps¹⁶⁹, but in the RosenScore three tasks are selected, as they reflect the most typical grips that are affected in nerve injuries – **Mini Sollerman**¹⁵⁴. The three tasks include complex fine motor manipulation with and without seeing, picking up coins from a purse, putting nuts on bolts, and buttoning. The maximum (and normal) score of the three tasks together is 12¹⁵².

Motor Domain

Grip strength

Grip strength is measured using a **Jamar dynamometer** (North Coast Medical Inc), and the test procedure is carried out according to Mathiowetz et al.^{113, 114}. The grip strength of an injured hand can be interpreted in different ways, including comparison with normative data or pre-treatment scores⁷. In the RosenScore, the grip strength of the contralateral hand is considered to be normal¹⁵⁴.

Muscle innervation

Motor innervation is assessed in terms of motor function/**manual muscle test** of palmar abduction for median nerve injuries (m. abductor pollicis brevis) and radial abduction dig II, adduction dig V and abduction dig V and for ulnar nerve injuries (1st dorsal interossei, 3rd volar interossei, and m. abductor digiti minimi)¹⁵⁴ using an adapted muscle power grading of 0–5 according to the Medical Research Council²³. A grading of 5 for each muscle is considered to be normal, giving 5 as normal for median nerve injuries and 15 as normal for ulnar nerve injuries¹⁵⁴.

Pain/Discomfort Domain

Hyperesthesia and Cold intolerance

The patient is asked to respond to two **self-rating questions** regarding their pain/discomfort regarding hyperesthesia and cold intolerance. The questions have four answer options with verbal descriptors (none/minor, moderate, disturbing, and hinders function) and are graded from 0 to 3^{152, 154}. None/minor (3) is considered to be normal¹⁵⁴.

Self-rated function and level of activity

In Study 3, 11 single-item questions were added to evaluate the patient's subjective opinions regarding function and activity. The 11 items were tingling/numbness in the fingers, clumsiness, pain at rest, pain in movement without load, pain at load, cold intolerance, aesthetics, fine motor skills, ability to perform daily activities, grip function, and weakness. A numerical 11-point box scale (NRS 11) supported with numerical descriptors below the box was used. The verbal anchors at the endpoints were 0, representing "no problem", and 100, representing "worst possible problem" (Table 2).

Table 2. The NRS 11 used in Study 3.

No problem					Worst possible problem					
0	10	20	30	40	50	60	70	80	90	100

Outcome measures: Activity and Participation

The Cold Intolerance Symptom Severity questionnaire (CISS)

Post-traumatic cold intolerance commonly develops within the first months after the injury and usually does not improve over time^{48, 161}. For patients with hand injuries, cold intolerance may have a profound effect on upper extremity disability and health-related quality of life^{33, 98, 152}. For evaluation of subjective experiences of cold intolerance, the Cold Intolerance Symptom Severity (CISS) questionnaire was used^{31, 86}. CISS is a self-reported questionnaire with six questions regarding symptoms when exposed to cold and the impact of cold intolerance on daily life. A possible total score of between 4 and 100 represents the severity of cold intolerance³¹. Abnormal cold intolerance is defined as having a total CISS score of >50^{33, 83}.

Subjective experiences of early sensory relearning

Subjectivity in health research can be studied using **Q-methodology**, which combines the richness provided by analyzing qualitative data and the stringency provided by analyzing quantitative data^{46, 55}. The Q-method is an innovative approach for qualitative analysis of patterns of attitudes, enhanced by quantified conceptual categorization¹⁶⁵, and is an effective approach in research that involves exploring and comparing different views⁶⁴.

When using Q-methodology, a number of statements based on patient views covering a wide range of possible opinions of the topic under study are ranked from “totally agree” to “totally disagree”, and sorted in a pyramid-shaped cell grid (Figure 9) consisting of the same number of cells as statements, with one statement in each cell. This means that the patient has to rank each statement in relation to the others ^{17, 46}.

Q-methodology has four distinct phases:

- 1) Development of the “Q sort pack”. A “Q sort pack” is a number of statements, which together cover most aspects of the topic to be studied. The statements in our study arose from pilot interviews with 10 patients with nerve injuries, and from an expert group consisting of three occupational therapists experienced in sensory relearning, one occupational therapist experienced in Q-methodology, and two hand surgeons.
- 2) Participants undertake “Q sort”. In this step, participants rank the statements (the Q sort pack) by placing each statement into a cell grid with the shape of a normally distributed curve (Figure 9). The statements are ranked from “totally disagree” to “totally agree” in the cell grid.
- 3) Analysis of the data. Factor analysis using statistical software designed for Q-methodology ¹⁶³ creates groups of statements, factors, that are interconnected and indicates participants who share these views.
- 4) Interpretation of the factors. The factors that emerge are unique regarding perceptions of the topic, and are interpreted for their significance. When comparing and contrasting the positioning of the statements in each factor, representative patterns appear for each factor. At this stage, the factors are given labels to describe the patterns of the statements in the given factor ⁴⁷.

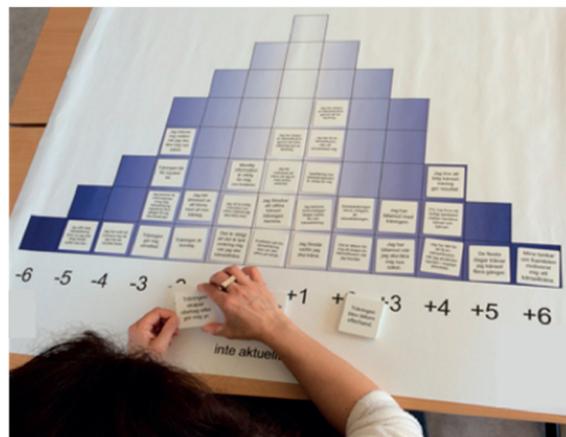


Figure 9. Participant undertake the Q-sort into the cell grid.

The Adolescent/Adult Sensory Profile™

The Adolescent/Adult Sensory Profile™²⁵ is a self-reported 60-item questionnaire based on Dunn's model of sensory processing^{24, 58}, and it is used to assess sensory processing patterns. The patient is asked to relate to the 60 questions/statements based on a 5-grade ordinal scale ("almost never", "seldom", "occasionally", "frequently", and "almost always")²⁵.

The 60 items are divided into four Quadrants, based on a combination of behavioural response and neurological threshold; see Figure 10. The four Quadrants are "Low registration", "Sensation seeking", "Sensory sensitivity", and "Sensory avoiding". The questions concern experiences of sensory processing in everyday sensory experiences across different sensory processing domains ("Taste/Smell", "Movement", "Visual", "Touch", "Activity", and "Auditory").

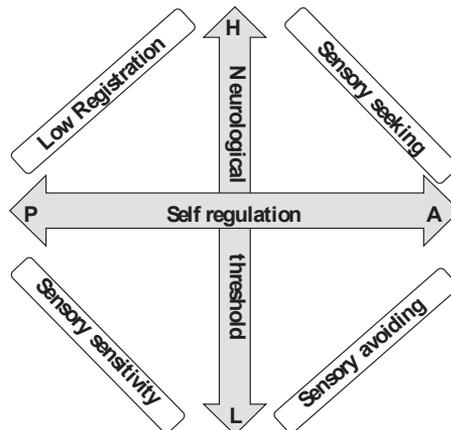


Figure 10. The four Quadrants of the Adolescent/Adult Sensory Profile™ in relation to the self-regulation continuum and the neurological threshold continuum. P = Passive, A = Active, H = High, L = Low.

Every item is scored on a 5-point scale regarding the frequency in the response to each item, from 1 (meaning "almost never") to 5 (meaning "almost always"). Summed scores for each Quadrant and the six Domains are calculated.

There is no cut-off for abnormal scores; the result is considered to be inconvenient when the person being tested experiences problems in ADL²⁵. Normative values on a group level are available for the Swedish population, for interpretation of whether the patient responds to the stimulus as most people do or more/less than most people do²⁶. Each patient was matched with four to six individual age-matched (± 2 years) and gender-matched controls from the Swedish normative population. Patients who scored

± 1 SD compared to the control group mean in each quadrant were interpreted as being Atypically High or Atypically Low. Patients scoring ± 2 SD compared to the control group mean in each quadrant were interpreted as being Definitely High or Definitely Low.

Disabilities of the Arm, Shoulder, and Hand questionnaire (DASH)

How the patient experienced his or her symptoms after the nerve injury and how these symptoms affected daily life was assessed using **The Disabilities of the Arm, Shoulder, and Hand (DASH) questionnaire**. DASH is a self-rated, region-specific outcome instrument with 30 items (body functions/activity/participation) to be ranked on a 5-grade Likert scale with verbal anchors from “No difficulty” to “Unable to perform activity/very severe symptoms”. A possible DASH score of between 0 and 100 is calculated, which represents the severity of disability^{11, 83}. A higher score means worse disability.

Statistics

Group comparisons for total score, domains, and subtests in the RosenScore (Studies 1 and 3) were done with t-tests due to quota scales. For changes within groups over time for the same parameters, paired t-tests were used.

In Study 3, group comparisons of results from DASH and CISS scores were calculated with Mann-Whitney U test due to ordinal scales. Group comparisons in self-reported questions regarding symptoms and function were done with the t-test.

Table 3. Statistical tests used in the four studies.

Test used	Study 1	Study 2	Study 3	Study 4
t-test	X		X	
Paired t-test	X		X	
Mann-Whitney U test			X	
Factor analysis		X		
ANOVA matched design				X
Binomial distribution				X

In Study 2 we used the Q-method, which is a mixture of qualitative and quantitative approaches. For the quantitative part, factor analysis was used.

