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2013

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Citation for published version (APA):

Chemnitz, A. (2013). *Median and Ulnar Nerve Injuries in Children and Adolescents- Long-term outcome and Cerebral reorganisation*. [Doctoral Thesis (compilation), Hand Surgery, Malmö]. Hand Surgery Research Group.

Total number of authors:

1

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Median and Ulnar Nerve Injuries in Children and Adolescents

Long-term outcome and Cerebral reorganisation

Anette Chemnitz



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DOCTORAL DISSERTATION

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

To be defended at Jubileumsaulan, Skane University Hospital, Malmö

Friday Oct 11, 2013 at 09.00 am

Faculty opponent

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Author(s) Anette Chemnitz		Date of issue October 11, 2013
		Sponsoring organization
Title and subtitle: Median and Ulnar nerve injuries in children and adolescents- Long-term outcome and Cerebral reorganisation		
Abstract A peripheral nerve injury may lead to serious disability and influence the individual's quality of life. It is considered that children can regain better sensory and motor function after a peripheral nerve injury, but the exact mechanism behind such superior recovery is not known. The aim of the thesis was to study the long-term clinical outcome after a peripheral nerve injury in patients injured in childhood and adolescence and to relate the clinical outcome to changes in the central and peripheral nervous systems. In addition, the consequences of the nerve injury for the patient's life were explored. A short-term pilot study with four patients showed remaining clinical and electrophysiological abnormalities and functional Magnetic Resonance Imaging (fMRI) showed that the cerebral activation pattern after tactile stimulation of the injured hand was different compared to the pattern of the healthy hand. In a larger study, the long-term functional outcome after nerve repair in those injured in childhood was compared to the outcome of those injured in adolescence. Patients below the age of 21 years, operated on at our hospital for a complete median or ulnar nerve injury at the level of the forearm 1970-1989, were followed up at a median of 31 years. Outcome was significantly better in those injured in childhood, i.e. below the age of 12 years, with almost full sensory and motor recovery. No significant differences in recovery were seen between patients with median and ulnar nerve injuries, or even when both nerves were injured. The median DASH scores (i.e. questionnaire; Disability Arm Shoulder and Hand) were within normal limits and cold sensitivity was not a problem in either age group. Those injured in adolescence (i.e. above the age of 12 years) had a significantly higher impact on their profession, education, and leisure activities. Electrophysiological evaluation (amplitude, conduction velocity and distal motor latency) showed pathology in all parameters and in all patients, irrespective of age at injury. This suggests that the mechanisms behind the superior clinical outcome in children are not located in the peripheral nervous system. With fMRI it was shown that patients injured in childhood had a cortical activation pattern similar to that of healthy controls and it was observed that cerebral changes in both hemispheres may explain differences in clinical outcome following a nerve injury in childhood or adolescence. Finally, fifteen patients injured in adolescence, who were interviewed to explore the experiences after a nerve injury and its consequences for daily life, described emotional reactions to trauma. Even symptoms related to post-traumatic stress disorder were mentioned and the patients described different adaptation strategies used. Educational and professional life had changed completely for some. The present thesis shows that age is an important factor that influences outcome after a peripheral nerve injury. The reason for the age-related difference in outcome is alterations in the central nervous system. In addition, a nerve injury had a severe impact on the individuals' life. By further exploring the mechanisms of plasticity and by modifying the rehabilitation, we might eventually improve the outcome after a peripheral nerve injury.		
Key words Nerve injury, age, outcome, brain plasticity, consequences		
Classification system and/or index terms (if any)		
Supplementary bibliographical information		Language English
ISSN and key title 1652-8220		ISBN978-91-87449-80-2
Recipient's notes		Number of pages Price
		Security classification

Signature _____ Date _____

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Long-term outcome and Cerebral reorganisation

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Front cover picture taken by Anette Chemnitz: *Mount Everest, North Face - "Nothing is impossible"*

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ISBN 978-91-87449-80-2
ISSN 1652-8220

Printed in Sweden by Media-Tryck, Lund University
Lund 2013



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In memory of Jan Reimertz (1952-2011)

To my family

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List of papers

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

I. Cerebral changes after injury to the median nerve

Rosén B, Chemnitz A, Weibull A, Andersson G, Dahlin LB, Björkman A. J Plast Surg Hand Surg. 2012 Apr; 46(2):106-12.

II. Functional outcome 30 years after median and ulnar nerve repair in childhood and adolescence

Chemnitz A, Björkman A, Dahlin LB, Rosén B. J Bone Joint Surg Am 2013; 95:329-37

III. Poor electroneurography, but excellent hand function 31 years after nerve repair in childhood

Chemnitz A, Andersson G, Rosén B, Dahlin LB, Björkman A. Neuroreport. 2013 Jan 9; 24(1):6-9.

IV. Normalized activation in the somatosensory cortex 30 years following nerve repair in children - an fMRI study

Chemnitz A, Weibull A, Rosén B, Andersson G, Dahlin LB, Björkman A. Manuscript

V. Consequences and adaptation in daily life – patient’s experiences three decades after a nerve injury sustained in adolescence

Chemnitz A, Dahlin LB, Carlsson IK. BMC Musculoskeletal Disorders 2013, 14:252.

Permission to reprint the published articles has been granted from the publishers.

Abbreviations and definitions

CISS - Cold Intolerance Symptom Severity; a patient-reported outcome instrument to evaluate sensitivity to cold.

DASH - Disabilities of the Arm, Shoulder and Hand; a patient-reported outcome instrument that measures disability in patients with upper extremity disorders.

Electroneurography - An electrophysiological non-invasive test to examine the function of a peripheral nerve.

fMRI - Functional Magnetic Resonance Imaging; a method that can assess nerve cell activity based on changes in blood oxygenation.

ICF - International Classification of Functioning, Disability and Health; the WHO (World Health Organization) framework for measuring health and disability.

Laterality Index -The relative contribution of the two different brain hemispheres during a task.

Rosen score - A standardised clinical evaluation instrument used to assess outcome after nerve repair. Total score and three domains; sensory, motor and pain/ discomfort.

Sense of Coherence - A patient-reported questionnaire; the patient's disposition to see the world as comprehensible, manageable and meaningful is reflected in the questionnaire.

Tactile gnosis – A sensory function based on active touch and enables recognition of shapes and textures without using vision.

VAS - Visual Analogue Scale; patient-reported instrument to measure subjective states such as pain or satisfaction.

Thesis at a glance

I. Cerebral changes after injury to the median nerve

A pilot study to investigate long-term changes in the central nervous system and clinical outcome in young patients after injury to the median nerve at wrist level.

Patients: Four patients with a median nerve injury at wrist level. Mean follow up time was 14 years and mean age at operation was 21.5 years

Method: The patients were examined by the Rosen score, by electroneurography and by fMRI and the results were compared.

Conclusion: Sensory deficits were found while motor function recovered much better. Electroneurography showed remaining pathology. fMRI showed cortical changes in both hemispheres which indicate a cortical reorganisation after a peripheral nerve injury.

II. Functional outcome 30 years after median and ulnar nerve repair in childhood and adolescence

Evaluation of the long-term functional outcome of nerve repair or reconstruction at forearm level in patients with a complete median or ulnar nerve injury in childhood vs adolescence.

Patients: Forty-five patients were assessed at a median time of 31 years after a complete median or ulnar nerve injury to the forearm. The median age at nerve repair or reconstruction was 14 years (range 1-20 years).

Method: The outcome was quantified with the Rosen score, locognosia, sensitivity to cold and DASH, together with the patient's estimation about overall outcome and impact on their education, work and leisure activities. Comparisons were made between childhood injuries (<12 years) and adolescent injuries (12-20 years), and between the injured nerves (median nerve, ulnar nerve or both).

Conclusion: Outcome was significantly better in those injured in childhood than in those injured in adolescence with almost full sensory and motor recovery in the former group. The median DASH scores were within normal limits and cold sensitivity was not a major problem in either of the groups. Those injured in adolescence experienced a considerably greater influence on education, leisure activities and choice of profession.

III. Poor electroneurography, but excellent hand function 31 years after nerve repair in childhood

Study of the long-term electrophysiological outcome after nerve repair in children and young adults and comparison with clinical outcome.

Patients: Forty-four patients were assessed at a median time of 31 years after a complete median or ulnar nerve injury at the level of the forearm.

Method: Electroneurography (amplitude, conduction velocity and distal motor latency) was performed and the results were related to the clinical outcome using the Rosen score.

Conclusion: Electrophysiological evaluation showed pathology in all parameters and in all patients, regardless of age at injury. Those injured in childhood showed a superior clinical recovery and the mechanism behind the superior recovery is not located in the peripheral nerve.

IV. Normalized activation in the somatosensory cortex 30 years following nerve repair in children - an fMRI study

Investigation of the long-term changes in the central nervous system following a median nerve injury in patients injured in childhood and adolescence and to relate the changes to the clinical outcome and electroneurography.

Patients: Twenty-one patients with a median nerve injury sustained at the ages of 1-8 years, 13-15 years or 18-20 years were investigated at a median time since injury of 27 years. Seven healthy controls without a nerve injury were also examined for comparison of the activation.

Method: fMRI was used to assess the cortical activation during tactile finger stimulation of the injured and healthy hands. The results from the fMRI were compared with the clinical outcome and electroneurography.

Conclusion: The cortical activation pattern in patients with a nerve injury sustained before the age of 9 years of age was similar to the cortical activation pattern of the healthy controls. Cerebral changes in both brain hemispheres may explain differences in clinical outcome following a median nerve injury in childhood or adolescence.

V. Consequences and adaptation in daily life – patients’ experiences three decades after a nerve injury sustained in adolescence

Exploration of the patient’s experiences of the nerve injury and its consequences for daily life during the three decades following the repair of the nerve injury. Which personal qualities and strategies were used to facilitate adaptation?

Patients: Fifteen patients with a complete median and/or ulnar nerve injury repaired between the ages of 13-20 years. The median follow up time was 31 years.

Method: The patients were interviewed using a semi-structured interview guide and the interviews were analysed using content analysis.

Conclusion: Treatment of patients with a nerve injury in the upper extremity is complex and needs to address other aspects as well as repairing the damaged nerve. Educational and professional life can change completely, as well as work performance. Emotional reactions should be identified, counselling offered when needed and coping strategies can be promoted.

Introduction

“The brain controls the hand but the hand can shape the brain” (Göran Lundborg)

The central and the peripheral nervous system consist of the brain, spinal cord, and a complex network of nerve cells or neurons with their extensions, like the axons, out in the periphery connecting with the end organs. The nervous system is responsible for sending, receiving, and interpreting information from all parts of the body. Peripheral nerves are biologic cables that convey the impulses from peripheral receptors to the brain and send information from the brain to the muscles. A peripheral nerve injury may lead to structural and functional changes in the central and peripheral nervous systems. This results in a reduction of the individual's activity and quality of life [1, 2]. Treating patients with a peripheral nerve injury in the upper extremity is expensive for the society [3, 4], since the nerve-injured patients generally are in their working years [5]. The hand is the most common injured body part in children and adolescents [6] and peripheral nerve injuries in the upper extremity are rare in children, but frequent between the ages 16 and 20 years [7]. A high degree of suspicion of the examiner is needed to identify nerve injuries. Previous studies, with a shorter follow up, [8, 9] have shown that patients injured in childhood can regain almost normal sensory and motor function after a peripheral nerve injury. It is not known if this depends on a superior recovery in the child's peripheral nerve or whether the young brain has a higher capacity to interpret the altered information from the peripheral nerve.

The aim of this thesis was to study the clinical outcome and long-term effects of a peripheral nerve injury to the central and peripheral nervous systems in those injured in childhood versus those injured in adolescence. In addition, to assess how the injury has had an impact on the patient's life.

Background

The peripheral nerve

A neuron consists of a cell body, dendrites and an axon. The axon serves as the extension of the neuron to the end organ and the axons are bundled together into groups called fascicles. Each fascicle is wrapped in a layer of connective tissue called the perineurium. Finally, the entire nerve is wrapped in a layer of connective tissue called the epineurium. Schwann cells encircle the axonal projections and produce myelin, which facilitates the electrical conduction along the nerve. A motor unit describes a single motor neuron, its axonal projection, and the muscle fibers that it innervates. The sensory neurons are found in the dorsal root ganglia next to the spinal cord and receive sensory information from cutaneous mechanoreceptors.

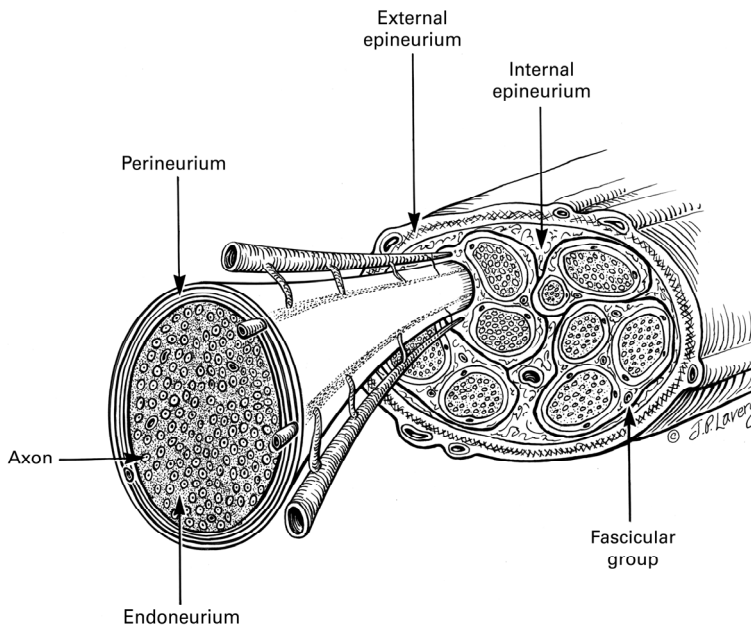


Figure 1:

The macroscopic organization of peripheral nerve. Illustration from Thomas M. Brushart, *Nerve Repair*, Oxford University Press 2011, with permission.

Peripheral nerve injury

A nerve injury triggers a complex cascade of events proximally and distally. In the distal nerve segment a process called Wallerian degeneration is started [10] when the distal axon is separated from the cell body of the neuron with subsequent degeneration process leading to a cell death and atrophy of the denervated end organs [11]. This process usually begins within minutes after the nerve injury and can be described as a cleaning process that prepares the distal nerve segment for reinnervation. From the proximal nerve end, various signals are elicited up to the nerve cell body that eventually results in sprouting of new axons growing from the proximal nerve segment into the distal nerve segment [12]. When crossing the site of injury, regenerating axons must be directed through the correct endoneurial tubes in order to be guided back to their original target organs; the receptors in the skin and the muscles. Misdirection of regenerating axons is common [13-15] and an important factor influencing outcome after a nerve injury. The rate of axonal outgrowth in humans is 1-2 mm/day [14] and with such a slow rate of outgrowth, the level of the nerve injury influences the distance and time needed for the axons to reach their target organs. The mechanism of nerve injury is very important and different types of nerve injuries have to be considered and treated individually. In 1943, Seddon introduced a classification of nerve injuries based on three main types of nerve fibre injuries and whether there is continuity of the nerve; neurapraxia, axonotmesis and neurotmesis [16]. Neurapraxia means a disruption of conduction of electrical signals, but the axons are intact. Neurapraxia leads to recovery without surgical intervention. Axonotmesis involves disrupted axons, but with intact epi- and perineurium. This means that the outgrowing axons can find their way to correct targets and recovery is possible without surgical intervention. In contrast, neurotmesis is a complete transection of the nerve and its surrounding tissue and surgery is necessary to restore continuity. In 1951, Sunderland expanded Seddon's classification to five degrees of peripheral nerve injury according to the structures damaged, usually observable by histological examination only [17]. A sixth-degree injury was subsequently added to the classification by Susan Mackinnon to describe a nerve injury including a combination of two or more of the degree I-V [18].

Past and present treatment of a peripheral nerve injury

The history of the peripheral nerve repair may date back as far as Hippocrates' era [19], but this remains uncertain. In the 7th century, Paulus Aeginatus (626-696 AD) postulated a restoration of severed nerves and the modern concept of suturing the ends of transected nerves was described by Gabriele Ferrara (1543-1627) in Italy [19]. During the last decades, specialized instrumentation, delicate suture materials and introduction of operative magnification have contributed to an improved surgical technique for nerve

repair [20]. The patients examined in this thesis were operated on in the 1970s and 1980s when the epineurial nerve repair technique was most commonly used. With the investigations of the microanatomy of the peripheral nerve, the group fascicular repair technique was introduced to improve the correct coaptation of the nerve ends during the surgery [21]. Furthermore, timing has been shown to be an important factor and a primary suture under appropriate conditions as soon as possible is recommended for neurobiological reasons [21, 22]. More nerve cells may die and the regrowth of nerve fibers, as well as their remyelination, may be poor following delayed nerve repair [23]. It is crucial to avoid tension during nerve repair as this may compromise the blood supply to the nerve with subsequent effects on Schwann cells, like an increased apoptosis and a reduced activation of Schwann cells [21, 24]. A primary suture may not be possible when a nerve defect is present. In these cases, a nerve graft can be an alternative. An autologous nerve graft, such as the sural nerve from the lower leg, is a well-established option for nerve defects in the clinical setting [25]. It is recommended that a nerve repair or a nerve reconstruction is protected by immobilisation [12, 21] which may last up to six weeks depending on the location of the nerve injury.

Past and present rehabilitation after a nerve injury

The postoperative rehabilitation after a peripheral nerve injury in the upper extremity has changed during the last decades with the introduction and development of sensory re-education or sensory relearning [26-28]. Sensory re-education is a learning process by which nerve injured patients can use vision and higher cortical functions, such as memory, to interpret the changed and the reduced sensory input from the hand to the brain in order to enhance the functional sensibility of the hand, i.e. the ability to recognise, identify and manipulate objects and shapes without the use of vision. Sensory re-education is divided into Phase I and Phase II rehabilitation. Phase I rehabilitation begins immediately postoperatively after nerve repair before reinnervation of the end organs has occurred [29]. Phase II starts when the axons have reached their targets and when the patient is expected to be able to perceive touch distally, i.e. around 3-6 months after repair at wrist level [29, 30]. Previously, the sensory re-education was initiated once the reinnervation could be identified in the hand, i.e. in Phase II, however, studies have showed limited evidence for such rehabilitation [30, 31]. Nevertheless, with further research, Phase I rehabilitation was introduced [29]. The purpose is to use the brain's ability to perceive sensibility e.g. by using mirror visual feedback to give the brain an illusion of functioning sensibility or to substitute one sense with another by using the sound of friction from textures – “the patient can listen to what the hand feels” [32]. This would provide the deprived somatosensory cortex with an alternative sensory input and might hypothetically keep the cortical hand representation map intact [28, 29] There is

limited research published on the effects of early onset sensory re-education after a nerve injury in the upper extremity and it remains to be investigated and clarified [30].

In recent years, studies have also shown a high rate of psychological stress and depression after upper extremity nerve injuries [1, 33]. It has been emphasized that the health care system should consider both physical and emotional needs when treating and rehabilitating these patients in order to improve the overall satisfaction [1, 34]. However, these aspects have not been investigated a long time after a nerve injury and repair and particularly not, how adolescent patients are affected by such an injury. Moreover, the current rehabilitation programs can be further improved by a greater knowledge of the plasticity of the central nervous system.

Cerebral changes after a peripheral nerve injury

Sensation of touch is transmitted from the receptors in the skin to the sensory neurons in the dorsal root ganglion, adjacent to the spinal cord, via relay neurons in the cuneate nucleus and thalamus to the contralateral primary somatosensory cortex (S1). S1 is located in the postcentral gyrus of the parietal lobe of the brain. This means that touch sensation in the right hand is predominantly processed in the left S1 and vice versa. S1 is subdivided into different Brodmann areas - area 1, 2, 3a and 3b [35] and each of the four regions contains a map of the body [36]. The neurons of the different areas are believed to be involved in different elements of sensation [37]. Area 1 and area 3b mainly receive the input of cutaneous mechanoreceptors while area 2 is involved in computation of surfaces curvatures and shape. Area 3a neurons primarily receive proprioceptive input and input from the joints, fascias and periosteum. Information from all four areas projects to the secondary somatosensory cortex (S2), which is located on the superior bank of the lateral fissure, and to higher association areas in the posterior parietal cortex. The cortical representation of the body surface is commonly referred to as the homunculus and was created by Wilder Penfield, a Canadian neurosurgeon.

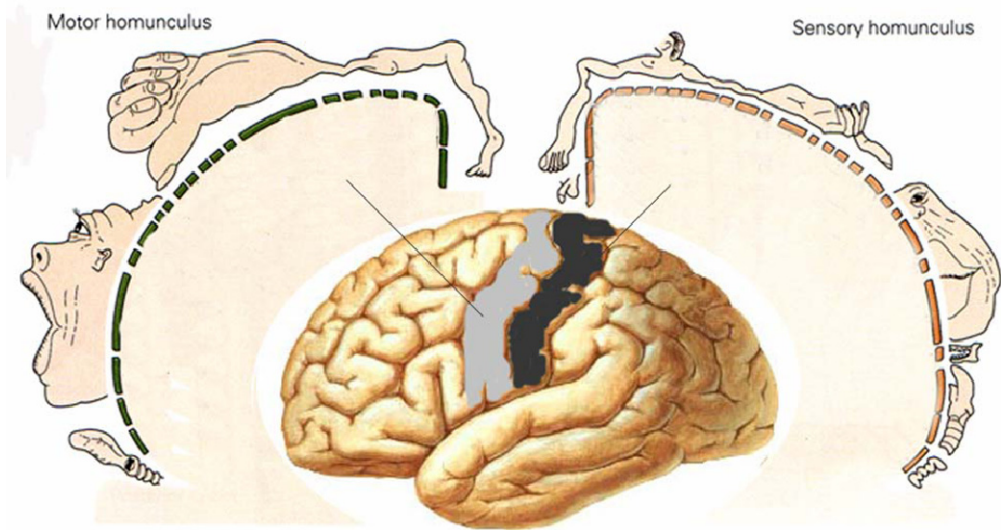


Figure 2

Penfield's homunculus- a cortical map of the body. S1 contains a complete map of the body surface and represents the innervation density, not the actual size of the body surface. The motor cortex represents patterns of movements rather than specific muscles.

The ability of the brain to adapt to new requirements is defined as brain plasticity but the exact mechanisms of plasticity are not fully understood. Previous studies have shown functional and structural changes after a peripheral nerve injury in several cortical areas in adult patients, mainly contralateral to the peripheral nerve injury [38, 39]. The peripheral nerve injury leads to a complete deafferentation in the central nervous system and triggers an immediate and complex reorganization with unmasking of latent excitatory synapses [40] and expansion of the adjacent areas for the processing of information from intact sources [41]. This rapid plasticity, occurring within minutes and hours, involves release of excitatory neurotransmitters, such as glutamate, or inhibitory, such as GABA (gamma-aminobutyric acid) [42]. Following the outgrowth of the new axons, misdirection at the repair site will lead to an incorrect innervation of the end organs and a remapping of the cortical representation of the hand [39]. Over a longer time, changes in plasticity include growth of new connections (sprouting) and long-term potentiation or depression, which refers to changes in the frequency or strength of activation across synapses [39, 43]. The development of modern neuroimaging, like fMRI (functional magnetic resonance imaging) and DTI (Diffusion Tensor Imaging), has created new opportunities to examine the complexity of human brain plasticity.

Factors influencing outcome after a peripheral nerve injury

Age is believed to be the most important factor influencing outcome after a peripheral nerve injury and several studies have confirmed superior results in children [8, 44, 45]. It is not known if the superior outcome in children after a peripheral nerve injury is attributed to changes in the peripheral nerve or to changes in the brain. The young brain is believed to be more plastic, i.e. to have an increased ability to adapt and interpret the altered signals from the peripheral nerve, but the exact mechanisms behind brain plasticity are not known. It has also been suggested that children have a better peripheral regenerative capacity with a faster regeneration and a shorter distance for the regenerating axons [46]. A greater specificity of regenerating axons for targets in immature nerves has also been proposed [47] and another possible explanation could be that children with a peripheral nerve injury experience less neuronal cell death. However, this is contradicted by results from experimental animal studies showing a greater cell death in young animals compared to adults and indicates the complexity of this research area. Patient **motivation and adherence** to treatment and rehabilitation are important for the outcome after a peripheral nerve injury [33, 48]. Previous research has also shown that certain **cognitive capacities**, such as verbal learning and visuo-spatial logic capacity, are correlated with restitution of functional sensibility after nerve repair [49]. **Timing** of surgery has been shown to be a very important factor and a primary suture under appropriate conditions as soon as possible is recommended [12]. The **mechanism** of nerve injury will also affect the outcome. After neurapraxi or axonotmesis there is continuity in the injured nerve and the regenerating axons can more easily be guided back to their peripheral target organs. The **level** of the nerve injury is another factor believed to influence outcome since a nerve injury at a higher level will require a longer distance and time for the axons to reach their target organs. Additionally, the **type** of nerve injury is important and a superior functional outcome after a median nerve injury has been reported, compared to the outcome after an ulnar nerve injury [50]. Misdirection of regenerating axons in the mixed sensory and motor ulnar nerve could be the explanation.

Aims of the thesis

The general aim of this thesis was to investigate the long-term outcome after a median and/or ulnar nerve injury at forearm level sustained in childhood or in adolescence and to study if the explanation of any differences in outcome can be found in the peripheral nervous system or in the central nervous system.

Specific aims were:

- To compare the long-term functional outcome of those injured in childhood to those injured around adolescence. (Paper II)
- To compare the long-term functional outcome in those with a median nerve injury to the outcome of those with an ulnar nerve injury or both median and ulnar nerve injuries (Paper II)
- To evaluate long-term electrophysiological results following median and ulnar nerve injuries repaired or reconstructed at young age and relate them to clinical outcome. (Paper I and III)
- To investigate the long-term effects of a peripheral nerve injury on the central nervous system by fMRI and to relate the effects to clinical outcome and electrophysiology. (Paper I and IV)
- To explore the patient's experiences during the three decades following repair of a nerve injury in the forearm and its consequences for daily life. In addition, to investigate which strategies that were used to facilitate adaptation. (Paper V)

Patients and Methods

All studies were conducted according to the Helsinki Declaration and the local ethics committee approved the study designs. All participants gave their written, informed consent.

Patients

The Department of Hand Surgery, Skåne University Hospital, treats all children and adolescents with median and ulnar nerve injuries from the southern part of Sweden (currently 1.5 million inhabitants). In Paper I (a pilot study), four patients operated on at our clinic for a complete median nerve injury participated. These patients were recruited separately for the pilot study and the mean age at operation was slightly older and the mean follow up time shorter than the participants in Papers II-V. For Paper II-V, our aim was to examine patients with nerve injuries, below the age of 21 years, with a follow up time of at least twenty years. Patients, operated on at our hospital for a complete median or ulnar nerve injury at the level of the forearm during the years 1970-1989, were identified from the hospital administrative registry system. A search of the registry system gave 127 patients who met the criteria, 100 males and 27 females. Of the identified patients, 45 could not be reached. One patient with a nerve injury due to a suicide attempt was also excluded. Thus, 82 eligible participants were invited to participate in the year 2010. All participants were asked about taking part in the clinical examination, in the electroneurography study and in the fMRI study. An overview of the participants in Paper II, III and IV is presented in Figure 3. Paper V, the qualitative study, was performed in the 2012, where the patients injured in adolescence were further explored for impact on education, leisure activities and choice of profession. Purposive sampling was used and twenty eligible participants for the interview study were identified and fifteen accepted participation.

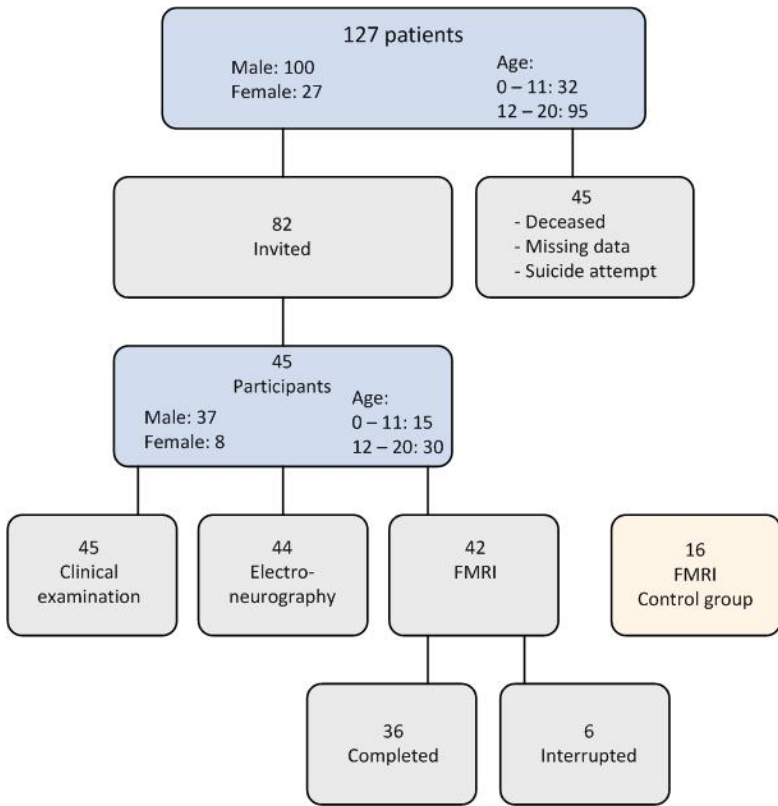


Figure 3 –
Overview of the participants in Papers II-IV

Methods

Outcome assessment

Rosen score

The Rosen score is a standardised, validated clinical evaluation instrument used after nerve repair and consists of three domains; sensory, motor and pain/discomfort [51, 52]. The total score is the sum of the three domains and the maximum score is 3, which indicates a normal sensory and motor function without pain.

Locognosia

Locognosia represents the ability to localize touch and is a standardised method to assess misdirection. The patient is asked to identify areas at fingertip level where the supra

threshold stimulus, using a monofilament, has been perceived [53]. The locognosia ratio represents the final score divided by the maximum score for the median and ulnar nerve, respectively.

DASH – Disability of Arm Shoulder and Hand

The DASH questionnaire measures the disability of the upper extremity and is a patient-reported outcome instrument. It consists of 30 items concerning symptoms and performance of activities. Each question has five response options and a score between 0 and 100 is calculated. A score of 10-15 has been described as the cut-off point for pathology [54, 55] and a higher DASH score reflects a greater degree of disability. The Swedish version [56] was used in Paper II.

CISS – Cold Intolerance Symptom Severity

The CISS is a reliable, validated patient-reported outcome instrument used to evaluate sensitivity to cold [57]. An arbitrary score ranging from 4 - 100 defines the severity of cold sensitivity and a score >50 indicates abnormality [58].

VAS – Visual Analogue Scale

The participant's subjective estimation about the impact of the nerve injury on education and on leisure activities was investigated using VAS [59]. The patients were asked to estimate the impact on a paper showing a continuous scale graded 0-100 where 0 mm indicates no symptoms or problems and 100 mm indicates worst outcome.

SOC – Sense of Coherence

Antonovsky, a professor of medical sociology, introduced sense of coherence more than 30 years ago [60]. He promoted the salutogenic approach, that is, the search for the origins of health rather than the causes of disease in order to explain why some people become ill under stress and others stay healthy. Sense of coherence has different dimensions and the patient's disposition to see the world as comprehensible, manageable and meaningful is reflected. Studies have shown that people who have developed a strong SOC manage disease better than those with a weak SOC [61]. The SOC questionnaire exists in different versions [62] and in Paper V; I used the validated Swedish version of the condensed 13-item scale [63]. The result from this SOC- questionnaire ranges from 13-91, where 13 indicates the weakest SOC possible.

Electroneurography

Electrophysiological studies provide a measure of the response amplitudes of a nerve as well as the velocity with which a nerve carries information over a known distance. A percutaneous depolarizing current is introduced and the action potential is measured a certain distance from the stimulus. The time from which the stimulus is initiated until it

is recorded is called the latency period. Since time and distance are known, conduction velocity can be calculated. The conduction velocity measures the integrity of the myelin sheath and the amplitude of response indicates the quantity of functionally conducting axons in a nerve. Orthodromic sensory nerve conduction studies are performed by stimulating the thumb, the index and the long finger for the median nerve and the little finger for the ulnar nerve. For motor conduction studies, responses from the abductor pollicis brevis muscle (median nerve) and abductor digiti minimi muscle (ulnar nerve) are recorded on stimulation at wrist and elbow levels.

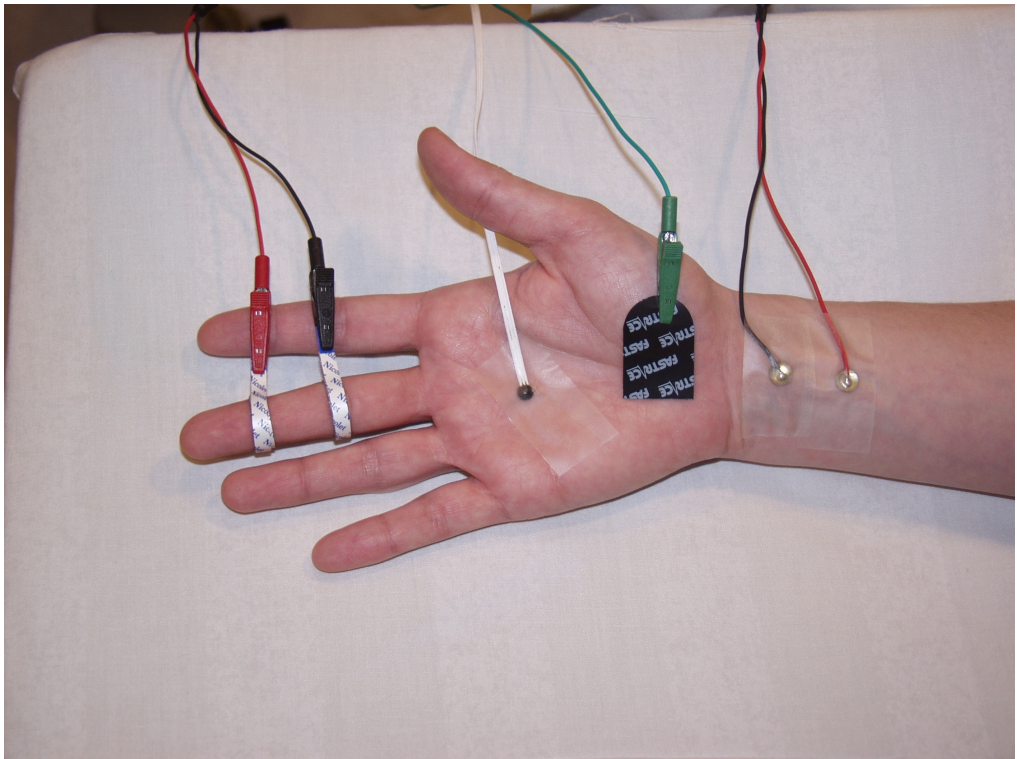


Figure 4

An illustration of the setup for a sensory electroneurography. The patient's skin temperature has to be above 30° C during the examination to avoid false slowing of conduction. Stimulation electrodes on the long finger, cathode (black) being proximal. Recording electrodes are placed over the median nerve proximal to the wrist. Thermometer and ground electrodes are attached to the palm.

fMRI

Magnetic resonance imaging is a medical imaging technique that uses powerful magnets and radio waves to create pictures of the body parts in detail. The strength of the magnetic field is defined as Tesla (T) and the MRI scans can be T1- and T2-weighted. In T2- weighted scans, water- and fluid-containing tissues are bright and fat-containing tissues are dark. The reverse is true for T1-weighted images. Several different MRI techniques such as fMRI and DTI (Diffusion Tensor Imaging) can evaluate functional changes in the CNS. fMRI is used to study functional activity in different regions of the brain by imaging magnetic, haemodynamic variations during neural activity. The most commonly used is the blood oxygen dependent imaging technique (BOLD) [64]. In the blood, oxygen is bound to haemoglobin and when oxygenated, haemoglobin is diamagnetic. When haemoglobin releases oxygen, it becomes paramagnetic and this will distort the magnetic field and affect the local MR signal. When the neural activity increases, the blood flow will also increase. However, the BOLD signal does not measure the neuronal activity itself; instead it reflects changes in the blood flow.

By using different neuroimaging techniques, the interconnection between the right and left somato-sensory cortices has been explored. During tactile stimulation of the digits, the sensory information from the hand can be processed in the ipsilateral primary somatosensory cortex as well. The interaction between the two S1 areas of the left and right hemispheres after unilateral cutaneous stimulation of the hand in healthy humans has previously been confirmed [65, 66]. Thus, the unilateral cutaneous stimulation of the hand will lead to an increased cortical activation in the contralateral S1, but also to a deactivation of the ipsilateral S1. It is believed that the corpus callosum is involved in these interhemispheric interactions but the exact mechanisms are not known [65]. Furthermore, an interaction between the two S2 areas has also been shown in humans [67, 68].

The Talairach system [69] is a predefined coordinate system that describes the three-dimensional location of brain structures independent from individual differences in the size and overall shape of the brain. It is defined by making two points, the anterior commissure and posterior commissure, lie on a straight horizontal line. Distances in Talairach coordinates are measured from the anterior commissure as origin. The Talairach coordinates are defined as the right hemisphere has positive X values, the anterior part has positive Y values, and the superior part has positive Z values. In evaluation of group data, each individual brain will be conformed to the Talairach system.

Mapping of the somatosensory finger regions by using fMRI has been interesting various researchers. In 2008, Weibull et al presented an in-house built pneumatically driven and computer controlled system for tactile stimulation of the skin and functional imaging [70]. Five membranes are attached with tape to all fingertips. When the membranes are inflated, the entire fingertip of each finger is stimulated. Both the median and the ulnar

nerves can be stimulated and simultaneous tactile stimuli of the five fingers are applied in block design alternating between rest conditions with no stimulation and activation. For a more detailed description of the technique, the reader is referred to Paper IV.

Details of each study

Cerebral changes after injury to the median nerve (Paper I)

The aim with this pilot study was to investigate the long-term changes in the central nervous system and clinical outcome after a complete median nerve injury at wrist level. The patients were assessed clinically by the Rosen score and examined by electroneurography and fMRI.

Functional outcome 30 years after median and ulnar nerve repair in childhood and adolescence (Paper II)

In Paper II, our aim was to evaluate long-term functional outcome of nerve repair or reconstruction at forearm level in patients with a complete median or ulnar nerve injury below the age 21 years. Of the 82 invited patients, 45 accepted participation and were examined (37 males and 8 females). The characteristics of the participants are presented in detail in Paper II. The participants were assessed by the Rosen score, locognosia, DASH, CISS and by using the VAS for estimation of impact on education and leisure activities. All participants were also asked for influence on professional career (yes/no) and about differences in hand size. The hand size was compared by visual inspection by the hand surgeon of both the un-injured and the injured hand and forearm to investigate whether a nerve injury at the level of the forearm at young age influences growth of the hand.

Poor electroneurography, but excellent hand function 31 years after nerve repair in childhood (Paper III)

The purpose of this paper was to investigate if the differences in clinical outcome can be explained by changes in the peripheral nervous system. Forty-four of 45 available patients were examined by electroneurography. The electrophysiological results of the injured side were expressed as the percentage of those of the un-injured side (controls) and related to the clinical outcome using the Rosen score.

Normalized activation in the somatosensory cortex 30 years following nerve repair in children, an fMRI study (Paper IV)

The purpose of this paper was to investigate if the differences in clinical outcome can be explained by changes in the central nervous system. fMRI at 3 Tesla was used to assess cerebral activation during tactile stimulation of the injured and un-injured hand in patients with a nerve injury sustained at an age below 21 years. Thirty-six patients completed the fMRI (Figure 3). Eleven patients with an isolated ulnar nerve injury or with a complete ulnar and a partial median nerve injury were not included in the analysis since the cortical activation pattern of the ulnar nerve can be difficult to detect [70]. The patients were sub-divided into different groups based on age at injury before the analysis. Seven patients had suffered from a nerve injury at young age (i.e. below nine years of age, range 1-8 years) and we divided the other patients into another two groups with seven (randomly selected) patients in each group; those injured in early adolescence (range 13-15 years old) and those injured during late adolescence or after (range 18-20 years old). Twenty-one patients, 18 male and 3 female, operated on for a complete median (n=14) or median and ulnar (n=7) were included in the analysis. A control group with healthy volunteers with no history of nerve injury or neuropathy also participated in the fMRI examination. The results from the fMRI were compared to the results from the Rosen score and from the electroneurography.

Consequences and adaptation in daily life- patients' experiences three decades after a nerve injury sustained in adolescence (Paper V)

The aim of the qualitative study was to explore the patient's experiences during the three decades following repair of a nerve injury in the forearm and its consequences for daily life. Personal qualities, support from others and strategies that were used to facilitate adaptation were also investigated. A purposeful sampling strategy was used to ensure a mixture of different perspectives, such as gender, type of nerve injury and results from the different outcome measures investigated in Paper II. The data from the interviews were subjected to content analysis and fifteen patients participated (twelve males and 3 females). The median age at the nerve injury was 16 years (range 13-20) and the median follow up time was 31 years (range 23-40). All participants completed the condensed 13-item scale SOC questionnaire, Swedish version [63].

Analyses

Statistical analyses

A statistician was consulted before, during and after the analysis of the data. Before analysis of any significant difference, the data were tested for normality. The data in this thesis were not normally distributed and a majority of the different variables were ordered. Therefore, non-parametric tests (Mann-Whitney and Kruskal-Wallis) were chosen to compare ordinal variables (Paper II, III and IV) and chi-square tests to compare categorical data (Paper II). Calculations were performed using SPSS version 18.0 (Statistical Package for the Social Sciences, IBM, New York, USA). A p-value of less than 0.05 was considered statistically significant in all the papers. Correlations (Spearman's rho) were performed to calculate any significant correlations between age at nerve injury and the different electrophysiological parameters and a significant correlation was estimated as $\rho \geq 0.35$ (Paper III). The fMRI data was evaluated separately by using Brainvoyager QX 2.2 software (Brain Innovations B.V., The Netherlands) and this is further explained in Paper IV.

Qualitative content analysis

This is an exploratory research method to gather an in-depth understanding of issues of interest and to explore nuances related to the research field. Different concepts are used to describe trustworthiness. The *credibility* refers to how well data and processes of analyses address the aim of the study and the *dependability* to the degree to which data change over time. Credibility can be achieved during the interview process by summarizing the information and then question the participant to determine accuracy or, after the interview process, by allowing members of the participants to read the written text in order to check the authenticity of the work. This is known as a member checks, or respondent validation. The *confirmability* of the findings deals with how well the results could be confirmed by other researchers and the *transferability* to the extent to which the findings can be generalized or transferred to other groups or contexts [71, 72].

In Paper V, fifteen participants with a nerve injury sustained in adolescence were interviewed by the last author, who is familiar with qualitative research methodology. Semi-structured interviews with open questions were used and all interviews were tape-

recorded by the last author. Follow-up questions were asked such as: How did you experience that? How did you handle that? Can you describe that in more detail? Member checks were done during the interviews by the last author. The text was read and reread by the first and last co-authors independently and the text data was subjected to a content analysis [71, 72]. The analysis started with a naive reading of each interview in order to gain a general impression of the content. Meaning units, that is words or phrases related to the aim of the study, were identified and coded with reference to the questions: What is it about? What does it mean? What effect does it have? [72]. The impression of the text was discussed with the last authors and we compared the selected meaning units. Meaning units and codes that were similar in content were grouped together as main categories and subcategories. Similar statements within each category were analysed critically, read and compared to achieve a reasonable interpretation. Credibility was achieved by using purposive sampling and by allowing the participants to validate their responses during the interviews. Dependability was ensured by the co-authors reading and coding the interviews independently and by in-depth discussion, analysis and interpretation of the text together. Representative quotations from all participants was presented in the text to increase the trustworthiness of the statements. Confirming and clarifying information during the interviews ensured confirmability and a consistent focus on the text throughout the analysis reduced the risk for overinterpretation. The transferability was limited since the participants represent a small, selected study group.

Ethical considerations

When searching the hospitals administrative registry for eligible participants, patients with a nerve injury due to a suicide attempt were excluded to avoid reminding them of this tragic event.

In Paper III, patients were specifically asked about any clinical signs of nerve compression or neuropathy on the healthy un-injured side. Two patients had clinical signs of a carpal tunnel syndrome (CTS) on the un-injured hand and another four patients had no clinical signs of CTS but showed mild pathological electrophysiological values indicating a slight compression of the median nerve in the un-injured hand. These participants were immediately informed about the values and treatment was offered.

Results and comments

For more detailed information, the reader is referred to Paper I-V. The following is a summary of the results.

Cerebral changes after injury to the median nerve (Paper I)

Four patients with a former median nerve injury in the forearm were investigated in this pilot study. The mean age at operation was 21.5 years (range 18–28) and the mean time since the operation was 14 years (range 9–18). All were operated on within 48 hours of the nerve injury. The cerebral activation patterns were evaluated by fMRI at 3 Tesla and the results were compared to the total Rosen score and electroneurography. Stimulation of the median nerve of the injured hand resulted in a larger activated volume in both hemispheres compared with the healthy hand, still present at a mean of 14 years after median nerve repair. The laterality index (LI) was calculated as a measure of hemispheric dominance and the hemispheric dominance was increased when stimulating the formerly injured median nerve. However, when the adjacent un-injured ulnar nerve was stimulated on the sectioned side, the hemispheric dominance decreased compared with the healthy side. All four patients showed sensory and motor deficits; the patient with the oldest age (28 years) at the time of the nerve injury showed the lowest score in the sensory domain. One patient, aged 20 years at the time of the nerve injury, had participated in early onset of sensory re education (in Phase 1) and showed the highest total score and the highest score in the sensory domain. However, electroneurography showed abnormalities in both sensory and motor nerve function in all four patients.