In Study 4 we used ANOVA matched design to take advantage of the patients’ different numbers of controls. Following the analysis of variance of the mean between the

patients and controls, the deviation from the mean was calculated for each direction, and the confidence interval was calculated according to Binomial distribution.

The statistical methods used are presented in Table 3.

The statistical software programs used were SPSS (versions 23 to 25) and DosBox (version 0.74). The level of significance for p-values was $p \leq 0.05$.

Effect size

Reporting of p-values alone has been questioned, because it does not say anything about how large or important the difference is ^{27, 112, 184}. Thus, we added calculation of effect size in the long-term follow-up (Study 3). Effect size was calculated with Cohen's *d* as follows: $d = (M_2 - M_1) / SD_{\text{pooled}}$, where M_2 was the mean result in the early relearning group and M_1 was the mean result in the control group. An effect size of 0.2 was considered to indicate a small effect, 0.5 a moderate effect, and 0.8 a large effect ¹³².

Ethics

All studies were approved by the local ethics committee.

The positive effects from the intervention in Study 1 have led to a situation whereby early intervention in rehabilitation after peripheral nerve injuries is now standard procedure at the Department of Hand Surgery in Malmö. Thus, today all patients can benefit from the effects shown in Study 1 and 3.

No harm or discomfort was reported during the studies.

My contribution to the four studies is shown in Table 4:

Table 4. The degree of my participation in the four studies

	Study 1	Study 2	Study 3	Study 4
Planning	1	3	3	3
Ethics application	1	3	1	3
Data collection	3	3	3	3
Interpretation of results	2	3	3	3
Writing of the manuscript	2	3	3	3

1 = Did not participate; 2 = Partly participated; 3 = Participated to a large extent.

Results

Functional outcome following early sensory relearning

(Studies 1 and 3)

No differences were seen between the groups at three-month follow-up postoperatively. At the six-month follow-up, the early relearning group showed significantly better tactile gnosis/discriminative touch, as measured with the STI test and the 2PD. Both groups improved between three and six months, but a significantly greater improvement was seen in the early relearning group (Table 5).

Table 5. Discriminative touch at 3 and 6 months postoperatively

	<i>3 months</i>			<i>6 months</i>			<i>Change 3-6 months</i>
	Phase 1	Control group	Difference between groups	Phase 1	Control group	Difference between groups	Difference between groups
	Mean score (SD)	Mean score (SD)	p-value (95% CI)	Mean score (SD)	Mean score (SD)	p-value (95% CI)	p-value (95% CI)
STI test 0-1	0.05 (0.12)	0	0.06 (-0.01 to 0.12) p = 0.33	0.19 (0.23)	0.03 (0.07)	0.16 (0.01 to 0.31) p = 0.02	0.13 (0.02 to 0.22) p = 0.018
2PD 0-1	0.04 (0.17)	0	0.04 (0.05 to 0.14) p = 0.10	0.20 (0.26)	0	0.20 (0.05 to 0.36) p = 0.01	0.15 (0.02 to 0.29) p = 0.027

Score between 0 and 1 (where 1 = normal function).

No differences in the MotorDomain or the Pain/Discomfort Domain were seen between the groups at six months or at long-term follow-up (Table 6).

Table 6. Scores for each domain at long-term follow-up

	Early relearning group n = 9	Control group n = 11	Differences between groups p-value
Total score of RosenScore	2.1 (1.5-2.3)	2.0 (1.3-2.3)	0.55
SensoryDomain	0.67 (0.41-0.84)	0.47 (0.20-0.82)	0.04
MotorDomain	0.72 (0.39-0.79)	0.69 (0.39-0.99)	0.85
Pain/discomfort Domain	0.83 (0.33-0.79)	0.84 (0.5-1.0)	0.54

Results presented as Mean (min-max) for the two groups for each domain

In the long-term follow-up (Study 3), SensoryDomain as a whole, 2PD, and MiniSollerman in the early relearning group were significantly better. All significant variables in group comparison at long term follow-up had a large effect size, and a moderate effect size was seen in the non-significant variables (Table 7).

Table 7. Outcomes in RosenScore and subtests at 6 months and long-term follow-up.

	Early relearning group			Control group			Differences between groups at long-term follow-up		
	6 months mean (SD)	Long-term follow-up mean (SD)	p-value Diff (95% CI)	6 months mean (SD)	Long-term follow-up mean (SD)	p-value Diff (95% CI)	p-value Diff (95% CI)	Effect size	
Total score (0-3)	1.4 (0.44)	2.1 (0.29)	0.007 0.7 (0.23, 0.97)	1.3 (0.21)	2.0 (0.29)	< 0.000 0.7 (0.43, 0.88)	0.55 0.1 (-0.20, 0.35)	0.34	
Sensory domain (0-1)	0.45 (0.17)	0.63 (0.13)	0.002 0.18 (0.09, 0.26)	0.31 (0.12)	0.47 (0.19)	0.006 0.16 (0.06, 0.27)	0.05 0.16 (0.00, 0.31)	0.98	
SWM (0-1)	0.64 (0.22)	0.86 (0.10)	0.013 0.22 (0.07, 0.40)	0.52 (0.19)	0.76 (0.20)	< 0.000 0.24 (0.14, 0.34)	0.22 0.10 (-0.06, 0.25)	0.63	
<i>Raw data</i> SWM (0-5)* <i>tip dig II or V</i>	3 (0-5)	4 (3-5)		2 (0-4)	3 (2-5)				
2PD (0-1)	0.17 (0.25)	0.33 (0.29)	0.17 0.15 (-0.09, 0.43)	0.00 (0.00)	0.12 (0.17)	0.038 0.12 (0.01, 0.23)	0.05 0.21 (0.00, 0.43)	0.88	
<i>Raw data</i> (0-3)**	0 (0-2)	1 (0-2)		0 (0-0)	0 (0-1)				
STI (0-1)	0.19 (0.29)	0.44 (0.34)	0.11 0.25 (-0.06, 0.43)	0.03 (0.07)	0.29 (0.40)	0.039 0.26 (0.02, 0.50)	0.37 0.15 (-0.20, 0.51)	0.40	
<i>Raw data</i> (0-6)	1 (0-5)	2 (0-6)		0 (0-1)	0 (0-6)				
Mini Sollerman (0-1)	0.85 (0.12)	0.88 (0.09)	0.38 0.03 (-0.06, 0.15)	0.68 (0.35)	0.70 (0.10)	0.76 0.02 (-0.13, 0.17)	0.04 0.18 (0.01, 0.34)	1.89	
<i>Raw data</i> (0-12)	11 (8-12)	11 (9-12)		10 (1-12)	9 (3-12)				

Ratio scale value of Rosen score for total score, Sensory domain and subtests in Sensory domain. Paired t-test was used for in-group changes, and t-test was used for differences between groups. Effect size: Cohen's $d = (M_2 - M_1) / SD_{\text{total}}$. Numbers in **bold** indicate significance at $p \leq 0.05$.

Italics in shaded areas indicate raw data scores for the subtests in the Sensory domain, with median and (range).

* 0 = not restable, 1 = 6.65 residual deep pressure, 2 = 4.56 loss of protective sensation, 3 = 4.31 residual protective sensation, 4 = 3.61 residual texture, 5 = 2.83 normal.

** 0 = 2PD \geq 16 mm, 1 = 2PD 11-15 mm, 2 = 2PD 6-10 mm, 3 = 2PD \leq 5 mm.

Patients' subjective experiences of sensory relearning

(Studies 2 and 3)

In Study 3, patients' subjective experience of function after the nerve injury was examined with self-rated single-item questions in addition to direct assessment. Clumsiness, fine motor skills, and grip function differed significantly between the groups in favour of the intervention group (Figure 11). No significant differences were seen for the other eight items: pain at rest, pain at load, pain in movement, tingling/numbness, weakness, cold intolerance, aesthetics, and ability to perform daily activities.

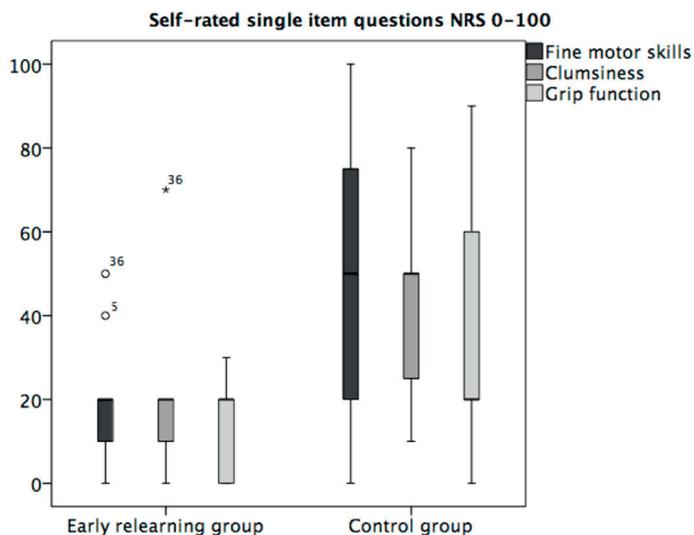


Figure 11. Distribution of scoring for significant self-rated single-item questions (0-100, where 0 = no problem and 100 = worst possible problem).

No significant differences were seen in DASH scores or CISS scores at long-term follow-up (Table 8).

Table 8. DASH and CISS scores at long-term follow-up (Study 3).

	Early relearning group n = 9	Control group n = 11	Differences between groups p-value
DASH (0-100)	4 (0-34)	13 (2-47)	0.20
CISS (4-100)	21 (4-60)	30 (13-80)	0.23

Patients' subjective experiences were the main subject of Study 2. Three factors emerged in the factor analysis using Q-methodology, explaining 45% of the variance, and 26 out of the 37 participants were included into a factor. The factors were labelled according to their characteristics. The first factor, Q1, was labelled "Believe sensory relearning is meaningful, manage to get an illusion of touch, and complete the sensory relearning" and represented 16 participants. The second factor, Q2, was labelled "Do not get an illusion of touch easily and need support in their sensory relearning" and represented five participants. The third factor, Q3, was labelled "Are not motivated, manage to get an illusion of touch but do not complete the sensory relearning" and represented five participants. The complete factor values for the three factors for each statement are shown in Table 9.

Table 9. Factor values for each statement, loading -6 to +6

STATEMENT	Factor 1	Factor 2	Factor 3
1 I believe early sensory relearning yields results	+6	+3	+4
2 The sensory relearning is exciting	+1*	-4*	-2*
3 The sensory relearning feels meaningful	+4*	+1	+1
4 The sensory relearning seems strange to me	-4	-1*	-4
5 The sensory relearning is boring	-2*	-1	0
6 The sensory relearning takes too much time	-3*	0*	-3*
7 The sensory relearning is hard	-4*	+2*	-2*
8 The sensory relearning makes me exhausted	-2*	0*	-4*
9 The sensory relearning gives me discomfort or makes me dizzy	-5	+1*	-5
10 I have patience with the sensory relearning	+2*	-2	-3
11 Written information is important to me (my understanding)	-1	-1	+2*
12 <i>Oral information is important to me (my understanding)</i>	+1	+2	+1
13 Pictures clarify information for me	0	0	+2*
14 The text in the information brochure is easy to understand	+1	0	+4*
15 I need to get the information on early sensory relearning repeated on several occasions to understand it	-3	0*	-3
16 <i>The information I got contained medical terms that were too difficult</i>	-4	-3	-5
17 I want clear instructions on what material I am supposed to use in my sensory relearning	0	+3*	+1
18 I can easily create an illusion of sensation in the mirror	0	-5*	0
19 I can easily get an illusion of sensation by using of my hand in daily activities	+3	-3*	+2
20 I can get an illusion of sensation without concentrating	-1	-4*	-1
21 I can create an illusion of sensation only by thinking about how it normally feels when I touch objects	+2*	-3*	0*
22 <i>It is easier for me to create an illusion of sensation when I close my eyes</i>	0	+1	+1
23 It is easier to create an illusion of sensation when I do the same thing with both my hands simultaneously	+1	0	+3*

24	I can create an illusion of sensation by seeing touch	+1*	-5*	-2*
25	I can create an illusion of sensation by hearing well-known sounds of touch	-1	-4*	-1
26	I can create an illusion of touch by handling objects	+2	-3*	+3
27	The mirror reflection feels like my own hand	+2*	-3*	0*
28	Motor training feels more important to me than sensory training	0*	+4*	+3*
29	I don't prioritize sensory relearning because I know it will not return back to normal anyway	-6*	-2*	-1*
30	Follow-up with my therapist is important to me	+3	+5*	+4
31	Most days, I do my sensory relearning several times	+3*	-2	-2
32	<i>The sensory relearning gradually became easier</i>	0	+2	+2
33	An empathetic approach of the therapist is important to me	+3	+6*	+3
34	I feel insecure when I am about to learn new things	-3	-2	-4
35	I have patience when I am about to learn new things	+2*	-2*	+1*
36	<i>I have an open mind to learn new skills</i>	+3	+3	+2
37	I am encouraged by a competitive element	-1*	+2	+1
38	I am stressed to keep up with all of my training	-3	-1	-2
39	To succeed with a sensory illusion motivates me to continue training	+2	+1	-1
40	I find it hard to motivate myself to do my sensory relearning	-3*	+3	+3
41	<i>Variation in training increases my motivation</i>	+1	+2	0
42	To do my training together with other patients makes me motivated	-1	-1	-3*
43	My thoughts about the future motivate me to do my sensory relearning	+5	+4	0*
44	I find it difficult to motivate myself when I do not see results instantly	-2*	+3	+1
45	I perform early sensory relearning even though I don't really understand the aim of it	-2	+1*	-2
46	<i>I understand why I am supposed to do my sensory relearning</i>	+5	+5	+6
47	I need to understand the purpose of early sensory relearning before I start it	-1	+1*	-1
48	I understand how the training is supposed to be conducted	+4	0*	+5
49	I learn about the sensory relearning by teaching it to someone else	-2	-1	-3
50	I prefer doing my sensory relearning at home	0*	-2*	+2*
51	The quality of my sensory relearning increases if I do it at the rehab. unit	-1	+2	0
52	To manipulate with the brain scares me	-5	-6	-6
53	I need to schedule/create routines for my sensory relearning	-2*	+4*	0
54	<i>It is important that it is quiet around me when I am doing my sensory relearning</i>	0	-1	-1
55	To me there is a clear connection between the hand and the brain	+4	0*	+5
56	The support from my relatives is important to me	+1	+1	-1*

Factor values in bold indicate a distinguishing statement for the factor ($p < 0.05$), whereas an additional asterisk (*) indicates significance ($p < 0.01$). Statements in italics are consensus statements; they do not distinguish between any factors.

Sensory processing patterns

(Study 4)

When comparing patients with a peripheral nerve injury with the normally distributed age- and gender-matched control group, a significant difference was seen in the “Low registration” quadrant (Table 10). No significant differences were seen in the sensory processing domains (Taste/Smell, Movement, Visual, Touch, Activity, and Auditory).

Table 10. Significance of differences between patients and controls for each quadrant.

	p-value
Low registration, Q 1	0.029
Sensory seeking, Q 2	0.956
Sensory sensitivity, Q 3	0.206
Sensory avoiding, Q 4	0.268

The patients scored higher in Quadrant 1 (Q1), Low registration, which meant that – to a greater extent than the controls – they had high thresholds to stimuli. They needed a greater amount of stimulus to react, in combination with a passive behavioural response. Altogether, 53% of the nerve-injured group scored atypically or definitely high, as opposed to 18.5% in the control group. There was also a smaller proportion scoring low in this Quadrant than in the control group. The percentage distribution of scoring Atypically High/Low and Definitely High/Low compared to the control group can be seen in Table 11.

Table 11. Percentage distribution of scoring Atypically High/Low and Definitely High/Low in Q1 (the Low registration Quadrant)

	Patient group	95% CI	Control group
Atypically High	40%	32–48	16%
Definitely High	13%	8–19	2.5%
Atypically Low	8%	4–14	16%
Definitely Low	0%	0–4	2.5%

The nerve-injured group as a whole had shifted to scoring higher in Q1 than the control group. The distribution of patient scoring compared to the normative distribution of the controls can be seen in Figure 12.

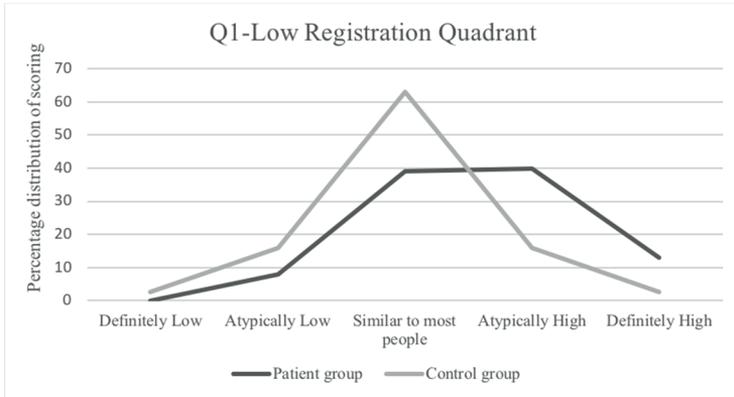


Figure 12. Nerve-injured patients' scoring distribution in comparison to the normative distributed scoring in the control group.

Discussion

Early sensory relearning is a new way to use brain plasticity, and the effect of early sensory relearning is a relatively unexplored field. To our knowledge, very few studies^{116, 157} have evaluated the effects of sensory relearning in the early phase following nerve transection and repair at wrist/forearm level, and the results were conflicting regarding the benefit of early sensory relearning. Other studies on sensory relearning are in their late phase and provide little evidence, so further studies are needed^{122, 137}.

This thesis strengthens the evidence that early sensory relearning makes sense, and it improves our knowledge and understanding of the importance of early sensory relearning. Furthermore, this thesis shows that the sensory outcome and patient-rated functioning can be improved following nerve repair using guided plasticity. It has also highlighted the complexity of the patient's experience of early sensory relearning and shown how the injury contributes to an altered sensory processing pattern. At the same time as our understanding has increased, the work described in this thesis also raises additional questions, such as how the early relearning should be done – to find the right method for each person.

Participants

Patients operated with nerve repair due to a complete transection of the median and/or ulnar nerve are not a very large group, seen in numbers. In Study 1, relatively strict inclusion criteria were used in order to get study groups that were as homogeneous as possible, which made the enrolment difficult. For Study 1, a sample-size estimation of 12 patients in each group was made to achieve a power of 80% and p-value ≤ 0.05 ¹⁵⁸. Thirty-seven patients were enrolled in the study after 5 years. For several reasons, including the complexity and advantages that a multicentre study implies, there were numerous external dropouts, so that 27 patients completed the six-month follow-up. This in turn gave 27 possible patients to include in Study 3 for long-term follow-up. Unfortunately, another seven patients could not be included in the long-term follow-up after four to nine years due to the inability to locate them, death, or unwillingness to participate. This resulted in smaller groups in the long-term follow-up than the required 12 per group that had been previously planned from the power calculation.