Functional outcome 30 years after median and ulnar nerve repair in childhood and adolescence (Paper II)

This retrospective study evaluated the long-term functional outcome after complete median or ulnar nerve injuries at the level of the forearm in patients, who sustained their injury and whose nerves were repaired or reconstructed below 21 years of age. The median age of the participants at the time of the nerve repair or reconstruction was 14

years (1-20 years) and the median follow-up time was 31 years (21-41 years). The participants were divided into two groups; those who sustained their injury when they were children aged < 12 years and those who were adolescents aged 12- 20 years when the injury occurred. This division was based on previous studies indicating that those injured in childhood show a superior recovery [45, 73-75] and that the growth acceleration of boys and girls around puberty might influence both the peripheral and central nervous systems [76, 77]. Comparisons were made between childhood (<12 years) and adolescent injuries (12-20 years), and between the nerves injured (median nerve, ulnar nerve or both). A significant difference in total score was found between those injured in childhood and those injured in adolescence (87% and 67% of complete recovery respectively, $p < 0.001$), with a better outcome (i.e. higher total score) in the former group. Eight of those injured in adolescence had been treated with a nerve graft procedure and their results were analysed separately but still I found a significantly higher total score for those injured in childhood. The total score is plotted against age in Figure 5 and the results of the participants treated with a nerve graft are marked separately. No significant differences were seen when median and ulnar nerve injuries were compared, or even when both nerves were injured. Motor function was close to normal and cold sensitivity was not a problem in either age group. Only four out of 45 participants suffered from abnormal cold intolerance (i.e. CISS score >50), all injured in adolescence. The median DASH scores were within normal limits and did not vary between the groups. The locognosia test showed significantly better result in those injured in childhood ($p = 0.02$) and in the entire study group, also in the participants with an ulnar nerve injury ($p = 0.01$). Adolescents indicated that their nerve injury had a significantly higher effect on their profession, education and leisure activities. There was no difference, as observed by visual inspection, in the size of the hand, even in participants who had injured both nerves at a very young age.

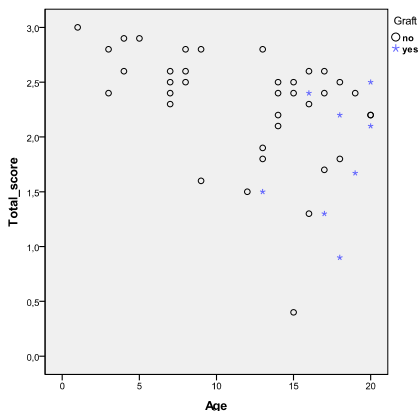


Figure 5

The total score of all 45 participants plotted against their age with the nerve grafted participants marked separately.

Poor electroneurography, but excellent hand function 31 years after nerve repair in childhood (Paper III)

In this study, the long-term electrophysiological outcome after nerve repair was investigated and if a better peripheral nerve regeneration could explain the differences in clinical outcome between the age groups. The results of the nerve-injured hand were expressed as percentage of those of the un-injured hand and compared to the clinical outcome, i.e. the Total score. All patients, regardless of age at nerve injury, showed reduced motor and sensory amplitudes, reduced sensory and conduction velocities as well as increased distal motor latencies. No statistically significant differences were found in the different parameters when the results of those injured in childhood and in adolescence were compared. In contrast, those injured in childhood had an excellent clinical outcome. A significant correlation was only seen between age at nerve injury and the motor amplitude ratio ($\rho = -0.53$, $p < 0.001$), but not with the other variables. Patients, where a direct nerve repair was done, showed significantly higher sensory amplitudes than in those where a reconstruction procedure with sural nerve grafts were performed.

Normalized activation in the somatosensory cortex 30 years following nerve repair in children, an fMRI study (Paper IV)

The possible mechanisms behind the superior clinical recovery of those with a nerve injury sustained in childhood were investigated in this paper. The patients with a history of a median nerve injury or combined median and ulnar nerve injuries were sub-divided into three groups based on age at injury. The results from the activation pattern detected by fMRI were compared with the clinical outcome and electroneurography. The cortical activation pattern following sensory stimulation of the median nerve innervated fingers was dependent on the patient's age at injury. Those injured at young age (i.e. below nine years of age) had an activation pattern similar to that of healthy controls without a nerve injury. The patients injured at young age also showed a clinical outcome significantly superior ($p = 0.005$) to the outcome in subjects injured at a later age, but the electroneurographical data did not differ between the groups. In the patients injured at the ages of 13-15 years or the ages of 18-20 years, fMRI showed a larger activation in the contralateral hemisphere. These patients also displayed reduced inhibition and activation of somatosensory areas in the ipsilateral hemisphere. Hence, a peripheral nerve injury will lead to cerebral changes in both hemispheres and the changes are dependent on the age of the patient at injury. This can perhaps explain the differences in the clinical outcome.

Consequences and adaptation in daily life – patients' experiences three decades after a nerve injury sustained in adolescence (Paper V)

The results from this qualitative study are derived from a content analysis of fifteen in-depth interviews with patients with a median and/or ulnar nerve injury in the forearm between the ages 13-20 and with a median follow up time of 31 years. The analysis showed that a nerve injury in the upper extremity leads to various consequences for the adolescent patient in the long-term perspective. Sensory and motor deficits in the injured hand, as well as cold sensitivity were described. Secondary problems, such as back problems, were also stated. Emotional reactions to the trauma and symptoms related to post-traumatic stress disorder were mentioned, as well as how the participants managed to cope with such reactions. Problem-based coping strategies were described, such as assistive devices, tricks or altered ways to perform tasks. The participants expressed a desire for support from the healthcare system and the necessity to consider both physical and emotional needs. The professional life and work performance changed completely for some while others could continue but changed their performance pattern. Life roles and the relations were also affected. The result from the SOC questionnaire showed a median score result of 68, which indicates that the participants had had a high ability to comprehend, manage and find a meaning in the situation.

General discussion

This thesis verifies that age is an important factor that influences the long-term outcome after a peripheral nerve injury in the upper extremity with almost full sensory recovery in those injured in childhood, while many adolescents showed results equal to adults. The mechanism behind the differences in clinical outcome seen in the different age groups are likely explained by changes in the central nervous system. All patients, regardless of age at injury, showed signs of incomplete peripheral nerve regeneration measured by electroneurography. Moreover, this work shows that a peripheral nerve injury can have a long-term impact on the patients' body functions and body structure with reduced sensibility and muscle function and dexterity problems. In addition, and earlier less emphasized, by affecting education, leisure activities, professional life and work performance, the injury can also lead to activity limitation and participation restriction. Thus, the peripheral nerve injury can have an impact on all levels outlined in the ICF (International Classification of Functioning, Disability and Health) by the World Health Organization [2] and our interventions should address all these levels.

Personal and environmental factors influencing outcome

The patients injured in childhood, i.e. at age <12 years, presented a significantly better clinical outcome than those injured in adolescence (at age 12- 20 years) with almost full sensory and motor recovery subjectively and as assessed with clinical test instruments. On the other hand, the results from the electroneurography showed decreased sensory and motor amplitudes (indicating the number of regenerating axons), as well as decreased conduction velocities (i.e. myelination of the regenerated axons). The discrepancy between the clinical recovery and the results from the electroneurography implies that electrophysiological data cannot be used alone as an evaluation tool after a peripheral nerve injury. Previous experimental studies have shown the same differences in results [78]. One may wonder- what do we measure with electroneurography? It is known that each regenerating motor axon can reinnervate as many as 4-5 times the normal number of muscle fibres [79], which means that less axons are needed for recovery. Another possibility could be that the morphology and composition of the myelin sheath have changed [80], which is not detectable with the currently used electroneurography except by the observed lower nerve conduction velocity. With the development and refining of new techniques to measure recovery in the peripheral nerve, the discrepancy found here

might disappear or actually, we might realize that we measure different aspects of the nerve regeneration processes. Moreover, perhaps it is not possible to compare the results of someone injured during the childhood whose peripheral nervous system is immature, since the “preinjury baseline measures” are constantly changing during the development and ageing. One should not exclude the possibility that, from the neurobiological point of view, the response of neurons and supporting cells, such as signal transduction mechanisms, to injury may be different dependent on the age of the patient at injury.

It was surprising to find that the functional outcome of those injured in adolescence was similar to what has previously been shown in adults [81]. However, there is a large variation in the Rosen score among those injured in adolescence with a total score range of 0.4-2.8 (maximum score indicating normal sensory and motor function without pain/discomfort is 3). In those injured in adolescence, eight participants required a nerve graft procedure and even among these participants, there is a variation with a range of 0.9-2.5 (Table 2, Paper II). Why do some adolescents recover better? The postoperative rehabilitation was very basic when the present patients were injured and repaired. Focus was on motor recovery and the rehabilitation was not standardized as it is today with modern rehabilitation programs with early onset based on cerebral re-learning procedures [28]. It is possible that verbal learning and visual- spatial logic ability can explain variations in the recovery after nerve repair in those injured in adolescence in the present study, as described in adults in a study comparing cognitive capacity and recovery of tactile gnosis following nerve repair [49]. A strong cognitive capacity and flexibility is probably one way in which some patients can compensate for the poor recovery after nerve repair with diminished afferent input and a changed cortical activity pattern [39]. One also has to consider the current age at testing since mechanisms of ageing could explain some of the variations of the results. The median age at investigation in the different age groups varies. In those injured in childhood the median age was 33 years (range 24-48 years), while the median age was 47 years (range 36-57 years) in those injured in adolescence. However, a difference in median age of 14 years is probably too small to explain the differences in the data and it is less probable that ageing would influence the results in Paper II.

Another important aspect for outcome after a peripheral nerve injury is variation in patient motivation and adherence to treatment. Environmental conditions can influence the adolescent patient, such as parental input, socioeconomic factors, social networks and possible co-occurring disorders, like a depression or a drug abuse. The restructuring of the brain during puberty and adolescence, together with regulation of the synapses and neuronal connections, are part of the maturation process and improvements in cognitive control, preparing the individual for adulthood. Hence, this process is also a sensitive period and the individual is vulnerable for disorders or injuries affecting the nervous system. Even if the appropriate treatment after a peripheral nerve injury is determined, the treatment may fail unless the patient’s adherence and motivation to treatment are adequate. Perhaps some of those injured in adolescence had a better access to stable and supportive relationships or could utilise abundant coping strategies. Strategies to improve

adherence for children, adolescents and adults will most probably differ and may involve working with parents, teachers and other important persons in the environment as well. There has to be time for explanation and answers, as well as time for instructions on how to succeed with the postoperative rehabilitation. Patients discharged from a medical ward do often not recall the given information [82]. Written information and educational brochures can reinforce oral information and by observing the patient's individual learning style, such as visual or auditory, healthcare staff can help the patients to recall and understand. In addition, the healthcare system has to take both physical and emotional needs of the patient into consideration. Emotional reactions and symptoms related to post-traumatic stress disorder, such as subsequent nightmares, flashbacks, avoidance and isolation, were described by some in Paper V. Asking for and dealing with the psychological distress and individual perception of the injury might improve patient adherence to rehabilitation and enhance the outcome of treatment.

Those injured in adolescence experienced a considerably greater influence on education, leisure activities and professional career, which was further explored in Paper V. Some participants had to retake a school year or change their course; findings that need to be considered when treating patients who are still students. The impact on engagement in leisure activities after nerve injuries should be explored and support should be given when needed. It might still be possible for the patients to engage in their activities if they receive guidance on how to change their performance technique or are provided with assistive devices. The ability to perform meaningful activities and to maintain their roles in life are important factors for the patients' quality of life [1, 83].

Brain plasticity and outcome

Neuronal plasticity allows the central nervous system to learn new skills and remember information. In addition, in response to environmental stimulation, the central nervous system can change the neurotransmission, reorganize neuronal networks and alter the density of dendritic arborisation [84]. By using fMRI with the BOLD technique, cerebral changes in both brain hemispheres were found (Paper I and IV). These changes may explain the different clinical outcome following a nerve injury in childhood or adolescence, particularly the superior sensory recovery and indicate that compensatory mechanisms exist after a nerve repair. In addition, the cortical activation pattern after tactile stimulation of the hand was found to be dependent on age at nerve injury (Paper IV). In previous fMRI studies in adult humans with a shorter follow-up, a gradual narrowing of the cortical activation pattern in S1 towards a more normal pattern has been seen [85]. The present fMRI-studies involved patients with a longer follow-up (Paper I and IV) and the larger contralateral activation pattern remained in those injured between 13-15 years and those injured between 18-20 years. Three patients in each of these two

groups had injuries to both the median and the ulnar nerve and one may speculate if a larger cortical area may be involved in these patients. However, this is less likely since the cortical activation after stimulation of the ulnar nerve is difficult to detect or may be absent [70].

Novel findings were revealed in the ipsilateral hemisphere after a median nerve injury (Paper IV). In those injured below the age of nine years and in healthy subjects, there was a deactivation in the ipsilateral S1 area, indicating a functional inhibition. The negative BOLD-signal can be caused by a synaptic inhibition that subsequently reduces the blood flow [65]. In those injured between ages 13-15 years, no deactivation (or functional inhibition) in the ipsilateral S1 was found and finally, in those injured between ages 18-20, activation was found in the ipsilateral S1. What does this tell us? The decreased inhibition and the activation in the ipsilateral S1 may represent compensatory mechanisms to the changed afferent signals from the injured nerve to the contralateral S1. After the peripheral nerve injury, the brain is provided with changed afferent input and this is communicated to both hemispheres, possibly by Brodmann area 2. This area is known to have bilateral hand representations in the S1 [86]. The simultaneous processing of afferent input in both hemispheres requires regulative mechanisms to coordinate outputs from both hemispheres and most probably, the corpus callosum is involved in this regulation. Higher order centres in the brain then process and integrate this information and modulate the patterns of activation or inhibition as demanded. Interhemispheric inhibition is also believed to play a role in motor disabilities. Lewis et al. showed that patients with a stroke had a decreased ability to modulate this inhibition during unilateral muscle activation [87]. In patients with a stroke, the inhibition was greater in individuals with an intact dominant hemisphere. Can hand-dominance have a role in functional inhibition after a median or ulnar nerve injury as well? Injuries to the dominant hand in the different groups were distributed as follows; 5/7 participants injured their dominant hand of those injured below nine years, 6/7 participants injured their dominant hand of those injured between 13-15 years and 3/7 participants injured their dominant hand of those injured between 18-20 years (Paper IV). If hand dominance would decide the functional inhibition in the ipsilateral hemisphere, one would expect a larger inhibition in those injured between ages 13-15 years. However, this was not seen. On the contrary, we saw a decreased inhibition in this group of patients. One explanation for the decreased inhibition can be that functional inhibition between the hemispheres are subordinated other, cortical centres, responsible for the processing and integration of the information received by the somatosensory cortices. By regulating the inhibition and using the ipsilateral hemisphere as well, the brain can compensate for a poor peripheral nerve function. Westerhausen et al. suggested that around the ages of 6 and 12 years, a critical period exists for the development of the inter-hemispheric connections [88]. After this period, the interhemispheric communication and interaction might resemble its adult form.

Age and plasticity

The results of this thesis imply that already around the age of 12 years, the cerebral changes after a peripheral nerve injury are similar to those seen in adults (Paper IV). What happens around the age of 12 years? Children can acquire new languages and motor skills, such as playing an instrument, more rapidly than adults [42]. An abundant formation of neurons, dendritic spines and synapses in children contribute to enhanced plasticity, as well as a superior reorganization of neuronal circuits [42]. The onset of puberty will lead to increases in sex steroid levels (i.e. testosterone, progesterone and oestradiol) and puberty will have a profound effect on the brain. The impact of the rising steroid hormones is different in male and female brains and girls advance into puberty earlier than boys do. Hormonal alterations will influence the organisation of the brain with changes in the grey matter (i.e. neuronal cell bodies, dendrites, non-myelinated axons and glial cells), as well as in white matter structure [76, 77].

In the central nervous system, glial cells produce myelin and when axons are grouped together into bundles (i.e. tracts), they appear white. With the development of different imaging techniques, such as diffusion tensor imaging (DTI), it is possible to study the white matter tracts of the brain and the development of the nervous system in childhood and adolescence. In early childhood, the brain volume expands with a decrease in the grey matter volume while the white matter increases [89]. Sex hormones are all able to stimulate outgrowth of neurites, number of synapses, dendritic branching and myelination by impact on glial cells [90] and Schwann cells [91]. Hence, puberty will lead to not only development of the white matter but it also influences the functional connectivity and the communication between different brain regions and within the peripheral nervous system. The volume of the white matter increases faster in male than in female children and the proportion of the white and the grey matter is also altered, i.e. a larger white matter volume in males. These gender differences could imply that functional activity in the brain differs and that the brain will respond differently after disorders in males and females. In fact, in recent years, it has been shown that sex hormones (progesterone and oestradiol) play an important role as neuromodulators between the hemispheres in adults. Progesterone and oestradiol can reduce transcallosal inhibition, thereby regulating the dominance of the hemispheres during the menstrual cycle in females [92]. Males, however, have shown to be more stable in their functional brain asymmetries [92]

It is not known if the outcome after a peripheral nerve injury depends on the gender of the patient and this is an area for future research. Interestingly, a gender difference in axonal outgrowth, with a possible influence through the activation and apoptosis (programmed cell death) of Schwann cells, has recently been reported in healthy rodents and in rodents with diabetes [93], indicating that gender differences might exist in the peripheral nervous system as well. I did not perform any comparison of the results between males and females since there were a small proportion of women that was injured

(18%). Such skewed gender-representation with male dominance corresponds to the typical pattern found in nerve and hand injuries in general [3, 5] and makes it difficult to study any differences.

In recent years, the role of white matter plasticity in connection with information processing, cognitive function and learning, have gained increasingly interest. Ageing and an impaired cognitive ability might be related to changes in the white matter integrity [94]. Development of white matter and myelination are also believed to be activity-dependent and can respond to environmental changes [94]. For example, rapid changes in microstructure of the white matter have been seen in adult patients with dystonia, who were treated with botulinum toxin to inhibit motor afferent feedback to the brain [95]. Differences in the functional activation in the left tempo-parietal cortex have also been shown in those with a reading disability, suggesting that variations in the structure of the white matter may be associated with important differences in human functioning [89].

Motor plasticity

The control of movement is dependent on a network of cortical areas interacting to create a motor signal to the muscles. A peripheral nerve injury leads to changes in several areas of the central nervous motor system, making it more difficult to study. Cerebral motor plasticity was not investigated in this thesis, since most patients regained a good motor function (Paper II) and I did not see any age dependent differences in the clinical motor recovery. The peripheral motor reinnervation is likely subject to the same degree of misdirection as the sensory system. However, the motor axons can reinnervate more muscle fibres, thus compensating for motor fibres that have died or reinnervated the wrong target. It is probably very difficult to show evidence of reorganization in the motor cortex after a median or an ulnar nerve injury since the existing motor function tests are too coarse for the small muscles involved, such as the thenar muscle or the other intrinsic muscles of the hand. In addition, in order to manage activities of daily living, a very fine motor control is perhaps less involved and this makes it difficult to evaluate the impact on daily living. To study reorganization in the motor cortex after a median or ulnar nerve injury would also require a very high imaging resolution, which currently does not exist. Sokki et al. showed that cortical reorganization exists following nerve transfers in injuries of the brachial plexus in adult patients [96]. They studied the development of new connections in the motor areas of the brain by using fMRI and DTI in patients after transfer of intercostal nerves to the musculocutaneous nerve. A transfer of the motor activity from the original intercostal muscle motor area to the motor area involved in elbow motion was found in the brain. Interestingly, genetic components have been observed for the observed plasticity in the human motor cortex and perhaps in the peripheral nervous system, such as differences in expression of brain-derived neurotrophic factor (BDNF) [97, 98]. Genetic variations between individuals may explain why patients with identical peripheral injuries have a different capacity for plasticity and recovery.

Misdirection and outcome

Misdirection is a problem that accompanies the reinnervation process after a peripheral nerve injury or reconstruction. Several sprouts may grow at the same time and compete for reinnervation at the target organ level [99]. This can lead to loss of innervation selectivity and eventually modify the structure of the target organ [99]. While some axons may grow too many connections, others are misdirected. In mixed motor/sensory nerves, such as the ulnar nerve, the possibility exists that the outgrowing motor axons may follow an endoneurial tube that leads to a sensory terminal [99]. The mechanisms of pruning are relevant for misdirection of the peripheral nerve. Pruning involves strategies to selectively remove excessive neuronal branches and connections in the immature nervous system to modify and ensure the proper development of the nervous system [15, 100]. Misdirection at the repair site is probably a key feature in the cerebral response following a peripheral nerve injury. If the outgrowing axons could be modulated and guided, we could perhaps improve outcome. Interestingly, the results from the locognosia test (Table 3, Paper II) indicate that the capacity to localise suprathreshold touch, as detailed as to a quarter of a finger pulp [53], does not seem to be a major problem in patients who sustained nerve injuries below 21 years of age. On the other hand, the results from the sensory domains, specifically the tactile gnosis, were poor in those injured in adolescence. The sensory domain in the Rosen score measures touch thresholds, tactile gnosis and dexterity. Hence, not only detection and discrimination are included, but also identification and integrated functional sensibility as well as fine motor control. The discrepancy between the results from the locognosia test and the sensory domain could perhaps be explained by the fact that tactile gnosis and dexterity require restitution of more complicated cerebral networks to function properly. The locognosia test used here is reliable, valid and depends on the density and integrity of the end organs in the skin, as well as an intact somatotopic representation in the brain [53]. Still, it may not be sensitive enough. For example, testing the ulnar nerve includes only six areas on the ring and the little finger and subsequently, it may be difficult to detect minor errors. Currently, we have no clinical instrument to measure misdirection of the peripheral motor axons and it is probably difficult to detect minor errors here as well.

Level, type of nerve injury and nerve reconstruction

Level and type of nerve injury

Most of the participants' nerve injuries in Paper II were at wrist level (76 %). The results might have been different if more proximal nerve injuries had been included [50]. After a high ulnar nerve injury, the strength of the intrinsic muscles is generally poor [101]. More proximal injuries can perhaps lead to a less favourable outcome because the regenerating fibres have to elongate for a longer distance to reach their targets in the hand and that the condition of the Schwann cells deteriorate over time (i.e. less activation and a higher number of apoptotic cells) with subsequent less stimulation of the regenerating process [102]. In contrast, the lower nerve injuries are much closer to the motor endplates and sensory receptors.

Previous studies have indicated a superior motor and sensory outcome after median nerve injury compared to an ulnar nerve injury [50, 103]. The ulnar nerve innervates the distal, delicate movements, working in different directions, which require a more precise innervation. Ruijs et al. showed that age, level of injury (proximal-distal) and delay are significant predictors of a successful motor recovery and that the ulnar nerve injuries had a poorer recovery [104]. On the other hand, for sensory recovery, only age and delay were significant predictors. Studies have also shown that the sensory recovery may continue for a longer period than the motor recovery [51]. When considering the long follow-up in the present papers, the nerve regeneration process is likely finished. In the whole study group, I found no differences in the total Rosen score between participants with a median or an ulnar nerve injury. Furthermore, by analysing the results from the sensory and motor domains separately, I found no significant difference in the results of the sensory domains when different nerve injuries were compared. However, the participants with a single median nerve injury show a significantly better result in the motor domain (Table 2, Paper II) compared to the participants with a single ulnar nerve injury. Interestingly, no significant differences were found in the motor amplitudes of the electroneurography, indicating the number of regenerating axons in the nerve, when comparing isolated median and ulnar nerve injuries (Table 1, Paper III). In addition, participants with a median nerve injury presented significantly lower sensory amplitudes and lower motor conduction velocities (i.e. myelination of the regenerated axons) compared to patients with an ulnar nerve injury. These are confusing results and again, I wonder - what do we measure? The set-up when testing each nerve can perhaps explain the differences between the different results in the motor and sensory domains. For example in the motor domain, only one muscle test is performed for the median nerve, while testing the ulnar nerve comprises three different muscular tests that need more extensive reinnervation since the ulnar nerve innervate a much larger amount of intrinsic muscles than the

median nerve does. One has to consider that comparing the clinical outcome after a median or an ulnar nerve injury perhaps involves different neurobiological approaches and might not at all be possible. The outcome after a peripheral nerve may also differ depending on the presence of neural connections between the median and ulnar nerves in the forearm (Martin-Gruber anastomosis) or in the palm (Riche–Cannieu anastomosis). Cadaver studies have shown the presence of Martin-Gruber anastomosis in almost 25 % of normal individuals [105]. In this thesis, no systematic studies were performed to search for such connections [106], however, an existing anastomosis could affect the conclusions.