However, we consider this normal in a long-term follow-up of an RCT study. Despite the relatively small groups, Studies 1 and 3 generated interesting and new results in our efforts to gather evidence for the effect of phase-1 training. The randomized studies (Studies 1 and 3) are, to our knowledge, unique in the field of using guided plasticity in the early phase following nerve transection and repair.

There was an imbalance between the groups in Study 1, and especially in Study 3, regarding the number of participants with median or ulnar nerve repair. However, earlier research has not shown any significant differences in either sensory or total function between median and ulnar nerve injuries in the long run ^{95, 155}. In Studies 2 and 4, more patients were included due to broader inclusion criteria such as partial nerve injury (> 50%) and injury due to a suicide attempt. Despite the fact that there were some partial nerve injuries in these studies, interesting results were gained regarding sensory processing patterns and also experience of early sensory relearning. This indicates that even a minor injury has obvious effects on the individual.

Methods

RosenScore ¹⁵⁴ was used for evaluation of the primary outcome, discriminative touch, in Study 1 and Study 3. RosenScore is well established in the clinical setting, and is as close as one can get to a golden standard following peripheral nerve repair ^{111, 180}. The benefits of RosenScore are that it provides both detailed information and an overview of the outcome regarding level of body function, while being illustrative and comprehensible to the patient. In the long-term follow-up there were two tests, 2PD and MiniSollerman, which showed significant differences between the groups, and also the Sensory Domain as a whole with all four sensory tests merged. This shows the strength of a composite model instrument with several standardized tests combined, such as the RosenScore ¹⁵⁴.

Cold intolerance is a problem that most patients with a nerve disorder suffer from. Assessment of cold intolerance is part of the RosenScore, but the PROM CISS ³¹ evaluates cold intolerance in a more thorough way and assesses problems due to cold intolerance regarding both body function and activity level. The mean results of CISS in Study 3 were within normal values in both patient groups at long-term follow-up ³³, but there were patients in both groups with abnormal cold intolerance. These abnormal reactions to cold exposure in a proportion of our patients with median or ulnar nerve repair may influence on ADL and work ability.

DASH ¹¹ is a widely used PROM for assessment of the impact of upper extremity disorders in terms of physical function and symptoms involving the upper extremity ⁸³. Vordemvenne et al. suggested the use of a PROM in combination with RosenScore to

capture activity limitations following nerve repair¹⁸⁰. DASH was the most appropriate instrument at the time of planning of Study 3. The fact that mean DASH scores were within normal limits at long-term follow-up may indicate that DASH was not sensitive enough for this patient group. Many of the tasks and activities that nerve-injured patients mention as being limited are not captured by the DASH⁹. Recently, a newly developed and validated patient-rated outcome measure, specifically developed for all nerve disorders, i.e. both nerve trauma and nerve compressions, has been published: the Impact of Hand Nerve Disorders (I-HaND) Scale⁹. The expectations are that I-HaND will be able to distinguish the limitations that the nerve disorder creates for the individual. Either way, it will not be available to our patients until it has been translated into Swedish and been validated in the Swedish context. Hopefully, the new I-HaND questionnaire will be able to distinguish the subjective impact of the nerve injury.

To gain a deeper understanding of the subjective opinion regarding symptoms and hand function, a numeric rating scale (NRS) was used in Study 3. NRS, together with the visual analogue scale, VAS, is mainly used for evaluation of pain. The NRS has been shown to be the most responsive scale; a good compliance rate, ease of use, and a good applicability relative to VAS has been reported⁸¹, as well as better or similar psychometric properties^{71,73}. However, the use of – and psychometric properties of – NRS for rating of symptoms other than pain should be further studied.

To investigate how patients experience early sensory relearning, a study with a qualitative approach should be carried out, and there are several approaches for this. We chose Q-methodology¹⁸⁵. An advantage of Q-methodology is that it mixes the depth of qualitative methodology with the accuracy of quantitative methodology. This reduces the risk of errors resulting from the authors' interpretation. Another advantage is that one can include many patients' opinions in the analysis, as compared to the use of a solely qualitative method. One disadvantage, however, is that there is no possibility of asking supplementary questions to explore interesting views, except for the obvious most extremes statements at the two endpoints. One way to proceed in designing individualized early sensory relearning programmes would be to select a few patients from Q2 and Q3 (those who did not perform their early relearning) and conduct deep interviews with them to gain an even greater understanding of the obstacles to exercise that are experienced. The results of Study 2, together with hypothetical results from further interviews, might serve as a knowledge base when identifying the needs and abilities of individuals, which should be taken into account and used in the design of future, individualized, rehabilitation efforts.

Mapping of sensory processing patterns is used in planning of treatment strategies in neuropsychiatric disorders²⁵. The ability to perceive, integrate, and respond to incoming sensory information from all senses is critical for functioning and it is reasonable to hypothesize that atypical sensory processing would be present and also possible to recognize following peripheral nerve injuries. To investigate whether a

median and/or ulnar nerve injury results in a changed sensory processing pattern, AASP was used. AASP²⁴ was developed for neuropsychiatric disorders. However, AASP has also been used to assess sensory processing patterns in more physical conditions such as asthma⁶⁶, multiple sclerosis⁴⁴, and atopic dermatitis⁶⁵ – with significant results recently. This made us interested in the potential that AASP could have in assessment of patients with peripheral nerve repair. The result from Study 4 showed altered sensory processing patterns regarding all sensory modalities, creating further questions about how to address this in early sensory relearning.

The effect of early sensory relearning and its impact on ADL

The results from Studies 1 and 3 add valuable information regarding the benefits of early sensory relearning. There were significant differences in discriminative touch/tactile gnosis in favor of early sensory relearning, with a large effect size, between the group that was instructed in early sensory relearning and the group that had only traditional rehabilitation. Backed up by the results from Study 2, we now know that at least 27%, and perhaps up to 57% of nerve-injured patients do not perform their sensory relearning as instructed. This is in line with what has been reported from WHO regarding adherence to long-term treatment, where about 50% of patients do not adhere to given guidelines¹⁹⁰. It is probably reasonable to believe that some of these “non-doers” were also included in the intervention group in Studies 1 and 3. However, due to the strict inclusion criteria, the proportion of non-doers may have been less. The idea that probably not everyone in the intervention group of Study 1 completed the training raises the following question: To what extent would the differences between the groups change if we compared the results between the control group, which did not receive any sensory relearning in the early phase, and those in the intervention group who actually completed the training? If the truth is that a proportion of the patients in the early relearning group did not perform their training, it may be possible that the benefits of early sensory relearning are greater than what we have concluded, as any “non-doers” would have been included in the analysis.

In any case, the benefits of early sensory relearning are so much more than a higher score in the outcome instruments, in this case the Sensory Domain of the RosenScore. For the phase-1 relearning group there were advantages in their daily life, since they achieved higher levels in the sensory hierarchy by more effectively mastering discriminative touch/tactile gnosis which, in turn, is essential for ADL functioning.

In the long-term follow-up (Study 3), we added self-rated questions regarding hand function in, or with a great influence on, activities of daily living. Less aggravating

effects were seen in fine motor skills, clumsiness, and grip function in the early relearning group. Vordemvenne et al.¹⁸⁰ suggested that DASH or a similar instrument should be used together with the RosenScore to better describe problems experienced by nerve-injured patients in ADL. Furthermore, Vordemvenne et al.¹⁸⁰ found a strong correlation between the TotalScore of the RosenScore and the DASH score in a population of nerve-injured patients similar to the one used in this thesis. Furthermore, when the RosenScore was developed it was found that the TotalScore correlated strongly with the patient's self-reported level of ADL functioning¹⁵⁴. The DASH questionnaire was added as a patient-rated outcome measure in the long-term follow-up (Study 3). The mean DASH values in our results were within "normal" range compared to Norwegian and US normal values^{3,85}, but a number of individuals were above the cut-off for normal, meaning that they were limited in ADL functioning because of their hand/arm function. Vordemvenne et al.¹⁸⁰ reported slightly higher, i.e. worse, DASH scores at 8-year follow-up, but they were still within one SD of the normal mean. However, it has been shown that a subtle sensory loss can have a huge influence on quality of life in the long run, even if it can be compensated for, and quantitative data such as DASH scores have shown good outcome^{37,38}. This highlights the importance of using outcome instruments measuring both ADL performance and details of body functions such as the subtests of the RosenScore, with the aim of initiating relevant interventions to reach the occupation-focused goals. Our results may indicate that DASH is not sufficiently sensitive for this patient group in the long term, but it was the best available patient-rated outcome measure at the time of implementation of Study 1. As mentioned previously, the recently introduced PROM I-HaND can be used as a complement to the RosenScore⁹.

It is well known that a nerve injury may have a huge influence on work, hobbies, and quality of life³⁸. In order to get as good hand function as possible, with as little impact as possible on work and leisure activities, it is of utmost importance to guide and coach the patients into doing their early sensory relearning. At the long-term follow-up (Study 3), the control group had of course also improved their discriminative function, but at a level that the early relearning group had reached already at six-month follow-up. Our results indicate that it is a matter of timing of the initiation of sensory relearning. The patients in our studies who received phase-1 training not only achieved better objective and subjective hand function, but they also achieved this level of functioning several years earlier. This should cause less suffering for the individual at the body function, activity, and participation level.

A sense of meaningfulness – a key factor in successful early sensory relearning

Early sensory relearning is, at least for most patients, a completely new way of thinking and performing an exercise – creation of “illusions of touch”. From clinical experience, it is known that many patients find it quite hard to understand and address the underlying neurobiological concepts and its effects on their future hand function. Another factor that can complicate the early sensory relearning is the lack of immediate feedback and results.

In order to better understand the patient’s experiences of early sensory relearning, we conducted the Q-study (Study 2). Three groups of viewpoints/factors regarding sensory relearning emerged in Study 2. One group (43% of the patients) expressed that they had a sense of meaningfulness in conducting their early sensory relearning. This was also the group that performed the training and experienced an illusion of touch easily. None of the other viewpoints/factors expressed they felt any sense of meaningfulness for the sensory relearning; nor did the patients defining those two factors perform the early sensory relearning. Thirty per cent of the patients did not fit into any factor, and therefore we do not know if they experienced the training as being meaningful, or if they had performed sensory relearning as instructed. Still, 27% did not experience a sense of meaningfulness in the training. One patient defined viewpoint 2 expressed: “I would have needed to see a clearer link between sensation and hand function. For me, it was two different things”. With such a view of the training, it seems clear why one would not experience a sense of meaningfulness in the early sensory relearning. In a study on flexor tendon repair, patients appreciated interventions directed towards performance of meaningful activities⁹⁶. Also, Che Duad et al. lifted the influence of purposeful activities in the intervention, as it made the patients engaged and motivated³⁵. To clarify the connection between the training and the potential hand function, one should concentrate on a clear connection with the activity of the individual patient for future development of the training concept.

A sense of meaningfulness seems crucial for succeeding and completing early sensory relearning, since it could only be identified in patients defining factor 1, the only factor in which the patients performed their relearning. No motivational factors for facilitating early sensory relearning could be identified for patients defining factor 3 in Study 2, even though they were truly able to create illusions of touch. A challenge for the therapist will then be to inform patients about the neurobiological processes in an understandable manner and convince them about the value of the exercise, and to help to guide them into training strategies that feel meaningful. The therapist should not be seen as being only a “treater”, but more of a teacher who wants to make the patients adhere to treatment, and crucial considerations may be motivation and a sense of meaningfulness. A sense of meaningfulness is dynamic and individual, and it is

probably important that the patient finds that the activity – in this case the specific exercise – is meaningful and that the relearning is clearly linked to meaningful, concrete activities and aims. Che Duad et al.³⁵ proposed the use of occupation both as mean, occupation-based, and as end, occupation-focused, for successful rehabilitation of hand injuries. A combination of both of these perspectives may help connect the training to meaningful activities.

Consideration of the importance of meaningfulness reflects opinions in various theoretical frameworks; a sense of meaningfulness is one of the key components in having a sense of coherence¹⁰² – one experiences meaningfulness when life make sense emotionally and problems and demands are seen as challenges rather than burdens. Such a state, together with a strong sense of manageability and comprehensibility when dealing with stress related to the consequences of an injury, may influence patients' ability to adapt and experience positive health¹⁰². The Value and Meaning in Occupations model (ValMO)¹⁴¹ states that the activity needs to have a value to establish a sense of meaningfulness, which is thought to be necessary to succeed with an intervention⁶⁷. This value may be of a different kind, such as having a concrete value in that it provides a satisfactory result, such as an improved or advanced ability⁶⁷. Also, Clark and colleagues⁴³ believe that the individual's hopes and expectations in themselves contribute to a sense of meaningfulness. For patients who experience a concrete value in the training situation, an occupation-focused approach – such as certain nerve-specific motion exercises in the mirror – would be appropriate.

Another value that has been described is the self-reward value associated with the immediate reward that the performance of the activity itself gives¹⁴¹. Activities with a wide scope for self-directed influence and creativity have great self-reward potential⁶⁷. An occupation-based approach is therefore appropriate in the rehabilitation process of patients who require self-reward value in the training situation. Such individualized early sensory relearning programmes could contain, for example, imagery exercises in activities that are chosen by the patient.

Thus, a way to proceed in early sensory relearning may be to individualize the training tasks. Patients who can experience meaningfulness through their hopes and expectations should be identified. These patients can be given, for example, specific sensory relearning exercises with an occupation-focused approach while those who need more self-reward in their activities might benefit more from a self-chosen occupation-based approach.

The challenge of early sensory relearning

We now know from our studies that the early sensory relearning yields both subjective and objective advantages in both the short term and the long term. We also know from our studies that not everyone succeeds in their early relearning, for reasons such as failed attempts to create an illusion of touch or motivational issues. This increase in our knowledge highlights the need to develop individualized rehabilitation programmes in order to take advantage of the benefits that early relearning provides. Both facilitating factors and aggravating factors to the design of such programmes can be identified:

Study 4 showed abnormal sensory processing patterns in relation to the healthy control group regarding all sensory impressions. Other studies using AASP on physical conditions have also shown deviating distribution in relation to the normal population, although trends in atypical sensory processing have not been the same as in our study^{42, 44, 65}. High scores in the “Low registration” quadrant were, among other things, significant in patients with multiple sclerosis⁴⁴, which is what we found in our sample. The nerve-injured group reported having a greater degree of low registration to sensory inputs, which means that an increased amount of impressions would be needed to become aware of them or to react. At the same time, this group of patients had a passive behavioural response, meaning they did not search for impressions actively. Our study did not show any correlation between having an altered sensory processing pattern and time since injury. It is likely, however, that this change occurred after the injury – but we do not know when. At least 6 months had passed since the injury. It might be a rapid process, which reduces the perception of other sensory modalities at the moment the sensory impulses from the hand to the brain disappear, or it may take a couple of weeks or months before occurring. It is important to take into account that not all patients developed high scores in the “Low registration” quadrant, only a significantly increased proportion compared to the normal population. At the same time, a lower proportion scored low in the “Low registration” quadrant compared to the normal population, i.e. those who responded to a small amount of stimuli were fewer in the nerve-impaired group, which means that the group as a whole tended to be “low registrars”. Adding the increased proportion who scored “Atypically High” or “Definitely High” compared to the control group to the proportion in the nerve-injured group who did not score “Atypically Low” or “Definitely Low” to the same extent as the control group gives a percentage of 45% who scored higher than their controls in the “Low registration” quadrant. In other words, almost 50% of the patients with peripheral nerve repair developed an altered sensory processing. The reasons for this – and which group of patients develops a change in sensory processing – are still unanswered questions. Could it be due to environmental or social factors, as no correlation was seen with age or time since the injury? Also, we do not even know if the altered sensory processing is actually a problem for these patients, since we have not asked them.

In patients with multiple sclerosis, high values in “Low registration” correlated with poorer quality of life ⁴⁴. As Brown, who developed the AASP ²⁵, stated, it is only a problem when there is a conflict between the patient’s will or wishes and the current performance. It may even be that it is an advantage to develop this change, and preferably early postoperatively, because an advantage for “low registrars” is that they can stay focused even in noisy environments. Early sensory relearning, with for example imagery exercises or observation of touch, usually requires careful concentration, something that should be easier to achieve if you have an increased ability not to absorb impressions from the surroundings to the same extent as the normative population. Another consideration to take into account in the rehabilitation process for these patients is that presenting new stimuli and information should be done at a reduced rate, to allow the “low registrars” time to process the information ²⁵. The patients in factor 2 in Study 2 did not perform their training as desired, and asked for more support in their relearning. In the clinical setting, it can be addressed by offering the patients to stay at the rehabilitation unit, which would give them time to practice their early sensory relearning until they feel confident. A qualitative study on wrist fractures revealed that patients’ motivation increased if they performed their training at the rehabilitation unit ¹³. This extended practice and guidance would also allow more support and varied exercises, if one found that patients failed to have illusions of touch, as for the patients in factor 2 in the Q-methodology study.

Early sensory relearning has components of abstract thinking such as “to imagine using the hand” and “to imagine experiencing touch”. Early sensory relearning is often perceived as being difficult, and the patient needs a great amount of coaching from the therapist, both regarding the training and about the injury and the cortical processes it initiates. A patient with knowledge and understanding of the consequences of his or her state of health, in this case a nerve injury and its training construct, is more likely to be engaged in their rehabilitation regimen and adhere to the necessary training ¹⁹². This would also empower the patient to find his/her own strategies to cope with the inconvenience caused by the injury ¹⁹⁰. Making the rehabilitation personalized by matching it to the patient’s learning style is a way to proceed ^{126, 168}. The ultimate relearning includes an ability to integrate the relearning into daily life by getting illusions of touch when handling everyday familiar objects. Unfortunately, this is not easy and may not be possible for everyone – and the challenge is to find the right rehabilitation technique for the right person, to reach a successful outcome. Imagery exercises themselves form an important part of early sensory relearning in addition to the imagery that is used as part of the concept of mirror visual feedback. In the Q-methodology study (Study 2), one of the factors represented a viewpoint whereby the patient was unable to create an illusion of touch. A condition of reduced or absent voluntary imagery is termed aphantasia ¹⁹⁴. Two to five per cent of the normative population is reported to have very poor or to completely lack the ability to create visual imagery, i.e. to have aphantasia ⁶⁹, and this would of course complicate their early

sensory relearning. In addition, the richness of imagery can be dimmed or abolished in psychological conditions such as depression and anxiety¹⁹⁵, which has been reported to be a possible consequence of peripheral nerve injury. These phenomena together may further complicate early sensory relearning. A way to easily assess the patient's ability to create an illusion of touch through observation of touch might be to conduct a test with the so-called "rubber hand illusion" experiment^{61, 93}. In this experiment, synchronous brushstrokes are applied to a rubber hand in full view and to the participant's real, but hidden, hand. This procedure produces an experience that the touch is located on the rubber hand, and it is believed that this illusion occurs as the brain's perceptual systems attempt to interpret the conflicting visual, tactile, and proprioceptive information – a re-calibration of the location of the touch²². The proportion who find it difficult or do not succeed in creating the illusion is said to be 13–28%^{61, 93}, which is in line with the proportion of participants who were categorized into factor 2 in the Q-methodological study. The discrepancy between the reported occurrence of aphantasia (2–5%) and those who are unable to create an illusion of touch in the rubber hand illusion (13–28%) might have the potential to cope with creating illusions if we can further develop the sensory relearning techniques.