Nerve reconstruction with nerve grafts

It has been suggested that a secondary nerve graft repair leads to a better recovery after a median nerve reconstruction [50]. However, others have reported no significant difference in sensory recovery of median and ulnar nerve after nerve grafting of the median and ulnar nerves in the forearm [107]. Only eight of the present participants had a reconstruction for a median nerve injury (n=5), an ulnar nerve injury (n=2) or both nerves (n=1). All had different denervation time and the length of the grafts could not be defined from the patient charts. With the long follow-up time, the healing and adaptation process is likely finished but the number of patients is too few to draw any conclusions if a reconstruction of the median or ulnar will lead to a different outcome. Most probably, the influence of denervation time and the length of the graft [107] are more important factors for recovery than which nerve is reconstructed.

Methodological considerations

Participants

The number of **missing patients** raises the question of a selection bias. In total, 127 patients were identified with a nerve injury in the hospital administrative system and among them 82 were invited with finally 45 examined patients (Paper II). The outcome of the missing patients is unknown and could be poor. However, the reason for not participating could perhaps be explained by having no current complaints or not wanting to be reminded about a difficult time in life. During repeated phone calls, other patients expressed that they had no time to participate or that they were living too far away. Seen in the perspective of the median 31-year follow-up time, the material is unique.

Why was it decided to set the **division around 12 years** of age to evaluate if age had an impact on functional recovery (Paper II and III)? My aim was to find out if the outcome differs between those injured in childhood and those injured in adolescence and previous studies, with fewer patients and a shorter follow-up, have indicated a better function after a nerve injury in very young patients compared to adolescents and adults [8, 45, 108]. It is known that puberty will lead to an increase of sex steroids, which may affect both the peripheral and the central nervous system as discussed previously [76, 77]. The onset of puberty is determined by a combination of influences in each individual and differs between boys and girls as well as between various populations [109]. Nevertheless, it was assumed that the age of 12 years was a reasonable mean for the onset of puberty in both boys and girls [110] and before this was decided, paediatric expertise were consulted to confirm this age division. Interestingly, the hypothesis, i.e. a superior clinical outcome in those injured in childhood was supported by the conformity of the results before and after 12 years of age in the presented scatter plots (Paper II).

Methods

Rosen score was used as the primary outcome measure and this instrument is easy to use in the clinical setting together with the patient and gives details as well as an overview of the outcome. It gives the examiner a possibility to quantify the result after a peripheral nerve injury and compare the results from different functions as well as to compare results of median nerve and ulnar nerve injuries. A potential improvement could be achieved by including a component that measures locognosia (the ability to localize touch) in the instrument. The symptoms, described as problematic by the study participants in Paper V, were in line with the different domains included in the score (sensory, motor, pain/discomfort). This further validates this outcome instrument on the level of body function [2]. However, a more activity-dependant instrument, specific for peripheral nerve injuries, would be useful when evaluating these patients.

The median **DASH** scores (Disability of Shoulder Arm and Hand) were within normal limits in our studies. This implies the necessity for future development of such an instrument.

Visual analogue scale (VAS) was used to investigate the impact on education and leisure activities (Paper II). VAS is mainly used for evaluation of pain and its reliability and validity remains a controversy [111] and to use VAS for evaluation of other parameters than pain is frequent but may be questioned. However, the aim was to give the patients a possibility to transfer their subjective opinion to an evaluation that can be measured objectively. Indeed, valuable information about the impact on education and leisure activities was revealed using this subjective scale.

No needle **electromyography** [112] was performed in the electrophysiological evaluation for several reasons. A needle electromyography is an invasive procedure and gives no information on the extent of damage or on the regeneration of the sensory fibres. On the other hand, an electroneurography requires less patient cooperation and offers the possibility to quantify the results in a simple and standardized manner. While the sensory amplitude correlates with the number of axons capable of transmitting impulses from the stimulating to the recording electrodes, the motor amplitude reflects the number of muscle fibres that are activated. In order to estimate the number of motor axons that had reinnervated a muscle, a Motor Unit Number Estimation (MUNE) would have to be performed. However, such a technique was not available at the start of the project, but the technique may add interesting information in the future.

A **qualitative content analysis** was used for a deeper exploration of the consequences of the nerve injury (Paper V) and that part of the thesis revealed new information of the consequences of a nerve injury sustained in adolescence, such as emotional reactions and the impact on life roles (Paper V). I believe that the use of qualitative content analysis is an important complement to quantitative research. If we only use qualitative assessment instruments to evaluate the outcome, we can lose valuable and important information from the individual patient. The possibility to allow the patients to tell their stories can provide us with new and deeper understanding. By identifying the patients' individual needs and capacities, healthcare staff can promote different treatment options and enhance patient satisfaction.

Future perspectives

The treatment of a peripheral nerve injury remains a challenge and a source for future research. Despite a refined surgical technique utilizing microsurgery after a peripheral nerve injury, a reduced time delay for the surgical repair and the early onset of rehabilitation, the clinical outcome and especially fine sensory function is often poor. By further exploring the mechanisms behind plasticity with different imaging techniques, we can perhaps understand the biology in more detail. In the future, we might be able to modify the postoperative treatment after such injuries and perhaps target plasticity to specific brain regions involved in sensory and motor function by the use of pharmacological drugs. In addition, the possibility to decrease the neuronal death in the dorsal root ganglia or in the spinal motor neurons following a nerve injury need further investigation, as well as the alternative to transplant stem cells into the distal nerve segment. The condition and apoptosis of the Schwann cells may be possible to orchestrate by pharmacological substances. The outcome can also be improved if we try to identify individual patient-specific factors that determine adherence to rehabilitation, involve the surrounding available resources and offer counselling when needed.

Going through the literature, I realize that researchers, like me, often include and combine the results of heterogeneous groups of patients at various ages, with nerve injuries at different levels, as well as a different time spans to repair or if a repair/reconstruction of a nerve defect was performed. Hence, the results may differ. The introduction of a database on peripheral nerve injuries would become a useful tool for the surgeon and for the researcher. By using a database with an organised collection of information, the treatment and postoperative rehabilitation after a nerve repair or reconstruction could perhaps be uniform. In addition, with larger and more homogeneous populations, it would also be easier to study.

Conclusions

Age is a factor that influences functional outcome after a median or ulnar nerve injury. The patients injured in childhood, i.e. before 12 years, showed a superior recovery with almost full sensory and motor recovery, at a median follow-up time of 31 years. Those injured in adolescence, i.e. between 12-20 years, experienced a considerably greater influence on education, leisure activities and professional choice.

Electroneurography showed pathology in all parameters and in all patients, regardless of age at injury. No significant differences in the electrophysiological results were observed between those injured in childhood and those injured in adolescence. The mechanisms behind the superior clinical outcome in children are not located in the peripheral nervous system.

fMRI showed a different cerebral activation pattern after stimulation of the injured hand, depending on the age when the nerve injury was sustained. The cortical activation pattern in those injured before the age of nine years was similar to the cortical activation pattern of the healthy controls without a nerve injury. Those injured at the ages of 13-15 years, or at the ages of 18-20 years, displayed a larger activation in the contralateral hemisphere, but showed also changes in the ipsilateral hemisphere with reduced inhibition and activation of somatosensory areas. Cerebral changes in both brain hemispheres may explain differences in clinical outcome following a nerve injury in childhood or adolescence.

Treatment of patients with nerve injuries at forearm level is complicated and requires attention to other aspects as well as to repair the damaged nerve. Promotion of different coping mechanisms should be encouraged in order to facilitate quality of life and the daily living for the injured patients. Emotional reactions to trauma should be identified and taken care of immediately.

Sammanfattning/Summary in Swedish

En nerv (eller en nervstam) i en arm kan jämföras med en kabel som förmedlar impulser från känselmottagare i handen till specifika områden i hjärnan där informationen behandlas och sedan återkopplas ut till musklerna i handen. Efter en skada på en nervstam med ett komplett brott på nervtrådarna, startar ett komplicerat reparationsförlopp som leder till att nya nervtrådar växer ut från skadeområdet och ner till känselmottagarna eller till musklerna. Ibland växer dessa nervtrådar fel vilket får hjärnan att tolka informationen från nerven i handen annorlunda. Man talar om att handens kartbild i hjärnan förändras. Genom årens lopp har den kirurgiska tekniken och rehabiliteringen vid reparation av nervskador utvecklats. Idag lagar man nerver med mikroskopisk förstoring och forskning har visat att resultaten blir bättre om man reparerar nervskadan så snabbt som möjligt. Trots dessa förbättringar blir patienternas handfunktion, särskilt känseln, aldrig helt återställd. Nervskador i armen är ovanliga hos barn, men tidigare undersökningar har visat att de oftast återfår sin handfunktion och känsel. Varför det är så vet man inte och det finns forskare som har föreslagit att barn har en bättre läkningsförmåga och framför allt att barnens hjärnor har en bättre kapacitet att tolka den förändrade informationen från nerven i handen. Vi vet idag inte hur länge läkningsprocessen efter en nervskada pågår, men tidigare undersökningar har visat att känseln kan fortsatt förbättras i upp till fem år efter en nervreparation.

Syftet med mitt forskningsprojekt var att undersöka hur handfunktionen blir efter en komplett nervskada i underarmen hos patienter som skadat sig när de var 20 år eller yngre och där det har förlöpt minst 20 år sedan skadan. Jag ville också ta reda på om de som skadat sig som barn hade en bättre handfunktion jämfört med skadade tonåringar och i så fall varför. Kunde eventuella skillnader bero på en bättre läkningsförmåga i nerven eller kunde de bero på det förändrade mönstret i hjärnan?

Handkirurgiska kliniken i Malmö tar emot patienter med nervskador i armen från hela Södra Sjukvårdsregionen med ett upptagningsområde på cirka 1,5 miljoner människor. Patienterna till projektet identifierades genom att studera medicinska journaler på dem som opererats på kliniken för en komplett nervskada i underarmen mellan 1970 och 1989 och som då var 20 år eller yngre. Totalt 127 patienter identifierades, 82 kunde lokaliseras genom befolkningsregistret och 45 personer accepterade att delta. Dessutom deltog ytterligare fyra patienter i en separat studie i vilken uppföljningstiden var kortare och åldern vid skadan något högre (Delarbete I).

Patienterna intervjuades, fyllde i olika självskattningsinstrument av sin funktion och undersöktes tillsammans med en arbetsterapeut. Vidare tillfrågades alla om de var villiga

att delta i en nervfunktionsundersökning (så kallad neurografi) och en magnetkameraundersökning av hjärnan vid stimulering och aktivering av handen. Resultaten analyserades och presenteras i olika delarbeten. Muskelkraften och muskelfunktionen hade återhämtat sig nästan helt hos samtliga (Delarbete I och II). Däremot var känseln sämre hos de patienter som skadat sig i tonåren. Endast ett fåtal hade problem med kvarstående smärta och överkänslighet för kyla. Dessutom framkom att de som skadat sig som tonåringar upplevt stora problem i skolan och på fritiden. Vissa hade fått gå om ett år eller byta inriktning i skolan och hos en del hade yrkesvalet förändrats. Nervfunktionsundersökningen visade att alla patienter, den långa uppföljningstiden till trots, hade kvarstående mätbara sjukliga förändringar jämfört med den friska handen (Delarbete III). Den bättre känseln hos dem som skadat sig som barn kunde därmed inte förklaras av en bättre återhämtning av funktionen i nerven. Med en magnetkameraundersökning kan man numera studera hur hjärnan aktiveras vid känselstimulering av handen. När vi analyserade våra resultat, konstaterade jag att det fanns skillnader i hjärnans aktivering hos dem som skadat sig som barn, jämfört med tonåringarna (Delarbete I och IV). De i barndomen skadade uppvisade en aktivering av hjärnans känselcentrum som liknade den hos individer utan nervskada. Hos dem som skadat i tonåren, skiljde sig aktiveringen mellan de båda hjärnhalvorna. Efter en nervskada kan alltså hjärnans hantering av känselinformation ha normaliserats hos dem som skadat sig som barn medan tonåringarna inte hade denna kapacitet utan måste utnyttja andra delar av hjärnan som kompensation. I barnets hjärna finns ett överskott av nervceller och nervförbindelser och en kommunikativ förbindelse mellan de båda hjärnhalvorna som skiljer sig från den vuxna hjärnan. Det finns mycket forskning som talar för att igångsättning av puberteten och frisättning av könshormoner leder till stora förändringar i hjärnans struktur och interna kommunikation. Pubertet och tonår innebär en tid med stora förändringar i både kropp och själ. En nervskada i underarmen medför månader av intensiv och lång rehabilitering och kan leda till stora följdverkningar för skolgång och framtida yrkesval. I mitt sista arbete ingår 15 patienter som valts ut enligt särskilda kriterier och vilka samtliga var tonåringar vid skadetillfället (Delarbete V). Dessa genomgick en djupintervju tillsammans med en arbetsterapeut. När vi analyserade dessa intervjuer framkom ny och viktig information. Patienterna beskrev väldigt tydligt hur de mädde omedelbart efter nervskadan trots den långa tid som förflutit och vittnade om chock, mardrömmar, minnesluckor och depressionsliknande tillstånd. På 70- och 80-talet var kuratorskontakt i sjukvården inte lika etablerad som den är nu och många patienter saknade ett sådant omhändertagande. Det framhölls brist på bra och förstälig information om nervskador och konsekvenserna av dem och man önskade att det funnits kommunikation med skola och arbetsplats för ökad förståelse. Olika fritidsaktiviteter hade fått avbrytas och samliv och föräldraroll hade påverkats. En nervskada har konsekvenser för hur kroppen fungerar men förändrar även möjligheterna att utföra aktiviteter och att vara delaktig i tillvaron.

Min förhoppning är att vi kan fortsätta att förbättra omhändertagandet av patienter med en nervskada i armen. Genom att lära oss mer om hjärnans funktion, utveckla

rehabiliteringen och framställa läkemedel som kan förbättra läkningen i nerven och kompensera för hjärnans förändrade mönster, kan våra framtida patienter återfå en bättre handfunktion.

Acknowledgements

This project could not have been possible without the patients participating in the different examinations. I am very grateful for you sharing your experiences. I would also like to thank all the financial supporters involved in the project: the Swedish Medical Council (Medicine), the Swedish Medical Association, the Promobilia Fund, Lund University, Funds from Skane University Hospital, Region Skåne, Thelma Zoéga's Fund, Lundgren's Fund, HKH Kronprinsessan Lovisa's Fund, Carlsson's Foundation and by the European Community's Seventh Framework Programme (FP7-HEALTH-2011) under grant agreement no. "278612".

Others have contributed to this book in different ways.

Anders Björkman, Birgitta Rosén and Lars Dahlin; my supervisors from the Department of Hand Surgery, Malmö. Since the beginning of this project, you have guided me, sometimes in different directions, but always with a goal in mind. I appreciate your patience and professionalism.

Dr Gert Andersson and technician Lena Goldberg, from the Department of Neurophysiology, for your invaluable cooperation and support when performing and interpreting all the electroneurography examinations.

Dr Andreas Weibull, from the Department of Medical Radiation Physics, for performing all the fMRI examinations and for excellent work with the analyses.

Ingela Carlsson, occupational therapist at the Department of Hand Surgery in Malmö, for introducing me to another dimension of research. I appreciate your help with all the interviews and with the composition of the qualitative paper.

All my colleagues at the Department of Hand Surgery in Malmö, for giving me the opportunity to fulfil the project and to write this book.

Trygve Strömberg, my colleague and clinical supervisor, who has supported me in different ways since 2006. Thank you also for helping me with the language correction of the Swedish summary.

Helen and Tina, for always helping me with practical matters, for encouraging me in difficult moments and for making me laugh, especially on Friday mornings.

Jan Reimertz, who introduced me to the world of hand surgery and who sadly passed away two years ago. I still think of you every day.

My former colleagues at the Department of Orthopedics in Växjö, for giving me the opportunity to grow up as a surgeon.

Nada and Bozidar Brdarski, my parents who emigrated from Serbia to Sweden in the year 1970 to give their children a better future. Despite only four years of school education each, they managed to raise ten children.

My nine siblings with their families, who have supported me since childhood.

Niels, Oliver and Katja, my beloved family and my next, lifelong project.

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Appendix

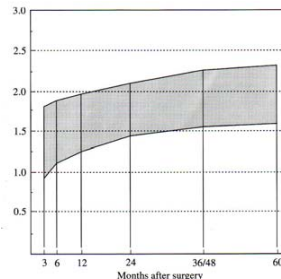
Rosen-score

Model Instrument for Outcome after Nerve Repair

Name:

Domain	Instrument and quantification	Month/ date								
Score (scoring key: result / normal)										
Sensory Innervation  Tactile gnosis Dexterity	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 unlar:15								
	s2PD (digit II el V) 0≥16 mm 1=11-15 mm 2=6-10 mm 3≤5 mm	Result:0-3 Normal:3								
	STI-test (digit II el V)	Result:0-6 Normal:6								
	Sollerman test (task 4,8,10)	Result:0-12 Normal:12								
Mean sensory domain:										
Motor Innervation Grip strength	Manual muscle test 0-5 Median:palmarabd Ulnar: abd dig II, V add dig V	Result medians:0-5 Result ulnar: 0-15 Normal median:5 Normal ulnar:15								
	Jamar dynamometer Mean of 3 trials in second position, right and left	Normal: Result uninjured hand								
Mean motor domain:										
Pain/discomfort Cold intolerance Hyperesthesi	Patienten's estimation of problem 0=Hinders function 1=Disturbing 2=Moderate 3=None/minor	Result:0-3 Normal:3								
	As for cold intolerance									
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 , 2001: 26B; 3: 196-200, J Hand Sure 2000: 25A: 535-543*



DISABILITIES OF THE ARM, SHOULDER AND HAND

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

	NO DIFFICULTY	MILD DIFFICULTY	MODERATE DIFFICULTY	SEVERE DIFFICULTY	UNABLE
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 chores (e.g., wash walls, wash floors).	1	2	3	4	5
8. Garden or do yard 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).	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 pullover sweater.	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., cardplaying, knitting, etc.).	1	2	3	4	5
18. Recreational activities in which you take some force or impact through your arm, shoulder or hand (e.g., golf, hammering, tennis, etc.).	1	2	3	4	5
19. Recreational activities in which you move your arm freely (e.g., playing frisbee, badminton, etc.).	1	2	3	4	5
20. Manage transportation needs (getting from one place to another).	1	2	3	4	5
21. Sexual activities.	1	2	3	4	5

DISABILITIES OF THE ARM, SHOULDER AND HAND

	NOT AT ALL	SLIGHTLY	MODERATELY	QUITE A BIT	EXTREMELY
22. During the past week, <i>to what extent</i> has your arm, shoulder or hand problem interfered with your normal social activities with family, friends, neighbours or groups? <i>(circle number)</i>	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? <i>(circle number)</i>	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 performed 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 DIFFICULTY	MODERATE DIFFICULTY	SEVERE DIFFICULTY	SO MUCH DIFFICULTY THAT I CAN'T SLEEP
29. During the past week, how much difficulty have you had sleeping because of the pain in your arm, shoulder or hand? <i>(circle number)</i>	1	2	3	4	5

	STRONGLY DISAGREE	DISAGREE	NEITHER AGREE NOR DISAGREE	AGREE	STRONGLY AGREE
30. I feel less capable, less confident or less useful because of my arm, shoulder or hand problem. <i>(circle number)</i>	1	2	3	4	5

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

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

DISABILITIES OF THE ARM, SHOULDER AND HAND

WORK MODULE (OPTIONAL)

The following questions ask about the impact of your arm, shoulder or hand problem on your ability to work (including home-making if that is your main work role).

Please indicate what your job/work is: _____

I do not work. (You may skip this section.)

Please circle the number that best describes your physical ability in the past week. Did you have any difficulty:

	NO DIFFICULTY	MILD DIFFICULTY	MODERATE DIFFICULTY	SEVERE DIFFICULTY	UNABLE
1. using your usual technique for your work?	1	2	3	4	5
2. doing your usual work because of arm, shoulder or hand pain?	1	2	3	4	5
3. doing your work as well as you would like?	1	2	3	4	5
4. spending your usual amount of time doing your work?	1	2	3	4	5

SPORTS/PERFORMING ARTS MODULE (OPTIONAL)

The following questions relate to the impact of your arm, shoulder or hand problem on playing *your musical instrument or sport or both*. If you play more than one sport or instrument (or play both), please answer with respect to that activity which is most important to you.

Please indicate the sport or instrument which is most important to you: _____

I do not play a sport or an instrument. (You may skip this section.)

Please circle the number that best describes your physical ability in the past week. Did you have any difficulty:

	NO DIFFICULTY	MILD DIFFICULTY	MODERATE DIFFICULTY	SEVERE DIFFICULTY	UNABLE
1. using your usual technique for playing your instrument or sport?	1	2	3	4	5
2. playing your musical instrument or sport because of arm, shoulder or hand pain?	1	2	3	4	5
3. playing your musical instrument or sport as well as you would like?	1	2	3	4	5
4. spending your usual amount of time practising or playing your instrument or sport?	1	2	3	4	5

SCORING THE OPTIONAL MODULES: Add up assigned values for each response; divide by 4 (number of items); subtract 1; multiply by 25.

An optional module score may **not** be calculated if there are any missing items.



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Cold Intolerance Symptom Severity (CISS) questionnaire

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.

The 13-item Sense of Coherence Questionnaire

Here is a series of questions relating to various aspects of your lives. Each question has seven possible answers. Please mark the number, which expresses your answer, with number 1 and 7 being the extreme answers. If the words under 1 are right for you, circle 1; if the words under 7 are right for you, circle 7. If you feel differently, circle the number which best expresses your feeling. Please give only one answer to each question.

1. Do you have feeling that you don't really care about what goes on around you?

1	2	3	4	5	6	7
very seldom often or never						very

2. Has it happened in the past that you were surprised by the behaviour of people whom you thought you knew well?

1	2	3	4	5	6	7
never happened						always happene d

3. Has it happened that people whom you counted on disappointed you?

1	2	3	4	5	6	7
never happened						always happene d

4. Until now your life has had:

1	2	3	4	5	6	7
no clear goals or purpose at all						very clear goals and purpose

5. Do you have the feeling that you're being treated unfairly?

1	2	3	4	5	6	7
very often						very seldom or never

6. Do you have the feeling that you are in an unfamiliar situation and don't know what to do?

1	2	3	4	5	6	7
very often						very seldom or never

7. Doing the thing you do every day is:

1	2	3	4	5	6	7
a source of deep pleasure and satisfaction						a source of pain and boredo m

8. Do you have very mixed-up feelings and ideas?

1	2	3	4	5	6	7
very often						very seldom or never

9. Does it happen that you have feelings inside you would rather not feel?

1	2	3	4	5	6	7
very often						very seldom or never

10. Many people – even those with a strong character – sometimes feel like sad sacks (losers) in certain situations. How often have you felt this way in the past?

1	2	3	4	5	6	7
never						very often

11. When something happened, have you generally found that:

1	2	3	4	5	6	7
you overesti- mated or under- estimated its importance						you saw things in the right proporti on

12. How often do you have the feeling that there's little meaning in the things you do in your daily life?

1	2	3	4	5	6	7
very often						very seldom or never

13. How often do you have feelings that you're not sure you can keep under control?

1	2	3	4	5	6	7
very often						very seldom

Paper I

ORIGINAL ARTICLE

Cerebral changes after injury to the median nerve: A long-term follow up

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Abstract

Injury to the peripheral nerves in the upper extremity results in changes in the nerve, and at multiple sites throughout the central nervous system (CNS). We studied the long-term effects of an injury to the median nerve in the forearm with a focus on changes in the CNS. Four patients with isolated injuries of the median nerve in their 20s were examined a mean of 14 years after the injury. Cortical activation was monitored during tactile stimulation of the fingers of the injured and healthy hand using functional magnetic resonance imaging at 3 Tesla. The neurophysiological state and clinical outcome were also examined. Activation in the primary somatosensory cortex was substantially larger during tactile stimulation of the injured hand than with stimulation of the uninjured hand. We also saw a redistribution of hemispheric dominance. Stimulation of the injured median nerve resulted in a substantially increased dominance of the contralateral hemisphere. However, stimulation of the healthy ulnar nerve resulted in a decreased dominance of the contralateral hemisphere. Neurophysiology showed low sensory amplitudes, velocity, and increased motor latency in the injured nerve. Clinically there were abnormalities predominately in the sensory domain. However, there was an overall improved mean result compared with a five year follow-up in the same subjects. The cortical changes could be the result of cortical reorganisation after a changed afferent signal pattern from the injured nerve. Even though the clinical function improved over time it did not return to normal, and neither did the cortical response.

Key Words: median nerve, injury, sensory, motor, fMRI, neurophysiology

Introduction

After transection and repair of injuries to nerves in the upper extremity, most adult patients regain poor sensorimotor function with substantial disabilities [1]. While motor function of the hand can become nearly normal over time, sensory function never recovers fully. Most patients also have intolerance to cold and hyperaesthesia [2].

After transection and repair of a nerve, substantial axonal misdirection is seen at the repair site [3]. As a result of this misdirection, peripheral areas of skin and muscles are not reinnervated by their original axons but instead by axons originally meant to innervate other parts of the hand. Studies of injuries to nerves in

adult humans have shown similar results as in animals, with incomplete regeneration of peripheral nerves with severe abnormalities in nerve conduction, atrophy of cortical grey matter, and changed activation patterns in the somatosensory cortex [4–7]. Clinical improvement of both sensory and motor function after an injury to a nerve, and repair, has been shown for as long as five years postoperatively [8]. It is presently not known whether the improved function of the hand over time reflects changes in the peripheral nerve or an increased ability of the CNS to adapt and interpret the altered peripheral nerve signals [9].

Several studies have rated age at injury as the most important predictor of sensory recovery after nerve repair [7,10,11]. There are two hypotheses for the

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(Accepted 25 October 2011)

ISSN 2000-656X print/ISSN 2000-6764 online © 2012 Informa Healthcare
DOI: 10.3109/2000656X.2011.653257

better prognosis for nerve injuries in children: better peripheral nerve regeneration and better cerebral adaptability (that is, plasticity) in children. However, equivalent degrees of sensory and motor fibre regeneration in adults and children have been shown [12,13], and it has therefore been suggested that superior plasticity in the young brain is the mechanism behind the improved clinical results.

Most previous studies have focused on changes in the immediate or medium term. Long-term cerebral changes after peripheral nerve injury and surgical repair have not been examined thoroughly [6], and the extent to which peripheral nerve regeneration influences functional and structural changes in the CNS has not been characterised. The aim of the present study was to investigate long-term changes in the central nervous system and clinical outcome after injury to the median nerve at wrist level in a group of young adults.

Patients and methods

Patients

Four patients operated on at the Department of Hand Surgery, University Hospital Malmö, for complete median nerve transections participated in the study. The mean age at operation was 21.5 years (range 18–28) and the mean time since the operation was 14 years (range 9–18). None of the patients had any systemic diseases at the time of the study. All were operated on within 48 hours of the injury. Two patients were operated on using a Silicone tube and two patients with epineural sutures. All patients had associated flexor tendon injuries and two had associated vascular injuries. Two patients had injuries to their dominant hand. All patients participated in traditional sensory re-education programmes during phase 2, starting when regeneration of the nerve was identified in the palm. Case 2 started sensory re-education during phase 1 [14].

The study design was approved by the local ethics committee and all participants gave informed consent. The experiments were conducted in accordance with the declaration of Helsinki.

Functional magnetic resonance imaging

We used functional magnetic resonance imaging (fMRI) using a whole body 3T scanner (Siemens Medical Solutions, Erlangen, Germany) equipped with a 12-channel head coil. An electronically-controlled pneumatic stimuli system built in-house was used for tactile finger stimulation as described by Weibull et al. [15]. It had eight individually-controlled channels, each consisting of a pneumatic valve (Festo,

Germany) connected by a plastic tube to a membrane (4-D Neuroimaging, area approximately 0.8 cm²). These membranes were taped to the tips of the thumb, index, middle, and little finger of both hands, stimulating both the median (thumb, middle, and long finger) and ulnar nerve (little finger). Each subject was instructed to position both arms in a way that was most comfortable with the help of cushions and other supports to ensure comfort and minimise errors induced by motion or fatigue.

Tactile stimulation of the right hand fingers (1 Hz pulse frequency, 100 ms pulse width, 2.5 bars pressure) were applied in a block design alternating between rest conditions with no stimuli, and stimulation of each nerve (rest = simultaneous stimulation of thumb, index, and middle finger; rest = stimulation of little finger; rest, and so on). The length of each block was 32 seconds, and each session included 8 blocks of stimulation (4 for each nerve's territory) and 8 blocks of rest. This was then repeated for the left hand. Before the functional imaging we acquired a high-resolution anatomical scan (3D – Fast Low Angle Shot, echo time/repetition time = 4.9/11 ms, flip angle = 15°, resolution = 1 × 1 × 1 mm³, 176 oblique transversal slices oriented to form a plane through the anterior-posterior commissures). We then used blood oxygen-dependent imaging (BOLD) with a gradient echo – echo planar-imaging pulse sequence with echo time/repetition time 30/2660 ms, 128 × 128 matrix, 23 slices and 2 × 2 × 2 mm³ voxel size with the same orientation as the anatomical scan. High spatial resolution was used, as this has been shown to be superior when mapping the primary somatosensory cortex [15]. The acquired volume was confined to the superior part of the brain – that is, from secondary somatosensory cortex and above, because of the limited slice coverage within the chosen repetition time and spatial resolution. After the scanning session each subject was asked if there had been any complications, to ensure the use of proper data and allow data to be excluded on reasonable grounds.

Neurophysiological examination

Motor and sensory nerve conduction studies were made on both hands using Nicolet Viking Select™ equipment. Surface electrodes were used. The skin temperature was monitored and kept above 30°C.

Motor responses were recorded from the abductor pollicis brevis and abductor digiti minimi muscles when the median and ulnar nerves were stimulated at the wrist (fixed distance 80 mm) and elbow. Amplitudes, distal latencies, and conduction velocities in the forearm segment were measured.

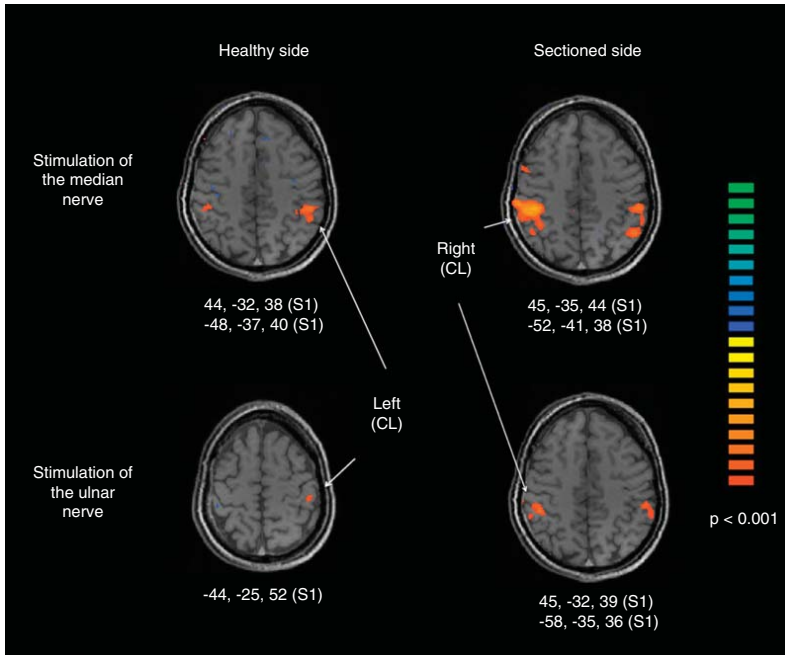


Figure 1. Cortical activation during tactile stimulation of the thumb, index, middle, and little finger in patients with a formerly injured median nerve. The activation volume was larger during stimulation of the hand in which the median nerve had been injured. This was also true for stimulation of the ulnar nerve, which had not been injured. The activation of the primary somatosensory cortex during stimulation of the little finger of the injured hand resulted in activation somatotopically close to the thumb, index, and middle finger. The right hand side in the images corresponds to the left hemisphere. CL is the hemisphere contralateral to the stimulated hand; S1 = primary somatosensory cortex; Talairach coordinates indicate the activation cluster centre-of-gravity and are shown below each image.

Orthodromic sensory nerve conduction studies were done by stimulating digits 1, 2, and 3 for the median nerve and digit 5 for the ulnar nerve. Ring electrodes were placed at the proximal interphalangeal and distal interphalangeal joints for digits 2–5, and for digit 1, just proximal and distal to the interphalangeal joint. Recording electrodes were placed over the respective nerve at the proximal wrist crease.

Clinical examination

The clinical assessment was made using the Rosén score [16]. This outcome instrument consists of three parts that examined the pain and discomfort and the motor and sensory function, respectively. Scoring in each domain from 0–1. A summary outcome is expressed in a “total score” 0–3.

Image processing and analysis

fMRI was used to assess cerebral activation during tactile stimulation of both the operated hand and the

healthy hand. The fMRI data was evaluated using Brainvoyager QX 2.1 software. The functional data series were corrected for motion; followed by spatial smoothing using a 4 mm kernel width and they were subsequently normalised to Talairach space by coregistration to Talairach processed anatomical data [17]. Low frequency modulation was suppressed using a high-pass filter with a cut-off frequency of three cycle/session. Activation maps were created using the general linear model and corrected for serial correlations using autoregressive characterisation of the first order [18].

Activation patterns were qualitatively and quantitatively evaluated. As a measure of hemispheric dominance the laterality index (LI) was calculated as $LI = \frac{CL_{act} - IL_{act}}{CL_{act} + IL_{act}}$, where CL_{act} is the contralateral activation volume and IL_{act} is the ipsilateral activation volume. LI was calculated at seven different thresholds ($p < 10^{-2}, 10^{-3}, 10^{-4}, 10^{-5}, 10^{-6}, 10^{-7},$ and 10^{-8}) as this measure is highly dependent on the threshold used [19]. The hemispheric dominance was compared at equal activation volume to rule out LI

changes simply resulting from an increase or decrease in the extent of activation [19].

Results

Stimulation of the median nerve territory in the injured hand resulted in a larger activated volume bilaterally in the primary and secondary somatosensory cortex compared with the healthy hand (Figure 1). This was also seen in patients in whom the mean activation volume of the contralateral primary somatosensory cortex was 4.9 cm² when the formerly injured median nerve was stimulated compared with 0.7 cm² when the healthy median nerve was stimulated. Interestingly, the same effect was seen on group level during stimulation of the ulnar nerve. Stimulation of the ulnar nerve in the injured hand resulted in activation of the same cortical area as the median nerve (activation cluster centre-of-gravity was 6 mm and 9 mm apart for the right and left hemisphere, respectively, compared with activation of the median nerve in the uninjured hand). This was in

contrast to ulnar nerve stimulation in the healthy hand where the activation was located more superiorly and 17 mm from the median nerve.

The hemispheric dominance was also substantially increased for the thumb, index, and middle fingers during stimulation of the injured hand (Figure 2). The activation increase was larger in the contralateral hemisphere. However, the hemispheric dominance for the little finger was decreased (Figure 2), albeit still showing an increase in activation (Figure 1).

The results of the clinical examination are presented in Table I. The Rosén score (a summary score of the eight variables included) constituting in all a maximum score of 3, varied from 2.2–2.7. The score in each of the three domains can vary between 0–1, and while the motor domain shows fairly uniform results (0.84–1.0) the score for sensory function (0.38–0.841 and pain/discomfort (0.67–1.0) are less so. Case 3, who had the older age at the time of injury, also had the lowest score in the sensory domain. Case 2, who had started sensory re-education early (in phase I, directly after the operation), showed the

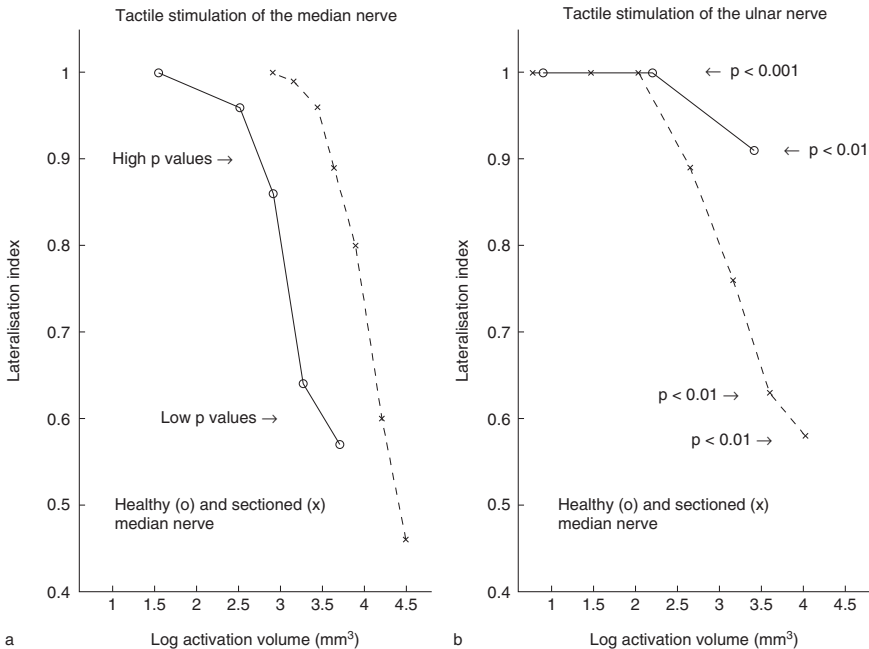


Figure 2. Differences in lateralisational index (LI) during tactile stimulation of the hand with a formerly transected median nerve. The contralateral dominance increases when the formerly sectioned median nerve is stimulated compared with the healthy side, seen as a substantially increased LI at equal activation volume. However, when the ulnar nerve is stimulated on the sectioned side, the hemispheric dominance decreases compared with the healthy side. Cortical activation generally increases during stimulation of the injured hand, which can be seen as increased activation volume compared with the healthy hand at equal statistical thresholds.

Table I. Results from the clinical examination at follow-up at 1 year/5 years/mean 14 years after the operation (range 9–18 years).

Case No.	Age at injury (years)	Sensory domain (0–1)	Motor domain (0–1)	Pain/discomfort domain (0–1)	Total score (0–3)
1	18	0.42/0.69/0.65	0.85/0.84/0.88	0.67/0.84/0.67	1.9/2.4/2.2
2	20	0.51/0.62/0.81	0.84/0.93/0.93	1.0/1.0/1.0	2.4/2.5/2.7
3	28	0.32/0.38/0.38	0.85/1.0/1.0	0.67/0.67/0.84	1.8/2.0/2.2
4	20	0.33/0.56/0.50	0.76/0.81/0.84	0.67/1.0/1.0	1.8/2.4/2.3
Mean		0.40/0.56/0.59	0.83/0.90/0.91	0.75/0.88/0.88	2.0/2.3/2.4

Results from the clinical examination measured by the three domains of the Rosén score [16]; sensory, motor, and pain or discomfort. Each domain consists of multiple tests; sensory consists of monofilament, 2PD, Sollerman and STI test, motor of dynamometer and manual muscle testing and pain and discomfort of subjective problems with cold and hyperaesthesia reported on a graded scale (0–3). The test results for each domain is then converted into a score (0–1) by dividing with the “normal” results. The total score (0–3) is the sum of the three domains.

highest total score and the highest score in the sensory domain.

On stimulation of the median nerve on the injured side, motor responses from the abductor pollicis brevis muscle were recorded with slightly prolonged latencies. The amplitudes varied from 14% to 114% of normal (Table II). The sensory conduction velocities were slightly reduced while the response amplitudes were considerably reduced (Table II). In case 4, there were clinical and electrophysiological signs of a carpal tunnel syndrome on the uninjured side with reduced sensory response amplitudes and velocities. The percentage values therefore probably underestimate the reduction on the injured side.

Discussion

We have shown that at a mean of 14 years after peripheral nerve injury at wrist level the patients had profound sensory deficits while motor function has recovered. Nerve conduction studies showed severe abnormalities in both sensory and motor nerve function. fMRI showed changes in the cortical map of the primary and secondary somatosensory cortex with a larger activated volume in both hemispheres compared with the healthy hand. The hemispheric dominance was substantially increased when stimulating the formerly injured median nerve compared with the uninjured hand. However, the hemispheric dominance was lowered when the ulnar nerve of the injured side was stimulated.

Plasticity after peripheral nerve injury and repair can occur throughout the CNS in non-human primates [4,5]. This is thought to be based on unmasking of previously silent synapses or axonal sprouting into the deafferented territory [5]. In both animal and human studies it has been shown that 1–5 years after a nerve repair the primary somatosensory cortex contains a larger, patchy, disorderly representation of the regenerated nerve [5,6,20]. This patchy representation has been attributed to incomplete regeneration of peripheral nerves as nerve conduction studies have shown severe abnormalities [6,12,13]. To evaluate the extent of peripheral nerve regeneration in our study subjects, we made sensory and motor conduction studies across the injured area. Our nerve conduction results largely corroborate previous studies in showing significantly decreased sensory amplitudes, lowered sensory velocity, and increased motor latency. The low sensory amplitudes probably reflect loss of peripheral nerve fibres, or incomplete remyelination, or both [21]. It has previously been shown that neither amplitude nor conduction velocity seem to correlate with sensory function [8,12,21]. Instead, age at injury has been shown by several authors to be the most important predictor of sensory recovery after peripheral nerve repair [10,11,22].

Fornander et al. [7] showed that the functional outcome after peripheral nerve repair was correlated to age at injury whereas the activated volume in the primary somatosensory cortex was more correlated to time since injury. A trend for correlation between

Table II. Results of the neurophysiological examination.

Case No.	Motor amplitude*	Distal latency*	Sensory amplitude**	Sensory velocity**
1	4.5 (83)	4.0 (121)	2 (16)	43 (76)
2	3.8 (38)	4.5 (122)	2 (7)	43 (75)
3	5.2 (70)	4.8 (117)	4 (27)	45 (95)
4	1.1 (14)	5.5 (122)	2 (11)	30 (64)

*Motor amplitude (mV) and distal latency (ms) of the median nerve in the injured hand measured by stimulation at the wrist, and percentage of the result from the uninjured hand (in brackets). **Mean amplitude (μ V) and velocity (m/s) on stimulation of the thumb, index, and middle finger of the injured hand and percentage of the result from the uninjured hand (in brackets).

better sensitivity as measured by 2PD and a smaller cortical activation area was also seen, though the results were not significant. However, Fornander et al. [7] and Taylor et al. [6] both showed that at a median of 5 years after peripheral nerve repair, the activated volume in contralateral primary somatosensory cortex was still increased. In the present study we have shown that this increase is still present at a mean of 14 years after median nerve repair. In addition to the changes in the contralateral primary somatosensory cortex we have shown a significantly increased activation of the ipsilateral primary somatosensory cortex. Several studies in animals suggested that homotopic cortical areas are connected and that a change in one hemisphere is immediately mirrored in the contralateral hemisphere [23]. This increased ipsilateral activation could indicate a compensatory mechanism to tackle the changed afferent nerve impulses.

A hierarchical processing of tactile information has been shown in both humans and non-human primates to suggest a serial processing of tactile inputs from the primary and secondary somatosensory cortex [24,25]. Patients with repaired peripheral nerves activate a network of brain areas known as the task positive network [6], areas that normally activate during processes that demand attention. Together, these findings indicate that patients with peripheral nerve injuries use other areas of the brain in conjunction with the contralateral primary somatosensory cortex to compensate and adapt to the changed afferent nerve impulses. Here, we have shown an increased activation in the contralateral secondary somatosensory cortex, which may indicate a compensatory mechanism.

This study had a long mean time (14 years) since the nerve was injured. This raises the question of how the clinical results compare to those of other studies with a shorter follow up. An earlier study showed appreciable clinical improvement up to 5 years postoperatively [8]. Though the limited population in the present study makes comparisons with other studies difficult it can be noted that mean "total" score in this group increased slightly compared with five-year follow-up (Table I). Interestingly, case 2, who had participated in sensory re-education during phase 1 (from day one after operation) [14], showed clearly better results throughout the clinical assessments (Table I). The aim of such early sensory re-education is to prevent the reorganisation in the somatosensory map. However, in this small group of patients this could not be verified from the fMRI findings.

Here we have shown, in a small group of patients, that after a mean of 14 years after median nerve repair in young adults, the patients show cortical changes in

both hemispheres that corresponded to both the injured nerve and the adjacent uninjured nerve compared with the uninjured healthy hand. Clinical outcome regarding sensory function is generally poor and profound changes are found in the peripheral nerve. Larger studies are needed to investigate the correlation between clinical outcome, neurophysiological changes, and cortical reorganisation in different age groups to understand better the factors that contribute to the clinical outcome over time after nerve repair in the wrist. This may also facilitate the development of new therapeutic interventions.

Acknowledgements

This study was supported by the Swedish Medical Research Council, project no 5188, the Medical Faculty, Lund University, the Skåne University Hospital, Malmö, and Region Skåne (ALF).

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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Paper II

Functional Outcome Thirty Years After Median and Ulnar Nerve Repair in Childhood and Adolescence

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Background: Age at injury is believed to be a factor that strongly influences functional outcome after nerve injury. However, there have been few long-term evaluations of the results of nerve repair and reconstruction in children. Our aim was to evaluate the long-term functional outcome of nerve repair or reconstruction at the forearm level in patients with a complete median and/or ulnar nerve injury at a young age.

Methods: Forty-five patients were assessed at a median of thirty-one years after a complete median and/or ulnar nerve injury in the forearm. The outcome was classified with a total score (the Rosén score), a standardized outcome instrument consisting of three separate domains for sensory and motor function as well as pain/discomfort. In addition, the DASH (Disabilities of the Arm, Shoulder and Hand) score, sensitivity to cold, and locognosia were assessed specifically, together with the patient's estimation of the overall outcome and impact on his or her education, work, and leisure activities. Comparisons were made between injuries that occurred in childhood (less than twelve years of age) and those that were sustained in adolescence (twelve to twenty years of age), and according to the nerve(s) that was injured (median nerve, ulnar nerve, or both).

Results: Functional recovery, expressed as the total outcome score, the sensory domain of that score, and the patient's subjective estimation of outcome, was significantly better after injuries sustained in childhood than after those that occurred in adolescence (87% and 67% of complete recovery, respectively; $p < 0.001$). No significant differences in recovery were seen between median and ulnar nerve injuries, or even when both nerves were injured. Motor function was close to normal, and cold sensitivity was not a problem in either age group. The median DASH scores were within normal limits and did not differ between the groups. Patients who sustained the injury in adolescence indicated that the nerve injury had a significantly higher effect on their profession, education, and leisure activities.