The optimum design regarding intensity and frequency in early relearning is not known. Learning as a concept is defined as encoding of memory, and is the process of "gradual change in behaviour as a function of training"¹⁴⁴. We base the intensity and frequency, among other things, on theories from other social sciences: the dual code theory and the spacing effect. The dual code theory is described as processing of information from different senses and coding the memories in parallel. This supports the idea of using multi-modality techniques in early sensory relearning. Also, Pusic¹⁴⁵ advocated the use of multiple senses to facilitate learning. Another concept arising from psychology and cognitive research is the spacing effect. The spacing effect means that learning times, i.e. early sensory relearning in this case, are spread over a longer period of time. The same time spent on training has the best effect on learning when spread over time^{34, 182}. In the randomized trial, the patients were instructed to conduct their early relearning 4–5 times a day, in line with the spacing effect. From clinical experience, we also know that patients cannot handle long training sessions with the amount of concentration needed in early sensory relearning, but 10 minutes at a time is usually manageable.

Guided plasticity in sensory relearning, and future work

Brain plasticity can be guided to support functions that have been damaged or lost due to a nerve injury⁵⁷. During the last decades, enormous advances have been made in our understanding of how the brain works – both in healthy people and in people with

different nerve disorders or injuries⁹⁴. This knowledge enhances the possibility of using guided plasticity to treat peripheral nerve injuries in the arm, for example.

Sensory relearning was first described by Wynn-Parry and Dellon in the 1970s^{54, 191}, and dealt with the training in the period that we now call the late phase, phase 2. Wynn-Parry stated that “it is a matter of learning to code afferent stimuli that have different electrical transmission properties than normal and by experience relate these to specific sensory function”¹⁹¹, and that this is possible because of the plasticity of the central nervous system.

A complete median or ulnar nerve injury results in a de-afferentation and de-efferentation of the skin and muscles in the hand innervated by the damaged nerve⁴⁹. In the sensory system, this de-afferentation means that no signals are sent to neurons that normally process sensory information from the hand. Because of plasticity these neurons start, within minutes after the injury, to respond to sensory signals from skin areas adjacent to the injured area^{120, 121}. Over the weeks following the injury, the primary somatosensory cortex in both brain hemispheres gradually adapts to the fact that no nerve signals are being sent to the brain from the injured nerve^{40, 94}. It is well known that cerebral changes are more consolidated over time. This means that when the injured nerve has re-innervated the target areas in the fingers about 3 to 6 months after the injury, the cerebral adaptation is somewhat “hard-wired”. From a neurobiological standpoint, it seems logical to try to stimulate the de-afferented neurons in the primary somatosensory cortex in a way that the stimulation is coupled to stimulation of the hand in general, and the injured area in particular. Furthermore, this should be done as soon as possible after the injury in order to prepare the neurons corresponding to the injured nerve for when the nerve has regenerated and starts to send afferent signals again. Bearing in mind the cerebral changes seen after a nerve injury, the most logical thing to do from a rehabilitation point of view, would be to divide the rehabilitation into one phase before re-innervation and one phase after re-innervation since the prerequisites to stimulate the de-afferented neurons in the primary somatosensory cortex are completely different in the two phases¹¹⁰.

The first report in which sensory relearning was used in the early phase, before re-innervation is established, was from Cheng et al.⁴¹ in 2000 where they studied patients who had been operated for a digital nerve injury. In the study by Cheng et al., the intervention group received tactile stimulation in the form of observation of touch for 1.5 h a day, starting 3 weeks after surgery and ending 6 months postoperatively. Because this study covered both Phase 1 and Phase 2, it is impossible to draw any conclusions about the effects of Phase-1 training.

In 2007, Lundborg and Rosén described the concept of sensory relearning in Phase 1 and Phase 2¹¹⁰. Even though this description was written more than 10 years ago, there have been very few studies apart from those presented in this thesis that have examined the clinical effects of sensory relearning in Phase 1.

The main challenge in sensory relearning in phase 1 is how to stimulate neurons in the primary somatosensory cortex, that usually respond to afferent signals from the injured nerve, without using the injured nerve. Again, basic neurobiology can be of help. It is well known that the different senses are connected and interact in the brain, the phenomenon called cross-modal plasticity¹⁵. An example of cross-modal interaction is action observation, which we used as intervention in Study 1. In this technique, the patient looks at a motor action or looks at a tactile act and corresponding motor or sensory areas are activated^{14, 127, 193}. In the work for this thesis, sensory action observation was used, where the patient – with his or her uninjured index finger – touched the index finger of the hand with a median nerve injury. Furthermore, previous studies^{108, 157} have shown that auditory stimuli can activate neurons in the primary somatosensory cortex. In addition, a Sensor Glove System^{103, 105, 157} has been developed whereby friction sounds, occurring when different textures/surfaces are touched, are transferred to the patient. An interesting way to refine the audio-tactile interaction concept in early sensory relearning would be to investigate whether auditory stimuli of different well-known sensory situations, such as the sounds of tapping of computer keyboard, activate somatosensory areas. Such associations would give additional opportunity to individualize the sensory relearning. Listening to sounds that can be linked to tactile stimuli would not require much effort from the patient, and might be more attractive for patients who do not perform their exercises, and thereby do not benefit from the improved discriminative touch/tactile gnosis provided by the early sensory relearning.

It is well known that imagining a motor action activates similar motor areas that are activated when an actual movement occurs, a phenomenon called motor imagery⁶⁰. An analogous phenomenon exists whereby sensory areas are activated by imagining sensory stimulation^{162, 193}. Sensory imagery was part of the phase-1 relearning used in Studies 1 and 3. Interestingly, in Study 2 it was found that a number of patients are not able to imagine sensory stimulation. Since sensory imagery is an important part of phase-1 relearning, it seems important to identify patients who are not able to imagine tactile stimuli before they start training. To do this, one possibility would be assessment of patients for the rubber hand phenomenon^{22, 93, 177}. Those who are not able to achieve the rubber hand effect should perhaps not do sensory imagery in phase 1. Instead, training of these patients should use other possible techniques.

In Study 1, an additional guided plasticity technique was used, mirror visual feedback (MVF). MVF was first described by Ramachandran and Hirstein¹⁴⁶ for treatment of phantom limb pain, to restore the disruption of the normal interaction between the residual limb movement and appropriate sensory feedback. MVF has since been mainly used in motor rehabilitation of other conditions such as stroke¹⁹⁶ and dystonia³⁰. The first time that MVF was used in rehabilitation of the hand was in 2005¹⁵⁶, and nowadays it is widely used for a wide range of hand conditions. MVF should be seen as a combination of different methods, as it mixes observation of touch and movement.

In addition, the mirror projects the healthy, functioning, hand to the position of the injured hand, while the injured hand is hidden out of sight. This means that when the patient looks in the mirror, he or she has the illusion of having a well-functioning hand. MVF was part of the training in phase 1, and from this study we know that by doing only motor exercises in the mirror, the sensory function in the injured hand improves.

From the interventions in Study 1, it appears that these plasticity mechanisms have contributed to improved sensory function, and discriminative touch/tactile gnosis in particular. The benefit of the results is enhanced by the patients being aware of the improvements through their experiences in everyday life. However, the methodology of the concept of early sensory relearning needs further refinement. As researchers unravel more and more of the mysteries of the brain, we have a better understanding of how plasticity mechanisms work and this will create more possibilities in designing better and more specific treatment regimes using guided plasticity.

An interesting multi-modal and cross-modal approach is a tactile meal as a technique in early sensory relearning¹⁰⁶. This could be in a self-chosen and familiar meal situation, and make use of all senses. The patient would be instructed to engage all the senses when eating and handling the food. An example would be when preparing a typical Swedish breakfast sandwich; *“listen to the scraping sound when grasping the hard, edgy and rugged piece of crisp bread and pull it out of the package. Feel the warm smooth eggshell and the sound when it breaks off when you peel your warm egg, and the egg dust reaches your nose. The caviar’s fragrance reach your nose directly when you twist the tube’s red, hard, and grooved cap. In the next moment, you bite a large piece of sandwich and feel the taste in your mouth”*. Such a multisensory experience may take advantage of the multi-modal plastic capacity of the brain and create enhanced neuron activation in cortical area processing tactile information from the hand, with the goal of preparing the somatosensory cortex areas for when the injured nerve has re-innervated its targets.

Technical advances could also be used in phase-1 sensory relearning. One way to continue developing early sensory relearning techniques might be to develop an “app” for smartphones. The majority of patients with nerve transection and repair are young or middle-aged. This means that to a large extent, they are familiar with – and perhaps even to some degree dependent on – smartphone usage. In many cases, using the smartphone probably has a self-reward value of its own, and the patient may have a subjectively meaningful relationship with his/her smartphone. If a sense of meaningfulness in the smartphone use itself is a given fact, an “app” would be a good base for occupation-based early sensory relearning. The new possibilities that an “app” could bring are several, including (1) having information repeated unlimited times, which is often sought by people with high neurological thresholds, i.e. “low registrars”; (2) almost unlimited possibilities in varying the stimulus in early sensory relearning, since people with high neurological thresholds need to be exposed to varied stimuli to react and stay alert; (3) if audio-tactile interaction could be useful, one possibility would

be to exercise passively just by putting in the earplugs. The possibility of performing early sensory relearning almost everywhere without the need to carry training equipment would be another benefit.

These ideas are in line with what has been addressed by Pusic ¹⁴⁵ for facilitation of learning situations for patients. They are the way to go in the future to further develop early sensory relearning methodology.