Conclusions: At a median of thirty-one years after a median or ulnar nerve repair at the level of the forearm, nerve function is significantly better in those injured in childhood than in those injured in adolescence, with almost full sensory and motor recovery in individuals injured in childhood.

Level of Evidence: Prognostic Level II. See Instructions for Authors for a complete description of levels of evidence.

The functional outcome after major nerve injuries in adults is often disappointing, especially in terms of the recovery of fine sensory functions^{1,2}. However, children have been reported to have better functional results after nerve repair than adults³⁻⁶. Experimental studies comparing nerve regeneration between mature and immature rodents have

shown axonal outgrowth to be more likely to be slow and incomplete, with substantial misdirection at the site of repair axons, in mature rodents^{7,8}. Misdirected axonal outgrowth leads to a changed signal pattern from the peripheral nerve and thus a cortical reorganization with remapping of the hand representation in the brain^{9,10}. In human adults,

Disclosure: One or more of the authors received payments or services, either directly or indirectly (i.e., via his or her institution), from a third party in support of an aspect of this work. None of the authors, or their institution(s), have had any financial relationship, in the thirty-six months prior to submission of this work, with any entity in the biomedical arena that could be perceived to influence or have the potential to influence what is written in this work. Also, no author has had any other relationships, or has engaged in any other activities, that could be perceived to influence or have the potential to influence what is written in this work. The complete **Disclosures of Potential Conflicts of Interest** submitted by authors are always provided with the online version of the article.

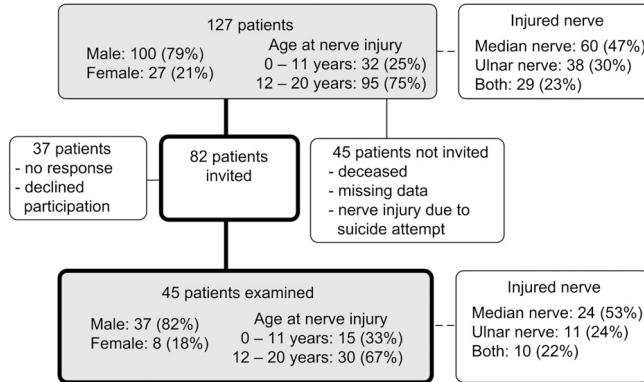


Fig. 1

Overview of the patients with nerve injuries. All were treated for a complete median and/or ulnar nerve injury when they were twenty years of age or younger, between the years 1970 and 1989.

the outcome after a peripheral nerve injury improves up to five years after nerve repair¹¹. The mechanisms behind such an improvement over time are not completely understood. In children, the superior ability of the central nervous system to adapt is claimed to be the most crucial factor in a favorable outcome^{12,13}. However, little is known about the long-term functional outcome following nerve injury and repair in childhood and adolescence.

In addition to the age at nerve injury, prognostic factors include the type of nerve injury, with a complete transection being more severe than a crush injury¹⁴. Furthermore, the timing of surgery is crucial, with better outcomes after early repair^{15,16}.

The aim of the present retrospective study was to evaluate the long-term functional outcome after complete median and/or ulnar nerve injuries in the forearm in patients who sustained the nerve injury and had the repair or reconstruction at a young age.

Materials and Methods

Patients who had been operated on in our hospital for a complete median and/or ulnar nerve injury in the forearm sustained when they were younger than twenty-one years of age, from 1970 to 1989, were identified from the hospital administrative registry system. The hospital receives all children and adolescents with median and ulnar nerve injuries from the southern part (currently 1.5 million inhabitants) of Sweden. A search of the registry system identified 127 patients—100 males and twenty-seven females—who met the criteria (Fig. 1).

The median nerve only was injured in sixty patients; the ulnar nerve only was injured in thirty-eight; and both nerves were injured in twenty-nine, in whom at least one of the nerve injuries was complete. Of the identified patients, forty-four could not be reached (four had died and forty had moved abroad or had an unknown address), and one with a nerve injury due to a suicide attempt was also excluded. Thus, eighty-two eligible participants, all with complete nerve injuries, were invited to participate in the study in 2010. Forty-five (thirty-seven males and eight females) accepted and were exam-

ined. Thirty-seven patients did not respond to our primary invitation and were contacted twice more. However, most of these individuals were currently living far away, and many said that they “had no time to participate” despite repeated letters and telephone calls.

Fifteen participants were eleven years of age or younger and thirty participants were twelve to twenty years of age at the time of the injury (Fig. 1). Of the forty-five participants, twenty-four had injured the median nerve only and eleven had injured the ulnar nerve only. Ten participants had injured both nerves and at least one of the nerve lesions was complete.

The characteristics of the participants and non-participants are presented in Table I.

Previous studies with fewer patients and a shorter follow-up have indicated better function after nerve injury in very young patients compared with adolescents and adults^{15,17-20}. On the basis of this clinical experience, but also the assumption that the start of the maximal growth acceleration in children is at the age of twelve years (eleven years for girls and thirteen years for boys)²¹ and that this might have an influence on the nervous system both peripherally and centrally^{22,23}, the participants were divided into two groups: those who sustained the injury when they were children (less than twelve years of age) and those who were adolescents (twelve to twenty years of age) when the injury occurred. The results of the two age groups were compared.

We also evaluated the results according to which nerve was injured—i.e., the median nerve, the ulnar nerve, or both nerves—and whether a nerve reconstruction procedure had been performed.

Ethics

The study was conducted according to the Helsinki Declaration, and the local ethics committee approved the study design (Dnr 2009/728). All participants gave written informed consent.

Examination

Two hand surgeons and four occupational therapists examined all participants. The same hand surgeon examined forty-two of the participants, and the same occupational therapist examined thirty-four of the participants. A specific protocol was used for all interviews to ensure conformity regarding the questions asked. The medical history of each participant was reviewed. Three participants had a psychiatric disease (two had bipolar disease and one had

TABLE I Participants' and Non-Participants' Characteristics*

	Participants (N = 45)	Non-Participants (N = 82)
Age at nerve repair† (yr)	14 (1-20)	16 (2-20)
Sex		
Male	37 (82%)	63 (77%)
Female	8 (18%)	19 (23%)
Follow-up† (yr)	31 (21-41)	33.5 (21-40)
Dominant hand affected		Unknown
Yes	26 (58%)	
No	19 (42%)	
Level of injury		
Wrist	34 (76%)	65 (79%)
Distal part of forearm	7 (16%)	7 (9%)
Middle of forearm	3 (7%)	5 (6%)
Proximal part of forearm	1 (2%)	5 (6%)
Time to surgery		Unknown
Within 24 hr	33 (73%)	
Delayed	12 (27%)	
Mechanism of injury		Unknown
Cut by glass	38 (84%)	
Cut by porcelain	3	
Cut by saw	2	
Cut by knife	1	
Crush injury	1	
Associated injury		
Total	41	70
Tendon	20 (49%)	30 (43%)
Tendon and artery	19 (46%)	37 (53%)
Subtotal amputation	1	2
Artery only	1	1
Suture technique		
Epineurial	37 (82%)	71 (87%)
Group fascicular	8 (18%)	11 (13%)
Nerve reconstruction (sural nerve graft)		
Total	8	8
Median nerve	5	8
Ulnar nerve	2	
Both nerves	1	
Reconstructive surgery		Unknown
Total	13	
Opponens transfer	6	
Tendon transfer (other)	4	
Flexor tendon tenolysis	2	
Neurolysis	1	

*The values are given as the number of patients unless otherwise indicated. †The values are given as the median with the range in parentheses.

depression); two had diabetes mellitus without current symptoms of neuropathy; and one each had autoimmune hepatitis, asthma, and a cervical disc herniation. These coexisting conditions all developed after the nerve injury.

Assessments

Total Score (Rosén Score) and Subdomains

A diagnosis-specific outcome instrument, the Rosén score, was used as the primary outcome measure²⁴. If both nerves were injured, a mean of the scores of the two tested nerves was calculated. The Rosén score is a standardized clinical evaluation instrument used after nerve repair and consists of three domains: sensory, motor, and pain/discomfort. Each domain comprises specific assessments, and each assessment as well as each domain produces a mean score of 0 to 1. The total score is the sum of the scores for the three domains and the maximum total score is 3, which indicates normal sensory and motor function without pain.

Locognosia (Misdirection)

Locognosia, the ability to localize touch, is an important outcome measure of functional sensibility after nerve repair, and a specific locognosia test was used to evaluate any signs of misdirection²⁵. The participants were asked to identify the standardized area where they perceived a stimulus applied with a monofilament. The locognosia ratio represents the final score divided by the maximum score for the median or ulnar nerve.

Two participants failed to complete the locognosia test because they had difficulties in understanding the instructions.

CISS and DASH

Each patient completed the Swedish versions of two questionnaires: the Cold Intolerance Symptom Severity (CISS)²⁶ and Disabilities of the Arm, Shoulder and Hand (DASH)²⁷ questionnaires.

The CISS was used to evaluate sensitivity to cold. The possible scores range from 4 to 100, and a score of >50 indicates abnormal cold intolerance²⁸. The DASH questionnaire measures the disability of the upper extremity and is a patient-reported outcome instrument^{29,30}. A higher DASH score reflects a greater degree of disability, and a score of 10 has been described as the cutoff point for pathology³¹.

Participants' Subjective Estimation of Overall Outcome and Impact on Education, Leisure, and Profession

The participant's subjective estimation of the overall outcome after nerve repair was investigated with use of a visual analog scale (VAS)^{32,33}. Each participant was asked to estimate the effect of the injury on a paper showing a continuous scale graded 0 to 100 mm, where 0 meant no symptoms or problems and 100 indicated the worst possible outcome. The same estimation was made in response to two questions concerning the subjectively experienced impact on education and on leisure activities after the nerve injury. All participants were asked about their level of education and current profession. In addition, they were asked whether the nerve injury influenced their professional career.

Hand Size

All participants were asked about differences in the sizes of their two hands, and the hand sizes were compared by visual inspection by the hand surgeon of the hand and forearm on both the uninjured and the injured side to investigate whether a nerve injury in the forearm at a young age influences growth of the hand.

Statistical Methods

The data were tested for normality before analysis of any significant difference. Results are presented as medians with the minimum and maximum. Non-parametric tests were used to compare ordinal variables, and chi-square tests were utilized to compare categorical data. A p value of <0.05 was considered significant.

TABLE II Summary of the Results

	Age Groups		
	0-11 Yr (N = 15)	12-20 Yr (N = 30)	P Value*
Functional outcome†			
Rosén score			
Total score (0-3)‡	2.6 (1.6-3.0)	2.2 (0.4-2.8)	<0.001
Sensory domain (0-1): touch thresholds, tactile gnosis, dexterity	0.83 (0.59-1.0)	0.53 (0.10-0.81)	<0.001
Motor domain (0-1): manual muscle test, grip strength	0.91 (0.47-1.0)	0.81 (0.08-1.0)	0.3
Pain/discomfort domain (0-1): cold intolerance, hyperesthesia	1.0 (0.50-1.0)	0.76 (0.17-1.0)	0.02
Questionnaires§			
DASH score (0-100): disability†	0 (0-15)	3 (0-61)	0.08
CISS score (4-100): cold sensitivity†	12 (4-34)	24 (4-74)	0.009
VAS (0-100)†			
Subjective result	12 (1-31)	30 (3-84)	<0.001
Influence on education	1 (0-14)	14 (0-98)	0.008
Influence on leisure	1 (0-99)	18 (0-99)	0.02
Influence on professional career (yes/no)	0 yes, 15 no	11 yes, 19 no	0.007

*Mann-Whitney analysis was used to compare the younger and older age groups, whereas Kruskal-Wallis analysis was used to compare the nerve injury groups. Chi-square analysis was used to compare yes/no answers. P values of <0.05 are indicated in bold. †The values are given as the median with the range in parentheses. ‡The maximum total score of 3 indicates full recovery. §Self-reported questionnaires asking specific questions about outcome and influence.

Source of Funding

The project was supported by grants from the Swedish Medical Research Council and Region Skåne (ALF).

Results

Demographic Characteristics

Demographic characteristics are presented in Table I, and the results are summarized in Tables II and III.

The median age of the participants at the time of the nerve repair or reconstruction was fourteen years (range, one to twenty years), and the median follow-up time was thirty-one years (range, twenty-one to forty-one years). Thirty-three participants underwent surgery within twenty-four hours after being injured, and twelve participants had a delayed repair (thirteen days to fifteen months). The dominant hand was affected in twenty-six of the forty-five cases.

An epineurial nerve repair technique was used in thirty-seven cases, and a group fascicular nerve repair technique was used in eight. Because of a delay in surgery ($n = 7$) or poor function after primary repair ($n = 1$), eight patients were operated on with a nerve reconstruction procedure, in which the sural nerve was used as a cable graft. (In seven patients, the nerve reconstruction procedure was done as the primary procedure; in one patient, the procedure was done as a secondary procedure because of poor function after the primary repair.) The eight patients were twelve to twenty years of age at the time of the reconstruction, and the median time from injury to surgery was four months (range, one to fifteen months). The most common injury mechanism in the series was a cut by glass, and forty-one participants had an associated injury

as described in Table I. According to the standard of care in the 1970s, no vascular structures were repaired in ten participants who had a complete injury to the ulnar or radial artery, as this was not considered necessary. No tendon suture was done in fifteen participants with injuries to the superficial flexor tendons as this also was not considered necessary in the 1970s.

According to their medical history, thirty-one patients (seven children and twenty-four adolescents) had taken part in rehabilitation programs postoperatively. None of those injured in childhood and only two of those injured in adolescence had participated in any sensory re-education program.

Total Rosén Score and Subdomains

We found a significant difference in the total score between those injured in childhood and those injured in adolescence ($p < 0.001$), with a better outcome in those injured as children. Considering that eight of those injured in adolescence had been treated with a nerve graft procedure, we also analyzed their results separately and still found a significantly better total score ($p = 0.001$) for those injured in childhood. The separate results for the patients treated with a nerve graft are summarized in Table II. No differences in the total score were found between the median and ulnar nerve injuries (Table II and Fig. 2). We also found no significant difference in the total score between those in whom both nerves had been injured and those in whom a single nerve had been injured.

In addition to the total score, each domain was analyzed separately (Table II and Fig. 2). In the analysis of the sensory domain and pain/discomfort domain, we found

TABLE II (continued)

Nerve Injury Groups			
Median Nerve (N = 24)	Ulnar Nerve (N = 11)	Both Nerves (N = 10)	P Value*
2.4 (0.4-3.0)	2.4 (1.3-2.8)	2.2 (0.9-2.8)	0.7
0.63 (0.10-1.0)	0.73 (0.36-0.92)	0.60 (0.19-0.88)	0.5
0.94 (0.7-1.0)	0.73 (0.22-0.93)	0.72 (0.08-0.97)	0.001
0.84 (0.17-1.0)	0.84 (0.50-1.0)	0.76 (0.50-1.0)	0.7
3 (0-61)	4 (0-48)	3 (0-28)	0.9
20 (4-74)	14 (4-45)	22 (4-57)	1.0
18 (1-61)	15 (5-84)	27 (3-81)	0.2
2 (0-97)	1 (0-97)	48 (0-98)	0.02
5 (0-79)	1 (0-96)	41 (1-99)	0.01
5 yes, 19 no	2 yes, 9 no	4 yes, 6 no	0.4

significantly better results ($p < 0.001$ and $p = 0.02$, respectively) for those injured in childhood but no difference between median and ulnar nerve injuries. We analyzed the different components of the sensory domain to further investigate the differences (Table III). Significantly better results were

found for all components (sensory innervation, tactile gnosis, and dexterity ratio) for those injured in childhood. However, only the dexterity ratio differed between affected nerves, with a higher ratio in the group with an ulnar nerve injury.

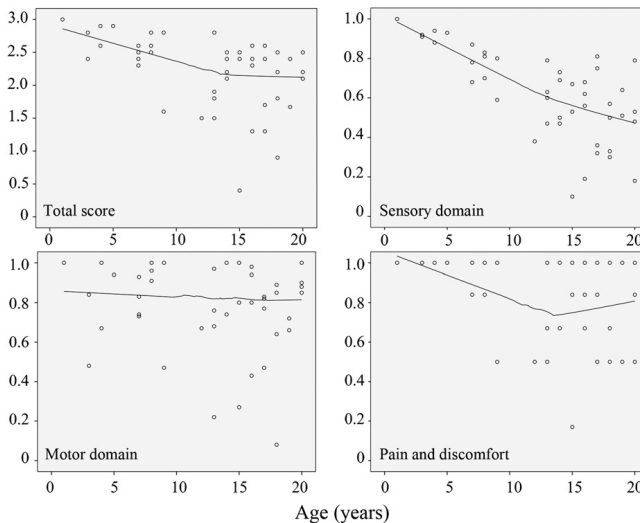


Fig. 2

Total Rosén score and its different domains plotted against age. Note that the total score ranges from 0 to 3, and the sensory, motor, and pain/discomfort scores range from 0 to 1. The smoothing line is fitted due to the Epanechnikov kernel and represents an estimation curve of the distribution of the non-parametric data.

TABLE III Results from the Test Instruments Included in the Separate Components of the Sensory Domain of the Rosén Score and the Locognosia Ratio

	Age Groups		P Value*
	0-11 Yr (N = 15)	12-20 Yr (N = 30)	
Touch threshold: Semmes-Weinstein monofilament ratio†			
Score (0-1)	0.87 (0.80-1.0)	0.80 (0.07-1.0)	0.007
Absolute value (g)	0.40 (0.07-0.40)	0.40 (0.07-450)	
Tactile gnosis: 2-point discrimination ratio†			
Score (0-1)	0.84 (0.00-1.0)	0.33 (0.00-1.0)	<0.001
Absolute value (mm)	6 (3-15)	13 (4-16)	
Tactile gnosis: STI ratio (0-1)††	0.67 (0.50-1.0)	0.33 (0.00-1.0)	<0.001
Dexterity: Sollerman ratio (0-1)†	0.83 (0.67-1.0)	0.67 (0.17-1.0)	0.001
Locognosia ratio (0-1)†	1.0 (0.79-1.0)	0.96 (0.63-1.0)	0.02

*Mann-Whitney analysis was used to compare the younger and older age groups, whereas Kruskal-Wallis analysis was used to compare the nerve injury groups. P values of <0.05 are indicated in bold. †The values are given as the median with the range in parentheses. ††STI = shape-texture identification.

Motor recovery was good overall (Fig. 2) with no significant difference between those injured in childhood and those injured in adolescence. However, a better result ($p = 0.001$) was found in the group that sustained an injury to the median nerve.

Locognosia

In the analysis of locognosia, we found a significantly better result in those injured in childhood ($p = 0.02$). In the entire study group, we found a significantly better result in the participants with an ulnar nerve injury ($p = 0.01$) (Table III).

CISS

Four of forty-five participants had abnormal cold intolerance (i.e., a CISS score of >50), and all had been injured in adolescence. However, a significant difference was found between those injured in childhood and those injured in adolescence ($p = 0.009$), with less cold intolerance in those injured in childhood. No difference in cold intolerance was found with respect to the affected nerve. Thirteen of the participants, all injured in adolescence, reported diminishing intolerance to cold with time.

DASH

We found a low DASH score (median, ≤ 4) among all participants (Table II), but no significant difference was observed between those injured in childhood and those injured in adolescence or between median and ulnar nerve injuries.

Participants' Subjective Estimation of Overall Outcome and Impact on Education, Leisure, and Profession

The estimation of the subjective result differed significantly between the two age groups ($p < 0.001$). Those injured in childhood rated their subjective overall results significantly

better than those injured in adolescence (Table II). However, no significant differences were observed when the injured-nerve groups were compared.

There was a significant difference in the results regarding the estimation of the influence on education between those injured in childhood and those injured in adolescence ($p = 0.008$), with the former having lower estimates (Table II). The participants with an ulnar or a median nerve injury only, in contrast to having both nerves injured, estimated less influence on education ($p = 0.02$).

The estimation of the influence on leisure activities also differed significantly between the two age groups ($p = 0.02$), again with the childhood-injury group estimating less influence. Participants who had sustained an injury to both nerves estimated a significantly higher influence on leisure activities ($p = 0.01$).

While no participants who were injured during childhood reported that the injury influenced their choice of profession, eleven participants who were injured during adolescence reported that their injury did influence their career path. However, no difference was found between the participants with a single nerve injury and those with an injury to both nerves with regard to who went on to a college or university education and who did not. Similarly, no difference in groups (age or nerve-injury) was found in terms of who went on to a white-collar job and who engaged in blue-collar employment. The nerve injury (median, ulnar, or both) had no significant influence on profession (Table II).

Hand Size

There was no difference, as observed by visual inspection, in the size of the hand on the injured side as compared with that on the contralateral side, even in participants who sustained injuries to both nerves at a very young age.

TABLE III (continued)

Nerve-Injury Groups			
Median Nerve (N = 24)	Ulnar Nerve (N = 11)	Both Nerves (N = 10)	P Value*
0.84 (0.07-1.0)	0.87 (0.60-1.0)	0.90 (0.60-1.0)	0.4
0.40 (0.07-0.450)	0.40 (0.07-2.0)	0.24 (0.07-2.0)	
0.67 (0.00-1.0)	0.67 (0.00-1.0)	0.42 (0.00-1.0)	0.8
10 (4-16)	8 (3-16)	13 (4-16)	
0.50 (0.00-1.0)	0.50 (0.00-1.0)	0.50 (0.00-1.0)	0.6
0.67 (0.25-1.0)	0.92 (0.75-1.0)	0.63 (0.17-1.0)	0.001
0.96 (0.63-1.0)	1.0 (0.79-1.0)	0.88 (0.69-0.98)	0.01

Discussion

A median or an ulnar nerve injury at the level of the forearm at young age is a substantial injury with potential long-term disability. Clinical improvement in tactile gnosis can be seen up to at least five years after nerve repair in adults¹¹. However, it is not known if the disabilities after median or ulnar nerve injuries differ according to whether the injury is sustained in childhood or adolescence. In our study, at a median of thirty-one years after median and/or ulnar nerve repair, those injured in childhood presented a significantly better clinical outcome than those injured in adolescence. The significant differences between the two groups were found in the total outcome score, with recovery averaging 87% of normal function in those injured in childhood compared with 67% in the adolescent group. The latter figure is similar to findings in adults five years after median or ulnar nerve repairs in the forearm¹¹. Furthermore, the differences were particularly notable in the sensory domain of the total outcome score. The scatterplots presented in Figure 2 show conformity of the median scores in the sensory domain for the participants who were injured before the age of twelve years and a more scattered pattern in participants aged twelve to twenty years at the time of injury. The observed differences in the total score and in the sensory domain between those injured in childhood and those injured in adolescence remained even after exclusion of participants with nerve injuries requiring nerve grafts in the latter group. This may imply that nerve reconstruction with use of a sural nerve graft is not associated with severely impaired functional results. In contrast to the recovery of sensory function, good overall motor recovery was found among all of the participants, with no difference between the age groups, implying that motor recovery may not be age-dependent. Furthermore, the subjective estimations of the later impact of the injury, evaluated with a VAS, showed generally low impact on participants injured in childhood. However, subjects who sustained the nerve injury in adolescence reported a significantly higher impact on their later profession and education and leisure activities. Thus, a general conclusion is that age is a factor that influences functional outcome.

There may be several reasons for the difference in outcome between those injured in childhood and those injured in adolescence. The young brain's superior capacity to adapt to alterations may be one reason for the better outcome following nerve repair in childhood^{2,34}. However, data on cerebral changes following nerve injuries in childhood are scarce¹³. Specific cognitive capacities of the brain, such as verbal learning and visual-spatial logic ability, help to explain variations in the recovery rate after nerve repair in adults³⁵⁻³⁸. Thus, a strong cognitive capacity is probably one way in which adults compensate for "poor" physiology after nerve repair. It is possible that this is the reason for the good functional outcome observed in some of those injured in adolescence in this study as well as in some adults in previous studies^{35,39}. The outcome following a nerve injury also depends on the postoperative rehabilitation and patient motivation. New strategies for sensory relearning based on the plasticity of the brain have recently been introduced, and studies⁴⁰⁻⁴² indicate that outcome can be improved by such training.

In the whole study group, we found no difference in the total score between participants with median nerve injury and those with ulnar nerve injury. Also, participants who had an injury to both nerves did not show a worse outcome, as measured with the scoring system, than those with a single-nerve injury. However, participants with injuries to both nerves reported a more severe impact on their education and leisure activities, indicating the need for different methods to evaluate outcomes after nerve injuries.

Few participants, and only those injured in adolescence, reported persistent severe cold intolerance. Our results confirm the findings from previous studies that children who are injured when they are very young are less likely to have cold intolerance or chronic pain^{43,44}. The DASH score was low overall, indicating a good patient-reported functional outcome for participants who sustained nerve injuries in the forearm, even if both nerves were injured. This finding is in contrast to those in studies of adults who sustained such injuries, in which a considerable level of disability has been reported⁴⁵. Interestingly, results from the

locognosia test indicate that misdirection does not seem to be a major problem in patients who sustain nerve injuries at the age of twenty years or younger, even if sensory recovery is insufficient in those injured in adolescence.

The present study also shows that a nerve injury in the forearm of a growing child is not associated with future hand size, even if both nerves are injured, in contrast to the hand size difference frequently observed in patients with a brachial plexus birth palsy⁴⁶. The mechanism behind the difference in size after a brachial plexus birth palsy is not known. It is also possible that there is a minor size difference after a median or an ulnar nerve injury in childhood but a visual inspection is not sufficient to detect it.

Measuring outcomes after nerve repair and reconstruction is complex since several different functions, such as sensory and motor dysfunction, pain, cold sensitivity, and impact on daily life as well as professional career and leisure activities, have to be considered. Several methods were used in this study, particularly the total Rosén score, which includes evaluation of many of these factors. On the basis of clinical experience and on animal experiments⁴⁷, it seems that use of different outcome measures may not address the covariance between them, making this a more complex issue. The DASH scores were low; thus a ceiling effect was obtained. This indicates that the DASH score may not be suitable to differentiate remaining symptoms and dysfunction after nerve repair and reconstruction in the forearm. In contrast, measurement of two-point discrimination might have a floor effect, since it is difficult for an adult patient to achieve a useful and measurable value.

Associated injuries to the forearm are common in patients with major nerve injuries⁴⁸, and during the 1970s it was

not standard procedure to repair superficial flexor tendons or isolated ulnar or radial artery injuries, although this currently is the accepted practice. One limitation of a long-term follow-up study such as the present one is that the surgical techniques change over time. We do not know whether the long-term functional outcomes of these injuries would have differed had the patients been treated with current techniques.

One major limitation of the present study is the number of missing patients, which raises the question of selection bias. However, this should be viewed from the perspective of the median thirty-one-year follow-up time and the difficulty in performing similar long-term follow-up studies.

The present study shows that the clinical outcome after median and ulnar nerve repair is better in those injured in childhood than it is in those injured in adolescence. However, this study does not explain the mechanisms behind the observed differences in clinical outcome. Thus, additional studies are warranted to better understand the biological mechanisms behind the clinical results. ■

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Paper III

Poor electroneurography but excellent hand function 31 years after nerve repair in childhood

Anette Chemnitz, Gert Andersson, Birgitta Rosén, Lars B. Dahlin and Anders Björkman

Children, in contrast to adults, show an excellent clinical recovery after a peripheral nerve injury, which may be explained by better peripheral nerve regeneration and a superior plasticity in the young brain. Our aim was to study the long-term electrophysiological outcome after nerve repair in children and young adults and to compare it with the clinical outcome. Forty-four patients, injured at an age younger than 21 years, were assessed by electrophysiology (amplitude, conduction velocity and distal motor latency) at a median of 31 years after a complete median or ulnar nerve injury at the level of the forearm. Electrophysiological evaluation showed pathology in all parameters and in all patients, irrespective of age at injury. No significant differences were observed in the electrophysiological results between those injured in childhood, that is, before the age of 12 years, and those injured in adolescence, that is, between 12 and 20 years of age. In contrast, the clinical nerve function was significantly

better for those injured in childhood (87% of complete recovery, $P=0.002$) compared with those injured in adolescence. We conclude that the mechanism behind the superior clinical outcome in children is not located at the periphery, but is explained by cerebral plasticity. *NeuroReport* 24:6–9 © 2012 Wolters Kluwer Health | Lippincott Williams & Wilkins.

NeuroReport 2013, 24:6–9

Keywords: age, electrophysiology, long term, median, nerve injury, outcome, ulnar

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Received 8 October 2012 accepted 12 October 2012

Introduction

Most patients operated on for a median or an ulnar nerve injury improve over time. Hand function often becomes excellent following nerve repair in those injured in childhood, whereas those injured as adults frequently show a poor clinical outcome [1–3]. The mechanisms behind these differences are not completely understood. It has been suggested that children have a better capacity for regeneration in the peripheral nervous system following an injury [4], whereas others believe that a better cerebral adaptability in the young brain is the reason for the better clinical recovery [5,6]. Few studies have addressed this neurobiological issue. Better knowledge is crucial for the design of new treatment strategies after nerve injuries.

Following a peripheral nerve injury, electrophysiological investigations can be used to localize the injury, analyze the pathophysiology of the injury, assess the severity of dysfunction, and to evaluate the progress of reinnervation [7]. However, there is limited knowledge about the value of electrophysiological studies in the long-term perspective. Previous studies, notably with a shorter follow-up, in animals [8], human adults [9,10], and children [11] have shown a poor correlation between electrophysiological results and clinical outcome after nerve repair.

Our aim was to evaluate long-term electrophysiological results following median and ulnar nerve injuries repaired

or reconstructed at a young age and relate them to the clinical outcome.

Methods

Patients younger than 21 years of age operated on at our hospital for complete median or ulnar nerve injuries in the forearm during the period 1970–1989 were identified and asked to participate in the study. Forty-four of 45 available patients were examined by electrophysiology, 36 males and eight females. The median age at injury was 14 years (minimum 1–maximum 20 years) and the median follow-up was 31 years (minimum 21–maximum 41 years). A difference in the short-term clinical outcome following median nerve repair in children and young adults has been shown [5], where those injured before the age of 12 years had a better clinical outcome compared with those injured between the ages of 12 and 20. Thus, we divided our study group into two subgroups. Fourteen patients (10 males and four females) were aged below 12 years at injury (i.e. childhood injuries) and 30 patients (26 males and four females) were aged 12–20 years (i.e. adolescent injuries). Of the 44 patients, 24 had a median nerve injury, 10 had an ulnar nerve injury, and 10 had injury of both nerves, where at least one of the nerve injuries was complete. Eight patients (all >12 years of age) underwent reconstruction of their nerve injury by sural nerve grafts.

Orthodromic sensory nerve conduction studies were carried out by stimulating the thumb, the index, and the long finger for the median nerve and the little finger for the ulnar nerve. Ring electrodes were placed at the proximal interphalangeal and distal interphalangeal joints for the index, long and little fingers, and just proximal and distal to the interphalangeal joint for the thumb. Recording electrodes were placed over the respective nerve at the proximal wrist crease and 3 cm more proximally. For motor conduction studies, responses from the abductor pollicis brevis muscle (median nerve) and abductor digiti minimi muscle (ulnar nerve) were recorded on stimulation at wrist and elbow levels. The patients' skin temperature was above 30°C during the electrophysiological examination. Amplitudes, conduction velocities, and distal motor latencies were measured. The electrophysiological results of the injured side were expressed as the percentage of those of the uninjured side (controls).

Clinical assessment was carried out using the total (Rosen) score and its subdomains, which is a diagnosis-specific instrument to assess outcome after nerve injuries in the upper extremity [12]. Patients included in this study have recently been included in a study focusing on epidemiology and clinical outcome after nerve injuries in childhood and adolescence (accepted for publishing in *J Bone Joint Surg Am*, Chemnitz et al., in preparation).

At the time of follow-up, two patients had been diagnosed with diabetes (type 1 and type 2) and one with a cervical disc herniation (level C5–6). Patients were specifically asked about any clinical signs of nerve compression or neuropathy on the healthy uninjured side. Two patients had clinical signs of a carpal tunnel syndrome on the uninjured hand and another four patients had no clinical signs of carpal tunnel syndrome, but showed mild pathological electrophysiological values indicating a slight compression of the median nerve in the uninjured hand. In two of these six patients, there were no sensory responses in the injured hand. In the other four patients, the comparison between the injured and the

uninjured hands was affected by the median nerve disorder in the uninjured hand. However, as the pathology in the uninjured hand was very moderate, the values in the tables are not significantly affected.

A nonparametric statistical analysis was carried out and the results are presented as median (minimum–maximum). A *P*-value of less than 0.05 was considered statistically significant. Comparisons were made between injuries sustained in childhood (< 12 years) and in adolescence (> 12 years), between isolated median and ulnar nerve injury (no nerve grafts), and finally, between nerve injuries without a nerve graft and those with nerve grafts in adolescence. Correlations (Spearman's ρ) were performed to calculate any significant correlations between age at nerve injury and the different electrophysiological parameters, and a significant correlation was estimated ($\rho \geq 0.35, P < 0.05$).

The study was carried out according to the Helsinki Declaration and the local ethics committee approved the study design (Dnr 2009/728). All participants provided their written, informed consent.

Results

The electrophysiological results of the injured side, expressed as a percentage of those of the uninjured side, are presented in Tables 1 and 2. All patients, irrespective of age at nerve injury, showed reduced motor and sensory amplitudes, reduced sensory and conduction velocities as well as increased distal motor latencies. No statistically significant differences were found in the different parameters when the results of those injured in childhood and in adolescence were compared (Table 1). Patients with a median nerve injury had significantly lower sensory amplitudes and lower motor conduction velocity compared with patients with an ulnar nerve injury. A significant correlation was only observed between age at nerve injury and the motor amplitude ratio ($\rho = -0.53, P < 0.001$), but not with the other variables.

Table 1 Results from electrophysiology and clinical assessments, comparing age groups and nerve groups

	Age 0–11 years (no graft) (n=14)	Age 12–20 years (no graft) (n=22)	<i>P</i> -value	Median nerve (single nerve injury, no graft) (n=20)	Ulnar nerve (single nerve injury, no graft) (n=10)	<i>P</i> -value
Sensory amplitude (0–100%)	35% (13–73)	32% (0–79)	0.6	26% (0–79)	44% (0–67)	0.04
Sensory conduction velocity (0–100%)	83% (76–97)	79% (0–100)	0.2	81% (0–100)	83% (0–88)	1.0
Motor conduction velocity (0–100%)	91% (76–102)	90% (66–107)	0.9	88% (66–107)	94% (83–102)	0.04
Distal motor latency (0–100%)	115% (89–144)	124% (90–184)	0.1	128% (90–184)	110% (89–155)	0.06
Motor amplitude (0–100%)	72% (23–122)	62% (6–105)	0.1	60% (6–122)	73% (54–88)	0.2
Total score (0–100%)	87% (53–100)	75% (13–93)	0.002	80% (13–100)	82% (50–93)	1.0
Sensory domain (0–100%)	85% (59–100)	60% (10–81)	<0.001	68% (10–100)	77% (38–92)	0.2
Motor domain (0–100%)	89% (47–100)	81% (27–100)	0.5	94% (27–100)	76% (47–93)	0.004

The results represent the value of the injured side to the value of the uninjured side. The total score and its domains represent the percentage ratio of the maximum value. The maximum value of the total score is equal to a normal sensory and motor function without any pain or discomfort. All values are medians (minimum–maximum). Mann–Whitney analysis has been used to compare groups. *P*-value < 0.05 is indicated in bold. When comparing age groups, the grafted patients were excluded. When comparing nerve groups, the six patients with both nerves completely injured were excluded. Three patients had injured both nerves, with only one nerve injury complete. They were included in the analysis as a single nerve injury, which explains the different number of patients.

Table 2 Adolescent nerve injuries, a comparison between nongrafted and grafted patients

	No graft (12–20 years) (<i>n</i> =22)	Nerve graft (12–20 years) (<i>n</i> =8)	<i>P</i> -value
Sensory amplitude (0–100%)	32% (0–79)	3% (0–33)	0.005
Sensory conduction velocity (0–100%)	79% (0–100)	14% (0–91)	0.02
Motor conduction velocity (0–100%)	90% (66–107)	75% (43–107)	0.05
Distal motor latency (0–100%)	124% (90–184)	143% (96–216)	0.5
Motor amplitude (0–100%)	62% (6–105)	27% (2–73)	0.09
Total score (0–100%)	75% (13–93)	63% (30–83)	0.2
Sensory domain (0–100%)	60% (10–81)	42% (18–60)	0.04
Motor domain (0–100%)	81% (27–100)	76% (8–100)	0.5

All values are medians (minimum–maximum). Mann–Whitney analysis has been used to compare the two groups. *P*-value < 0.05 is indicated in bold.

Patients who had undergone direct nerve repair showed significantly higher sensory amplitudes than those who had undergone a reconstruction procedure with sural nerve grafts (Table 2). A similar pattern was observed for sensory conduction velocities. However, with respect to the motor components of the electrophysiology, a significant difference between the two groups was only found in the motor conduction velocity.

The results from the clinical outcome score (total score) and its domains are presented as the percentage ratio of the maximum score in Table 1. Data from the eight patients operated on with a sural nerve graft to reconstruct the median nerve (*n* = 5), the ulnar nerve (*n* = 2), or both nerves (*n* = 1) are presented separately in Table 2.

Discussion

Here, we show that patients with a median and/or an ulnar nerve repair, irrespective of the age at injury and repair/reconstruction, showed pathological changes in all electrophysiological parameters studied after a median follow-up time of 31 years. Apart from the motor amplitude, which correlated with age, no correlations were found between the different electrophysiological parameters and age at nerve injury. Those injured in childhood, in contrast to those injured in adolescence, had an excellent clinical outcome. As the peripheral nerves show pathology to the same extent irrespective of age at injury, the most likely explanation for the difference is a better cerebral plasticity in those injured in childhood. Interestingly, those injured in adolescence show results similar to those injured as adults [13], which suggests that the capacity of the central nervous system to adapt to changed somatosensory information decreases already around the age of 12 years.

Patients who received sural nerve grafts showed very poor results, which may be explained by the fact the injury may have been more severe. Furthermore, a delay in nerve repair is known to influence the outgrowth of nerve fibers [14] and the outcome after nerve repair [15]. Experimental studies have shown that more nerve cells may die and the regrowth of nerve fibers, as well as their remyelination, may be poor following delayed nerve repair [16]. In addition, the sural nerve is a sensory nerve that is used as grafts for both sensory and motor

function. Differences in the myelin sheath [17], with less myelination in the sural nerve, together with an impaired axonal outgrowth through sural nerve grafts are possible explanations for the poorer electrophysiological results in grafted patients.

Following a peripheral nerve injury and repair, the patients often gradually recover both sensory and motor functions over time [13,18]. Interestingly, previous studies have shown that the sensory recovery may continue for a longer period of time than the motor recovery [13]. In addition, mechanisms related to regeneration, such as the presence of transcription factors (e.g. ATF 3) in the neurons, last longer in sensory neurons than in motor neurons [19]. However, when considering the long follow-up in the present study, the nerve regeneration process is most likely finished. The present findings imply that there could be different mechanisms behind sensory and motor recovery after a nerve injury, which is further supported by the fact that the motor amplitudes were less reduced than the sensory amplitudes.

Two interesting questions arise in this context. Why is clinical motor recovery superior to clinical sensory recovery and why is sensory recovery significantly better in those injured in childhood? One neurobiological explanation for the superior clinical motor recovery could be the ability of each regenerating axon to reinnervate as many as four to five times the normal number of muscle fibers [20], thereby compensating for the reduced number of axons that succeed in reaching the denervated muscle. However, the significantly better clinical motor and sensory recovery seen in those injured in childhood cannot be explained by electrophysiological detectable differences in the peripheral nerve. Instead, this suggests that the mechanism behind the better results could be changes in the central nervous system. It is likely that the misdirection of the outgrowing nerve observed at the repair site [21] is similar in all age groups and that the altered signal pattern from the periphery along the sensory axons to the central nervous system is similar. Using different neuroimaging techniques, considerable changes with a destroyed finger somatotopy in the hand area of the primary somatosensory cortex have been shown in adults following peripheral nerve injuries in the upper extremity [22,23]. It is well known that the young brain has a superior adaptability to change [24], and this

superior plasticity can allow the young brain to adapt to the change in afferent nerve signals as well as interpret the new signal pattern in a way not possible for the older brain.

Conclusion

Thirty-one years after nerve repair, when the nerve regeneration process is completed, electrophysiological results are still poor, irrespective of age. Thus, changes in the peripheral nervous system cannot explain the superior clinical outcome in patients injured in childhood.

Acknowledgements

Supported by grants from the Swedish Research Council (Medicine), the Swedish Society for Medicine, Zoega's Fund, HKH Kronprinsessan Lovisa's Fund, Lundgren's Fund, Region Skåne, and Funds from Malmö University Hospital. The authors thank technician Lena Goldberg for all the help.

Conflicts of interest

There are no conflicts of interest.

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Paper IV

Paper V

RESEARCH ARTICLE

Open Access

Consequences and adaptation in daily life – patients' experiences three decades after a nerve injury sustained in adolescence

Anette Chemnitz*, Lars B Dahlin and Ingela K Carlsson

Abstract

Background: To explore the patients' experiences during the three decades following repair of a nerve injury in the forearm and its consequences for daily life. Strategies that were used to facilitate adaptation were also investigated.

Methods: Fifteen participants with a complete median and/or ulnar nerve injury repaired in the ages from 13–20 years were interviewed using a semi-structured interview guide. The median follow-up time was 31 years (range 23–40). The participants were asked to describe the past and present symptoms of the injured hand, the consequences of the injury for daily life, personal qualities and support from others. In addition, they were asked to describe strategies used to facilitate adaptation. The interviews were subjected to content analysis.

Results: The nerve injury lead to sensory and motor deficits in the injured hand, as well as sensitivity to cold and secondary back problems. Emotional reactions to trauma and symptoms related to post-traumatic stress disorder were described, as well as how they managed to cope with such reactions. There was a noticeable impact on education, leisure, professional or domestic life for some, while others could continue by changing e.g. their performance pattern. The participants' life roles and relations were also affected. Both emotion- and problem-based strategies were used to manage challenges in daily life.

Conclusions: The present qualitative study can help us to provide the patient with honest and realistic information about what to expect after a nerve injury at forearm level, without eliminating hope. Emotional reactions to trauma should be identified and dealt with. In addition, health-care professionals can promote a variety of coping mechanisms to facilitate daily living for the injured patients.

Keywords: Peripheral nerve injury, Outcome, Consequences, Adaptation, Adolescence, Qualitative study

Background

Nerve injuries at forearm level may have a variety of serious consequences for the individual and for society. Reduced sensibility, grip function and dexterity as well as cold sensitivity are common, known symptoms [1-5]. However, patients may also be affected psychologically by such an injury. Recent studies have shown high rates of depression after nerve injury in the upper extremity [6] and after severe hand injuries [7-9]. Symptoms of posttraumatic stress disorder are often overlooked, despite the importance of considering the psychological

status when caring for patients with hand injuries [7]. In published papers about treatment after a peripheral nerve injury, the focus is mainly on how to enhance motor and sensory recovery [10-12]. Nevertheless, the patients' past medical history, personality, social and cultural background, occupation and hobbies all need to be considered in order to optimise long term satisfaction in the patient [13].

Recently, we published a long-term follow-up of functional outcome after repair of median and ulnar nerve injuries performed in childhood and adolescence [14]. This retrospective study with a median follow-up of 31 years shows that the nerve injury had had a significant impact on education, leisure activities and choice of

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profession for the patients injured in adolescence. Such aspects, as well as psychological aspects in the long term, have not been sufficiently considered previously. Our present aim was therefore to explore patients' experiences of the nerve injury and its consequences for daily life during the three decades following the repair. In addition, we wanted to investigate the personal qualities and strategies that were used to facilitate adaptation.

Methods

Participants

These participants were included in a larger study focusing on the epidemiology and the long-term clinical outcome after nerve repair in childhood and adolescence [14]. The results show a significant impact on education, leisure activities and choice of profession only for patients injured in adolescence. In the current interview study, we wanted to explore this group of patients further and purposive sampling was used giving a variation in age at injury, gender, type of nerve injury and whether the dominant or non-dominant hand was injured. The inclusion criteria were as follows: the participants should not suffer from other serious disorders that might overshadow the experience of the nerve injury; they should be free from current psychiatric or cognitive disorders; and they should be able to communicate in Swedish. Thirty participants in the former study were aged 12–20 years when the nerve injury occurred and was repaired. Two of these were suffering from a current psychiatric disorder and 20 participants were identified as eligible for the present study. The eligibility was decided by the results from the larger study [14] and defined by those who had experienced a considerable impact on their professional career, and/or on their education, and/or on leisure activities. Five declined participation due to lack of time or living too far away; fifteen accepted (twelve males and three females) and joined the present qualitative study in the year 2012. The median age when the nerve injury was sustained was 16 years (range 13–20) and the median follow-up time was 31 years (range 23–40). The dominant hand was affected in nine cases and there were nine participants with a median nerve injury, one with an ulnar nerve injury and five with both median and ulnar nerve injuries with a least one completely cut. Sural nerve grafts harvested from the lower leg were used in three participants. All participants completed several self-report questionnaires (Swedish version) before the interview; the DASH (Disability Arm Shoulder hand) [15], the CISS (Cold Intolerance Symptom Severity) [16,17] and the VAS (Visual Analogue Scale) [18] for impact on education and leisure activities and finally the Sense of Coherence (SOC) condensed 13-item scale [19]. The SOC questionnaire is based on the salutogenetic theory

introduced by Antonovsky more than 30 years ago [20] in which he claims that the way people view their life has a positive influence on health. The patient's replies in the questionnaires reflect their disposition to see the world as comprehensible, manageable and meaningful [21].

The participants' characteristics, including the clinical results, are presented in the larger study [14] and in Table 1 for comparison.