Conclusions

- Early relearning using guided plasticity has the potential to improve sensory function after nerve repair in the short term as well as in the long run.
- Limitations in fine motor skills, clumsiness, and grip function were estimated to be less in patients who performed early sensory relearning than in the group of patients who did not undergo early sensory relearning.
- Three unique viewpoints of the patients were discovered, where motivation and a sense of meaningfulness were key components.
- A peripheral nerve injury entails altered sensory processing patterns, and an increased proportion of patients have low registration to sensory stimulus overall.

Sammanfattning på svenska

Möjligheten att kunna använda sina händer och därmed förmågan till att utföra vardagliga aktiviteter baseras på ett unikt samspel mellan olika kroppsfunktioner. Dessa kroppsfunktioner, såsom känsel, rörlighet, styrka och finmotorik, styrs av en komplex interaktion mellan handen och hjärnan. Efter en nervskada i handledsnivå bryts kontakten mellan handen och hjärnan, dvs. inga känselintryck skickas från handen till hjärnan och inga signaler från hjärnan för att styra muskelaktivitet når ut i handen. Detta leder till att det komplexa samspelen mellan känsel och motorik som formar vår förträffliga handfunktion sätts ur spel.

Efter en nervskada återfår man inte sin tidigare handfunktion. Nedsatt känsel, motorik och styrka men även smärta/obehag och köldkänslighet är vanliga kvarstående effekter. Speciellt den fina känseln som möjliggör identifiering av föremål utan hjälp av synen s.k. diskriminativ känsel påverkas.

Efter en avskuren nerv har reparerats så skall nervtrådarna växa från skadestället ut till handen och fingertopparna. På grund av att de utväxande nervtrådarna inte växer ut och kopplas samman med exakt samma hudreceptorer som före skadan så kommer den reparerade nerven skicka förändrade känselsignaler till hjärnan. Dessa förändrade känselsignaler från handen till hjärnan brukar liknas vid att handen talar ett nytt språk. Detta ”nya språk” måste hjärnan lära sig att tolka för att återfå en bra känsel i handen.

Efter en nervskada har man traditionellt sett börjat träna känsel först när de nya nervtrådarna vuxit ut i handen och fingrarna igen vilket, tar flera månader vid en nervavskärning i handledsnivå.

Rehabiliteringen efter en nervskada utnyttjar på olika vis hjärnans förmåga till att förändras s.k. plasticitet. Att upprepad träning ger förbättrade färdigheter är ett uttryck för hjärnans plasticitet. Ett annat uttryck för plasticitet är hjärnans förmåga att väva samman intryck från alla sinnen, s.k. multimodal kapacitet.. Ett exempel på detta är att nervcellerna som normalt bearbetar känselintryck från handen kan aktiveras även då en person ser beröring. Detta innebär att observation av beröring ger en illusion av känsel i den egna handen. Hjärnans multimodala kapaciteten kan användas i rehabiliteringen efter perifera nervskador.

Att använda hjärnans plastiska förmåga i rehabilitering kallas guidad plasticitet. Detta innebär att olika metoder såsom observation av känsel och rörelser, eller att bara tänka

på och föreställa sig känsel används i rehabiliteringen. Hypotetiskt skulle man under tiden före nervtrådarna vuxit ut efter en skada och då det inte kommer några känselsignaler från handen till hjärnan med hjälp av guidad plasticitet, kunna skapa en aktivering i det område i hjärnan som normalt sett tar emot signalerna från handen med syftet att förbättra handfunktionen i ett längre perspektiv efter skadan. Detta skulle mycket tidigt efter skadan kunna ge hjärnan en uppfattning/illusion av att det är känselaktivitet i handen. Att utnyttja hjärnans multimodala kapacitet i rehabiliteringen under tiden det inte finns någon nervkontakt mellan handen och hjärnan kallas tidig känselträning, Fas 1-träning. Fas 1-träning kan ses som ett sätt att förbereda hjärnan inför de nya nervtrådarnas återväxt i handen.

Det övergripande syftet med detta avhandlingsarbete var att utvärdera betydelsen av tidig känselträning på såväl funktionsnivå som aktivitetsnivå. Syftet var även att undersöka patienternas erfarenheter/upplevelser av Fas 1-träning samt att undersöka om en omfattande nervskada i handen påverkar förmågan att uppfatta och hantera sinnesintryck från olika sinnesorgan i ett mer generellt perspektiv.

I studie 1 deltog 37 patienter som opererats pga. en komplett avskärning av en eller båda av handens två stora nerver (medianus-och ulnarisnerven) i handledsnivå. Studien var en prospektiv randomiserad multicenterstudie. De 37 patienterna lottades till att antingen få den nya, tidiga, typen av känselträning (Fas 1), eller traditionell känselträning, dvs inte någon känselträning förrän de nya nervtrådarna vuxit ut igen. Gruppen som lottades till Fas 1-träning startade sin känselträning senast en vecka efter operationen då man sytt ihop nerven. Patienterna i Fas 1-gruppen fick vid 4-5 tillfällen per dag träna känsel på två olika vis: 1) genom att observera beröring. Patienterna instruerades att med den friska handen beröra motsvarande delar av den skadade handen och samtidigt försöka föreställa sig känsel i den skadade handen 2) genom spegelträning. Vid spegelträning sitter patienten framför en vertikalt ställd spegel och placerar den skadade handen bakom spegeln. Patienten tittar in i spegeln och ser spegelbilden av sin friska hand – en illusion av den skadade handen. Med den friska handen gör patienten specifika rörelser som är relaterat till de rörelseinskränkningar som uppstår vid nervskador. Patienternas handfunktion utvärderades efter tre och sex månader med det vetenskapligt beprövade diagnosspecifika bedömningsinstrumentet RosenScore. Studien visade att gruppen som gjorde tidig känselträning hade signifikant bättre känsel funktion generellt och specifikt diskriminativ känsel, 6 månader efter skadan samt signifikant större förbättring mellan tre och sex månader jämfört med kontrollgruppen.

Studie 2 var en kombinerad kvalitativ och kvantitativ studie med 37 patienter som opererats på grund av en minst 50 % avskärning av medianus- eller ulnarisnerven och som hade genomfört, och avslutat, Fas 1-träning. Patienternas upplevelser och uppfattningar undersöktes med hjälp av den s.k. Q-metoden. Q-metoden bygger på systematisk framtagna av ett stort antal påståenden som speglar hela ämnesområdet

(i detta fallet tidig känselträning) och möjliga åsikter därom. Genom pilotintervjuer med patienter och genom expertgruppsutlåtanden skapades 56 påståenden. Patienterna värderar och rangordnar samtliga påståenden i förhållande till varandra på en skala från ”håller inte alls med” till ”håller med fullständigt”. Med hjälp av faktoranalys kunde man sedan få fram ev. grupperingar av åsikter som hör samman. Tre grupperingar av åsikter framkom vid analysen; 1) “Tycker Fas 1-träning känns meningsfull, får en illusion av känsel och genomför träningen” 2) “Får inte en illusion av känsel och behöver stöd i känselträningen” samt 3) “Får en illusion av känsel, men är inte motiverade och genomför inte träningen”.

I studie 3 gjordes uppföljning av 20 patienter från studie 1 fyra till nio år efter skadan. Samma bedömningsinstrument som användes i studie 1, RosenScore, användes för utvärdering. Därtill adderades 11 självskattningsfrågor angående symtom och aktivitetsförmåga samt två självskattningsformulär avseende aktivitetsbegränsning och funktionsnedsättning i axel/arm/hand samt köldkänslighet. Uppföljningen visade att de patienter som fått Fas 1 träning fortfarande hade signifikant bättre sensorisk funktion, specifikt avseende diskriminativ känsel och finmotorik. Även självskattad funktion skiljde sig åt mellan grupperna där de som fått Fas 1 träning hade mindre besvär avseende självupplevd greppfunktion, fumlighet och finmotorik. Ingen skillnad sågs avseende köldkänslighet.

Studie 4 är en beskrivande tvärsnittsstudie med 49 patienter vilka rekryterades bland de som deltog i studie 2 och 3. Patienterna undersöktes med ett bedömningsformulär avseende medveten och omedveten bearbetning av information från samtliga sinnen – Sensory Profile™. Patienterna fick förhålla sig till i vilken utsträckning de höll med om deras reaktion/agerande i olika situationer då de utsätts för sinnesintryck. Svaren jämfördes med ett svenskt normalmaterial. Resultatet visade att patienter med nervavskärning i underarm/hand i högre utsträckning än normalgruppen hade nedsatt registrering av sinnesintryck, dvs det krävs en starkare/ökad mängd sinnesintryck, avseende samtliga sinnen, för att patienterna i studien ska lägga märke till sinnesintrycket.

Sammanfattningsvis visar studierna i denna avhandling att tidig känselträning, Fas 1, ger bättre känsel och självupplevd handfunktion både på kort och lång sikt jämfört med traditionell rehabilitering. Vidare visar resultaten att en perifer nervskada kan leda till förändringar av hur sinnesintryck bearbetas. Avhandlingen har gett ökad förståelse för hur olika personer uppfattar och hanterar Fas 1-träningen. Avhandlingen har också gett värdefull information om faktorer på personnivå som kan underlätta fortsatt arbete i syfte att individanpassa rehabiliteringen efter nervskador i armen.

Resultaten från studierna i denna avhandling stärker evidensen för tidig känselträning efter perifera nervskador och kan bidra till att Fas 1 blir standard för patienter med omfattande nervskador. Vidare kan resultaten ligga till grund för fortsatt forskning avseende hur man bäst tränar känsel.

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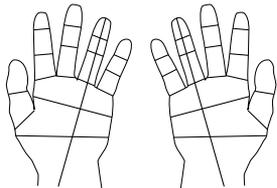
Appendix

RAW-DATAPROTOCOL: TEST OF SENSORY/MOTOR FUNCTION AFTER PERIPHERAL NERVE INJURY

Handsurgery Department of Rehabilitation Skåne University Hospital Malmö, Sweden	Name	Date
	Id	Therapist

SENSORY FUNCTION

Touch thresholds
 Semmes-Weinstein monofilament
 Striped red = not testable
 Red (6.65) = 300g, feels hard pressure
 Red (4.56) = 4g, no protective sensibility
 Purple (4.31) = 2g, diminished protective sensibility
 Blue (3.61) = 0.4g, slightly increased touch thresholds
 Green (2.83) = 0.07g, normal touch thresholds



MOTOR FUNCTION		Atrophy	yes /no
Manual muscle test 0-5	Right Left		
Palmar abduction	M..... M.....	Froment's sign	yes /no
Radial abduction Dig II	M..... M.....		
Abduction Dig V	M..... M.....	Claw finger	yes /no
Adduction Dig V	M..... M.....		

PAIN/DISCOMFORT

Ask the patient: Which of the following descriptions does best describe your perceived problems at.....

Touch of the hand?	None/minor	Moderate	Disturbing	Hinders me in activities
Exposure to cold?	None/minor	Moderate	Disturbing	Hinders me in activities

TACTILE GNOSIS

STI-TEST (max 6 points)

2PD, mm

Digit	Right			Score	Left			Score	
	■	●	⬡		■	●	⬡		
Shapes									Right
Ø15mm									
Ø 8mm									
Ø 5mm									Left
Textures		
15mm									
8mm									
4mm									
Sum									

I	II	III	IVr	IVu	V

INTEGRATED SENSORY/MOTOR FUNCTION

Mini Sollerman test task no.4,8,10 (max score 12)		
4 Pick coins from purse	R.....	L.....
8 Put nuts on bolts	R.....	L.....
10 Do up buttons	R.....	L.....
Sum		

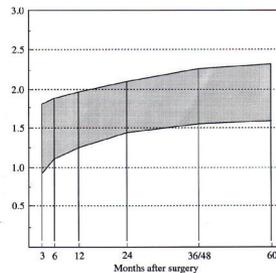
Grip strength (kg)	Right	Left
Transversal volar grip (Jamar)/...../...../...../.....
Key grip (Pinch gauge)/...../...../...../.....
Palmar Pinch (I,II,III)/...../...../...../.....

Rosen score

Model Instrument for Outcome after Nerve Repair

Name:

Domain	Instrument and quantification	Month/ date	Score (scoring key / normal)				
Sensory Innervation 	Semmes-Weinstein Monofilament 0=not testable 1=filament 6.65 2=filament 4.56 3=filament 4.31 4=filament 3.61 5=filament 2.83 Result:0-15 Normal median:15 Normal ulnar:15						
	Tactile gnosis S2PD (digit II or V) 0>=16 mm 1=11-15 mm 2=6-10 mm 3<5 mm Result:0-3 Normal:3						
	Dexterity STI-test (digit II or V) Result:0-6 Normal:6						
	Sollerman test (task 4,8,10) Result:0-12 Normal:12 Mean sensory domain:						
Motor Innervation	Manual muscle test 0-5 Median:palmarabd Ulnar: abd dig II, V add dig V Result median:0-5 Result ulnar: 0-15 Normal median:5 Normal ulnar:15						
	Grip strength Jamar dynamometer Mean of 3 trials in second position, right and left Normal: Result uninjured hand						
Mean motor domain:							
Pain/discomfort Hyperesthesia/ Allodyni	The patient's estimation of problem 0=Hinders function 1=Disturbing 2=Moderate 3=None/minor Result:0-3 Normal:3						
	Cold intolerance As for Hyperesthesia/Allodyni Mean pain/ discomfort domain:						
Total score: sensory + motor + pain/discomfort							



Estimated predicted values for "total score" after repair of the median or ulnar nerve in the distal forearm or at the wrist in adults. The shaded area represents the 95% individual prediction interval.
J Hand Surg 2000;25A:535-43, J Hand Surg 2001;26B:196-200.

DISABILITIES OF THE ARM, SHOULDER AND HAND – British English

Please rate your ability to do the following activities in the last week by circling the number below the appropriate response.

	<i>NO</i>	<i>MILD</i>	<i>MODERATE</i>	<i>SEVERE</i>	<i>UNABLE</i>
	<i>DIFFICULTY</i>	<i>DIFFICULTY</i>	<i>DIFFICULTY</i>	<i>DIFFICULTY</i>	
1 Open a tight or new jar	1	2	3	4	5
2 Write	1	2	3	4	5
3 Turn a key	1	2	3	4	5
4 Prepare a meal.	1	2	3	4	5
5 Push open a heavy door	1	2	3	4	5
6 Place an object on a shelf above your head	1	2	3	4	5
7 Do heavy household jobs (e.g. wash windows, clean floors)	1	2	3	4	5
8 Garden or outdoor property work	1	2	3	4	5
9 Make a bed	1	2	3	4	5
10 Carry a shopping bag or briefcase	1	2	3	4	5
11 Carry a heavy object (over 10 lbs/ 5kgs)	1	2	3	4	5
12 Change a lightbulb overhead	1	2	3	4	5
13 Wash or blow dry your hair	1	2	3	4	5
14 Wash your back	1	2	3	4	5
15 Put on a jumper	1	2	3	4	5
16 Use a knife to cut food	1	2	3	4	5
17 Recreational activities which require little effort (e.g. card playing, knitting, etc)	1	2	3	4	5
17 Recreational activities which require you to take some force or impact through your arm, shoulder or hand (e.g. golf, hammering, tennis etc)	1	2	3	4	5
18 Recreational activities in which you move your arm freely (e.g. playing Frisbee, badminton etc)	1	2	3	4	5
20 Manage transport needs (getting from one place to another)	1	2	3	4	5
21 Sexual activities	1	2	3	4	5

	NOT AT ALL	SLIGHTLY	MODERATELY	Quite a bit	Extremely
22 During the past week, to what extent has your arm, shoulder or hand problem interfered with your normal social activities with family, friends, neighbours or groups? (circle number)	1	2	3	4	5

	NOT LIMITED AT ALL	SLIGHTLY LIMITED	MODERATELY LIMITED	VERY LIMITED	UNABLE
23 During the past week, were you limited in your work or other regular daily activities as a result of your arm, shoulder or hand problem? (circle number)	1	2	3	4	5

Please rate the severity of the following symptoms in the last week (circle number)	NONE	MILD	MODERATE	SEVERE	EXTREME
24 Arm, shoulder or hand pain	1	2	3	4	5
25 Arm, shoulder or hand pain when you do any specific activity	1	2	3	4	5
26 Tingling (pins and needles) in your arm, shoulder or hand	1	2	3	4	5
27 Weakness in your arm, shoulder or hand	1	2	3	4	5
28 Stiffness in your arm, shoulder or hand	1	2	3	4	5

	NO DIFFICULTY	MILD DIFFICULT Y	MODERATE DIFFICULTY	SEVERE DIFFICULT Y	SO MUCH THAT I CAN'T SLEEP
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29 During the past week, how much difficulty have you had sleeping because of the pain in your arm, shoulder or hand? (circle number)	1	2	3	4	5
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	STRONGLY DISAGREE	DISAGREE	NEITHER AGREE OR DISAGREE	AGREE	STRONGLY AGREE
30 I feel less capable, less confident or less useful because of my arm, shoulder or hand problem (circle number)	1	2	3	4	5

DASH DISABILITY/SYMPTOM SCORE = $\frac{(\text{sum of n responses})-1}{n} \times 25$ (where n is the number of completed responses)

A DASH score may not be calculated if there are greater than 3 missing items.

Cold Intolerance Symptom Severity (CISS) questionnaire ^{31, 86}

1. Which of the following symptoms of cold intolerance do you experience in your injured limb on exposure to cold?
(0=no symptoms at all and 10=the most severe symptoms you can possibly imagine) * Not scored.

- Pain
- Numbness
- Stiffness
- Weakness (loss of grip strength)
- Aching
- Swelling
- Skin colour change (white/bluish white/blue)

2. How often do you experience these symptoms? (please tick) **Score**

- continuously/all the time 10
- several times a day 8
- once a day 6
- once a week 4
- once a month or less 2

3. When you develop cold induced symptoms, on your return to a warm environment are the symptoms relieved?
(please tick)

- within a few minutes 2
- within 30 minutes 6
- after more than 30 minutes 10

4. What do you do to ease or prevent your symptoms occurring? (please tick)

- take no special action 0
- keep hand in pocket 2
- wear gloves in cold weather 4
- wear gloves all the time 6
- avoid cold weather/stay indoors 8
- other (please specify) 10

5. How much does cold bother your injured hand in the following situations? (Please score 0-10) **

- holding a glass of ice water 0-10
- holding a frozen package from the freezer 0-10

- washing in cold water 0-10
- when you get out of a hot bath/shower with the air at room temperature 0-10
- during cold wintry weather 0-10

6. Please state how each of the following activities have been affected as a consequence of cold induced symptoms in your injured hand and score each (0-4) ***

- domestic chores 0-4
- hobbies and interests (exemplify....) 0-4
- dressing and undressing 0-4
- tying your shoe laces 0-4
- Your job 0-4

Total CISS score 4-100

* The scores in question number 1 do not count towards the final CISS score. ** In this thesis the original text (please score 0-10) was replaced by; 0=not at all and 10=extreme. *** In this study the original text (score each 0-4) was replaced by; 0=not at all and 4=extreme



Paper II



Paper III



Paper IV