Procedure and ethics

Written information was given by the first author emphasizing the aim and voluntary nature of the study. The last author then contacted patients and an interview time was set up with those who agreed to participate. Written consent was obtained in conjunction with the interview and patients were informed about how the data would be analyzed and were assured of confidentiality in the reporting. The study was conducted

Table 1 Participant characteristics in the study (n=15)

Age at nerve injury	16 (13–20)
Gender: male/female (n)	12/3
Years of follow-up	31 (23–40)
Dominant hand (n), yes/no	9/6
Mechanism of injury (n)	
Cut by glass (window or bottle)	13
Cut by porcelain	1
Crush injury	1
Injured nerve (n)	
Median nerve	9
Ulnar nerve	1
Both nerves	5
Rosen score (0–3)	2.1 (0.4–2.5)
	25/ 75 percentile 1.7/ 2.3
DASH (0–100)	8 (0–61)
CISS (4–100)	41 (10–74)
Impact on profession yes/no (n)	7/8
VAS education (0–100)	76 (0–98)
VAS leisure (0–100)	52 (1–98)
SOC (13–91)	68 (52–89)

Values are medians (min-max if not specified as number (n) or percentile). The participants are a heterogeneous group of patients from a previous study [14]. The total Rosen score is the sum of three different domains; sensory, motor and pain/ discomfort [27]. The maximum score is 3, which indicates a normal sensory and motor function without pain or discomfort. The cut-off for a pathological CISS score is 50 [17] and four participants had a pathological score. The impact on education and leisure activities was estimated with the use of VAS (Visual Analogue Scale) where 0 means no symptoms or problems and 100 indicate worst possible outcomes. We used the condensed 13-item version of the Sense of Coherence scale [19].

according to the ethical guidelines stated in the Helsinki Declaration and approved by the local ethics committee of Lund University (Dnr 2009/728). All interviews were performed and tape-recorded by the last author, in a quiet room at the clinic and lasted from 30-77 minutes (mean 45 minutes). The interview started with a repetition of the aim of the study. A semi-structured interview guide with open questions was then used and the participants were asked to describe the symptoms of their nerve injury, the consequences for their daily life, personal qualities and support from others. In addition, they were asked to describe strategies that facilitated adaptation and how symptoms and consequences had developed over time. Follow-up questions were asked such as: How did you experience that? How did you handle that? Can you describe that in more detail? A secretary transcribed all the interviews verbatim, marking nonverbal expressions and all transcripts were checked for accuracy by the last author. The first author did the translation from Swedish to English and the last authors then verified the translation.

Data analysis

The text was read and reread by the first and last co-authors and a content analysis was performed [22]. The analysis started with a naive reading of each interview in order to gain a general impression of the content. Meaning units, that is words or phrases related to the aim of the study, were identified and coded with reference to the questions: "What is it about? What does it mean? What effect does it have?" [23]. The first and last authors discussed their impression of the text and compared their selected meaning units. Meaning units and codes that were similar in content were grouped together as categories. Similar statements within each category were analyzed critically, read and compared to achieve a reasonable interpretation. The categories were then discussed with the second author and adjustments were made to make sure that the categories covered all aspects. Finally, the categories were compared with the text and with each other. The second author read seven randomly selected interviews and reviewed the different codes and the categories. Concerning the authors' pre-understanding, the first and second authors are experienced hand surgeons, the last author is an experienced occupational therapist specialized in hand rehabilitation. All three authors work in specialized unit. Both the second and the last authors are familiar with qualitative research methodology [24,25].

Results

An overview of the main categories and the subcategories is presented in Table 2, including the participants' experiences of symptoms related to the nerve injury, its

consequences for daily life and the strategies and personal qualities important for adaptation. Furthermore, the participants described the information and support they would like to receive from the health care system.

Symptoms experienced and adaption strategies

A reduced *sensibility* in the injured hand was described, still present after three decades - "It feels like dental anaesthesia" or - "My hand feels dead, like a clump". Certain participants described some improvement of the sensibility over time - "It took ten years" or - "It took twenty years before sensation came back". It was important to use *vision* or the *non-injured hand/non-injured fingers* to compensate for the reduced sensation when performing tasks that require hand control - "I have to see what my fingers are doing". Another participant with a median nerve injury said - "My little finger is mine for sensation". A participant with a left-side injury explained - "I never put my keys in my left-hand pocket". Others stated - "I have learned how to write with my other hand" or - "I have become more ambidextrous". Different *tricks* were mentioned by the participants for managing difficulties in daily life such as - "I use my nail to feel the edge" or - "When I sew, I will soak my finger to be able to push the needle through". *Assistive devices*, such as a pen or a potato peeler with a thickened grip, could enable participants to manage the challenges of daily life.

The reduced sensations led to an awareness of the risk of a new injury and many reported burning, cutting or squeezing their hands because of lack of sensation. However, there were participants who said that having sensibility was not as important for them as having strength - "I can do without sensibility".

Remaining *pain* and *allodynia* over the surgical scar were also symptoms described during the interviews - "Like an electrical shock". Other problems experienced were reduced *dexterity* and *numbness* in situations such as buttoning up a shirt or holding a pen and writing. While some participants said that it was difficult to know the amount of *grip strength* needed for a task, such as writing, others had no problems.

The symptoms described in connection with *cold sensitivity* were freezing more quickly, colour changes, stiffness and reduced dexterity. Pains, aches and dryness were other consequences. The symptoms had either decreased or increased over the years and were triggered by low temperatures, moist conditions or weather changes. Such symptoms were present even during summer time - "I cannot go on boat trips in summer time". Strategies to relieve cold sensitivity were mentioned such as wearing thick warm gloves when exposed to cold - "I wear a glove even in summer time" or - "I will put my hand in lukewarm water" - to speed up the time needed for re-warming.

Table 2 An overview of the main categories and the subcategories

Main categories	Subcategories		
Symptoms experienced and adaption strategies	Symptoms	Sensibility	
		Pain/allodynia	
		Dexterity	
		Numbness	
		Grip strength	
		Cold sensitivity	
		Secondary back/neck problems	
		Adaptive strategies	Vision
			Non-injured hand/fingers
			Tricks
Assistive devices/warm gloves/warm water			
Emotional reactions to trauma and adaptation	Symptoms	Shock*	
		Depressive symptoms	
		Isolated*	
		Bitterness	
		Frustration	
		Anger	
		Grief	
		Identity	
		Ashamed	
		Fear *	
Adaptive strategies	Social support		
	Dissociation*		
	Minimization		
	Avoidance*		
	Acceptance		
	Hide/cover up*		
Consequences for education and support provided	Consequences	Fell behind	
		Grades affected	
		Retake a school year	
		Choose different education	
		Not believed/no understanding	
		Adaptive strategies	Assistive devices
			Information and support teachers/school mates
			Oral instead of written task/examination
		Consequences	Choice of profession

Table 2 An overview of the main categories and the subcategories (Continued)

Consequences for professional life and adaptation	Adaptive strategies	Obstructed the performance	
		No support from employers and authorities	
		Realistic career plans	
		Vision	
		Avoidance	
		Changed performance	
		Develop new skills	
		Consequences	Role as a parent and spouse
			Managing daily life
		Adaptive strategies	Open communication
Ask for help			
Assistive devices			
Consequences for leisure activities and adaptation	Consequences	Activities impossible/could still perform	
		Avoidance	
Personal qualities	Adaptive strategies	Develop new interests	
		Persistence/ Endurance	
		Positive attitude	
		Problem-solver / Creative	
		Competitiveness	
		Purposefulness	
		Avoid showing vulnerability	
		Refusal to be a victim	
		Enhance other capacities	
		Information and support wanted from the healthcare system	Adaptive strategies
Help with assistive devices			
Help with insurance issues			
Consequences	Adaptive strategies	Psychosocial counselling	
		Meet other patients	

Consequences and adaptations strategies are presented as well as personal qualities and information and support wanted from the healthcare system. The asterisk represents symptoms related to post-traumatic stress disorder.

During the interviews there were reports of *secondary back and neck problems* related to the injured hand. The asymmetrical strain of trying to compensate for the reduced hand function had led to back pain and even sick leave in some cases. Since a few had undergone a nerve reconstructive procedure with a sural nerve graft harvested from the lower leg, there were also reports

about donor site morbidity, such as pain/ache and reduced sensibility in the foot.

Emotional reactions to trauma and adaptation

The participants gave very detailed descriptions of how the accidents occurred, despite the length of time that had passed. The trauma was a *shock* causing subsequent nightmares and flashbacks - "I can still wake up and hear the sound of broken glass". However, some had amnesia about the event. Distorted thoughts about the injured hand were described, such as - "It was not mine; it was strange and disgusting..."

As they were teenagers when the injury occurred some stated it made them realize that they were not immortal. *Depressive symptoms*, such as feelings of sadness, darkness and hopelessness were mentioned. In addition, participants described living a passive life after the injury, *isolated* and withdrawn from social events. *Bitterness*, *frustration* and *anger* over the situation were mentioned during the interviews and a sense of *grief* over the hand and the life they had before the trauma was expressed. Their *identity* changed with the trauma and one participant said - "I became the injury". Another participant still felt *ashamed*, 31 years later, for not telling the truth about how the injury occurred throughout the years. In the interviews, the participants described different strategies used to cope with the trauma experienced in the acute phase and later in life. Some participants described the *social support* from family and friends as very important for processing the trauma and stressed the importance of talking to others about it. Another strategy described was to try to *dissociate* oneself from the circumstances after the nerve injury. *Minimization*, comparing oneself with other hand-injured patients, was mentioned. In addition, comparisons with other disease groups, such as disabled people gave one perspective - "You have to play down the situation, it is only a hand". Following the trauma and currently, an awareness of risks and a *fear* of a new injury existed - "I am still afraid of windows". By *avoiding* certain situations, they tried to protect themselves and their family members. *Accepting* their limitations were important, as well as accepting the new appearance of the forearm - "You learn to live with your defects". Another way of dealing with the new appearance was to *hide* or to *cover* the hand with scarves or bandages. One participant said - "For several years, I wore a thin bandage around my hand to hide it, but later I decided I was done with that..."

Consequences for education and support provided

Being of school ages when the injury occurred created difficulties for the participants, according to their description. Hospitalization and time for rehabilitation led to absence and they *fell behind* with their schoolwork.

Their *grades* were *affected* negatively, especially in more practical school subjects, such as drawing, crafts and physical training. Some had to *retake a school year* or *choose a different education* - "The ninth grade was completely ruined". Another participant stated - "I was determined to become a physical education teacher, but no, it was impossible". However, others stated that the injury had no influence on their education and that they were able to choose future occupations such as truck drivers and janitors - "My injury has not been permitted to limit my career choices". No obvious associations were found between the consequences of a single nerve injury as opposed to injury to both the median and ulnar nerve, or to injuries affecting the dominant hand as opposed to the non-dominant hand. Several participants described how their teachers did *not believe* them when they said they had difficulties with writing for example. *Assistive devices* were scarcely used. During the interviews some mentioned that their teachers and schoolmates provided no support or had *no understanding*. However, others said that their friends in school did actually *help* them to perform difficult tasks. Another example of support received was that the head teacher *informed* all the other teachers about the participant's nerve injury and suggested alternative tasks for the student, such as an *oral instead of a written task*.

Consequences for professional life and adaptation

The nerve injury had influenced some of the participants' *choice of profession* and some expressed sorrow at being unable to follow their chosen path. However, others felt that the injury constituted no hindrance. One person explained - "With my job as an ambulance driver I meet patients like myself...when they say that their lives are ruined, I am a living example of the opposite". The participants advised future patients to talk to family and friends, teachers and guidance counsellors about their future *career plans* and to try to be *realistic* - "Maybe you cannot become the tennis player that you always dreamt about". The hand function after the injury, with reduced grip strength, dexterity and sensibility *obstructed the performance* of certain work tasks. Various occupations were represented in the study group, such as electrician, plumber, janitor, truck driver, ambulance driver and teacher. Through using *vision* and changing the technique they used, several participants could compensate for reduced function by themselves. Examples given were - "I know what the bolt looks like so I can screw it on anyway" or - "I wrote every article by hand using paper and a pen. I then proofread it and rewrote it on the typewriter". While some *avoided* difficult occupations, others continued, but *changed* their *performance pattern*. Certain participants described how they had altered their work tasks, *developed new skills* or

patience with their performance - "The impossible just takes a little more time". One participant worked as a chef, and had difficulties handling a knife and performing tasks that demand fine motor ability. However, this did not stop him from continuing in the same profession. Another participant had been in the military - "It takes a lot of time to assemble a weapon in the darkness". Some experienced problems such as pain, numbness and reduced grip function when working outdoors, exposed to a cold and windy environment, which meant they needed a longer time to perform the work. Other described experiences of receiving *no support* and little understanding from *employers and authorities* after the injury. They felt that they often had to struggle against social insurance and employment offices.

Consequences for domestic life and adaptation

Several situations were described where, in their *role as a parent*, the injury had had consequences, for example playing with their children and changing diapers - "When I walk with my child holding hands, if I use my healthy hand then I hold their hand, otherwise they hold my hand". Concerns about family members injuring themselves were expressed, as well as admissions to being overprotective - "I get angry if my children are taking risks". "The children are not allowed to be close to the glass window". In their *role as a spouse*, intimacy was affected in various ways - "I never fondle with my injured hand" one participant stated. Another described - "Walking with my girlfriend holding hands, I had to choose the right side". Furthermore, one participant stated - "In bed, I have to choose the right side; intimacy does not work so well, we are less spontaneous". However, some of these problems could be avoided by open *communication* with their partners. *Managing daily life* could entail difficulties in peeling potatoes or handling cutlery in the kitchen. Fastening and unfastening a necklace or a shirt with buttons could be impossible and *asking for help* led to irritation. Participants described how using assistive devices, such as a pen or a potato peeler with a thickened grip, enabled them to manage.

Consequences for leisure activities and adaptation

Several *activities* were reported as being *impossible* after the nerve injury, such as playing the guitar, tennis or table tennis. Numbness, a tendency to muscular cramp and tiredness in the hand were symptoms that affected performance. Various participants also *avoided* such activities as volleyball and soccer, because of the risk of the ball hitting the scar formation on the forearm. The participants said they *found new interests* and activities instead. While some reported difficulties with outdoor activities, such as fishing, hunting and playing hockey,

because of sensitivity to cold, others experienced no problems with skiing or skating. Running and riding a motorbike were other *activities* that some *could still perform*. One participant had been one of the most promising athletes in the country in his sport but - "Because of the injury, I lost so much, I could not come back".

Personal qualities

All participants were asked which personal qualities had been important for them when dealing with life after the nerve injury. *Persistence* and *endurance* were frequently mentioned - "You have to be patient...never give up". Participants said during the interviews that they had matured during the process of dealing with the consequences. A *positive attitude* towards obstacles, trying to see the possibilities instead, was also important - "You have to believe there is a solution for everything". Participants described themselves as *problem-solvers*, imaginative and *creative*, having to adjust to new ways of performing different tasks. Characteristics such as *competitiveness* and *purposefulness* were also reported - "Nothing is going to stop me". Some believed that they *avoided showing vulnerability* by being proud and not asking for help; others *refused to victimize* themselves. One statement explained how the nerve injury had *enhanced other capacities* - "At work, I will always turn down a written task, however I will always say yes to a verbal task".

Information and support wanted from the healthcare system

All participants expressed a desire for information and support from the health care system after the nerve injury. A need for *oral and written information* about the consequences of the nerve injury to be used in school or at work was stated. The participants importantly expressed the wish for clear and honest information about the expected consequences and prognosis, without eliminating hope. Other wishes were for help with *assistive devices* and *insurance issues*. Most participants were teenagers at the time of the nerve injury and sometimes did not understand the medical language used by adults. The importance of the healthcare staff involved in the treatment talking directly to the child or teenager, not only to their parents, was emphasized. Involving the relatives in the information and in the rehabilitation process could be a good support. *Psycho-social counselling* was introduced in our clinic in the middle of the 1970s and many described a wish for such support. It was emphasized that simple questions, like "how are you" or "how are you coping", should be asked and that enough time should be given to listening to the answers. Taking part in the rehabilitation program was

considered important and never giving up—"It is your choice". Meeting other patients with severe hand injuries was also said to be important, especially if the other patient had got further on in their rehabilitation process.

Discussion

This study shows that a nerve injury in the upper extremity will have various consequences for the adolescent patient from a long-term perspective. Our participants experienced the commonly known functional deficits in the injured hand, as well as cold sensitivity. However, secondary problems, such as back problems, were also mentioned. The symptom severity, its consequences and adaptation to daily life in this group of patients reveal an impact on all levels outlined in the ICF (International Classification of Functioning, Disability and Health) [26], including activity limitation and participation restriction (Figure 1). The novel findings are the different emotional reactions to trauma and symptoms related to post-traumatic stress disorder described by the participants as well as how they managed to cope with such reactions. The participants stressed the need for support from the healthcare system, taking into consideration both physical and emotional needs. In addition, schoolteachers should be informed about such injuries, allowing them to provide help and understanding. Professional life and work performance changed completely for some while others simply changed their pattern of performance. Finally, something not clearly emphasized earlier, their life roles and the relations were affected.

The symptoms described as problematic by the study participants are in line with the different domains included in the Rosen score (sensory, motor, pain/discomfort) [27]. This further validates this outcome instrument on the level of body function [26]. However, the impact on the activity and participation level needs to be addressed using other outcome measures, sensitive to changes over time and valid for nerve injuries [1].

New findings were symptoms related to post-traumatic stress disorder (PTSD) such as subsequent nightmares, flashbacks, avoidance and isolation. PTSD has previously been reported after acute hand injuries [7,9] and can have an impact on the outcome of the injury. However, there was no systematic screening for PTSD during the interviews in this study but this needs to be explored further in the future.

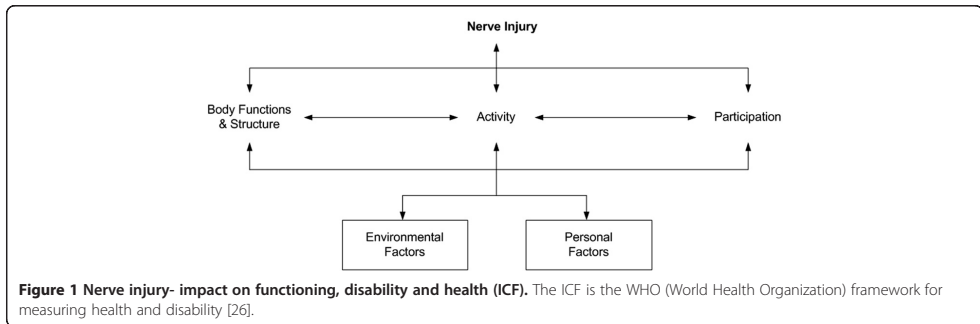
To learn more about the participants' disposition to respond to stressful situations we used the condensed 13-item SOC questionnaire. The results reflect the SOC of the study participants three decades after the nerve injury (Table 1), where the median score of 68 indicates that the study participants had a high ability to comprehend, manage and find a meaning in their situation [19].

This is further supported by the diverse and abundant adaptation strategies described during the interviews.

In our previous study, we asked the participants about the nerve injury's impact on leisure activities and education [14]. The current study adds more information about how their schoolwork was affected and shows that some participants had to retake a school year or change their course. This needs to be considered when treating patients who are still students. In addition, we should involve adults who see such youngsters in other settings, inform them about the seriousness of the injury and ask them to be aware of the symptoms and consequences following the trauma [28]. Healthcare staff should also consider how they communicate with adolescent patients and their individual learning style, such as visual or auditory. Written educational brochures can reinforce oral information. By helping the patient to recall and understand we can enhance adherence to treatment and satisfaction [29,30].

The impact on engagement in leisure activities after nerve injuries should be explored and support given when needed. It might still be possible for the patients to engage in the activity if they receive guidance on how to change their performance technique or are provided with assistive devices. The ability to perform meaningful activities and to maintain their roles in life are important for the patients' quality of life [6,25,31]. The interviews described changes in life roles, as a parent and as a spouse, over the years. After the nerve injury, some participants felt dependent on practical help but could not accept the need for help from their children, as this would mean defeat. Interestingly, in the interviews, the participants described how intimacy with a partner could be affected by a nerve injury in the forearm. Not only will lack of sensation and dexterity lead to difficulties with intimacy, one also has to consider the new appearance of the hand and the patient's perception of body image. Publications about sexual dysfunction after traumatic hand injuries are scarce [32]. These issues need more attention and should be further investigated to better help patients with hand injuries in general and nerve injuries in particular.

Coping strategies mentioned in this study are similar to those previously described after hand injuries [24,25,33]. Problem-based strategies [34], such as using vision or the non-injured digits or hand instead to compensate for the functional loss, were mentioned. Assistive devices, tricks or different ways of performing tasks and activities enabled them to master challenges in daily life. Enhancing other capacities or reorienting and finding other activities instead were also mentioned. Different emotion-based strategies [34] in the acute phase and later in life were described. Avoiding many questions from others by hiding or covering up the hand and accepting one's limitations



were ways of adapting to the situation, as well as comparing oneself with others in worse circumstances and minimizing one's own situation. Social support from others was important for processing the trauma and rehabilitation groups where patients can share their experiences and meet others who have got further in their rehabilitation process can play an important role.

Patients with a nerve injury today receive postoperative care that is quite different from that given to the participants in this study. It is believed that cerebral reorganisation plays a crucial role after a peripheral nerve injury [12] and early (phase 1) and late (phase 2) sensory relearning has been introduced. Studies indicate that sensory relearning can improve the functional outcome after a nerve injury [35] and early onset is advocated [2]. In addition, patient motivation is also important for the outcome after a nerve injury [36,37] and early referral to mental health professionals can reduce psychological morbidity after a severe hand injury [6,8,13]. Dealing with the psychological distress and individual perception of the injury might improve patient adherence to rehabilitation and enhance the outcome of treatment [38].

Content analysis was used to study an individual process occurring over long period of time and the trustworthiness of the findings was evaluated by establishing credibility, dependability and confirmability [22]. Credibility was achieved by using purposive sampling and as shown in Table 1, the participants' results show a wide variation in the different parameters. The small proportion of women corresponds to the typical pattern found in the clinic and to hand injuries in general [39,40]. Dependability was achieved by the co-authors reading and coding all the interviews independently and by in-depth discussions, analysis and interpretation of the text together. Representative quotations from all participants are presented in the text in order to increase the trustworthiness of the statements. Confirming and clarifying information during the interviews ensured

confirmability. The risk of over-interpretation was reduced by focusing consistently on the text throughout the analysis. We used pre-defined open questions, but the transferability in this study is limited since the participants represent a small study group. However, using in-depth interviews allows the patient to spontaneously reveal problems and other information not reported if more structured self-report questionnaires are used.

Conclusions

This study shows that treating patients with nerve injuries at forearm level is complex and requires attention to other aspects as well as to repair the damaged nerve. In the clinical practise today it can help us to provide the patient with honest and realistic information about what to expect after a nerve injury at forearm level. Healthcare professionals can promote different coping mechanisms in order to facilitate the daily living for the injured patients. In addition, emotional reactions to trauma and symptoms related to post-traumatic stress disorder should be identified and taken care of immediately. With a better understanding, we might be able to improve the outcome after a nerve injury and the patient satisfaction in the future.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

AC, LBD and IKC participated in the design of the study. IKC conducted the interviews. AC and IKC read and analyzed the data from the interviews. The categories were discussed with LBD and adjustments were made to make sure that the categories covered all aspects. LBD read seven randomly selected interviews and reviewed the different codes and the categories. AC wrote the manuscript and LBD and IKC revised and approved the manuscript. All authors read and approved the final manuscript.

Acknowledgements

This work was supported by grants from the Swedish Research Council, Promobilia, Region Skåne, Lund University, Carlsson's Foundation and by the European Community's Seventh Framework Programme (FP7-HEALTH-2011) under grant agreement no. "278612".

Received: 16 May 2013 Accepted: 21 August 2013
Published: 22 August 2013

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doi:10.1186/1471-2474-14-252

Cite this article as: Chemnitz et al.: Consequences and adaptation in daily life – patients' experiences three decades after a nerve injury sustained in adolescence. *BMC Musculoskeletal Disorders* 2013 **14**:252.

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