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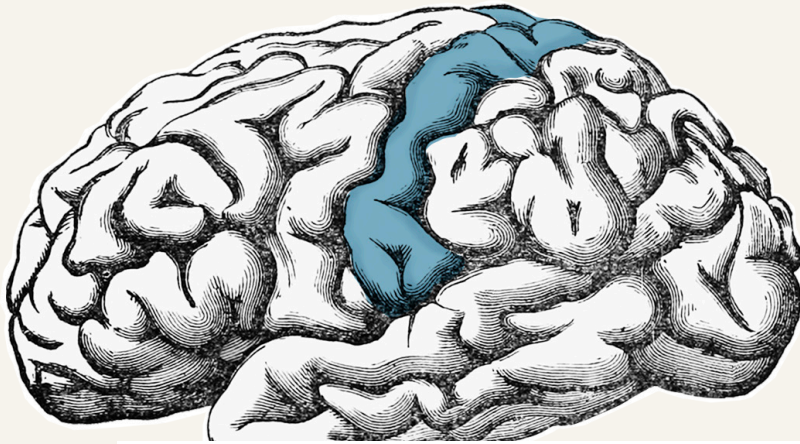
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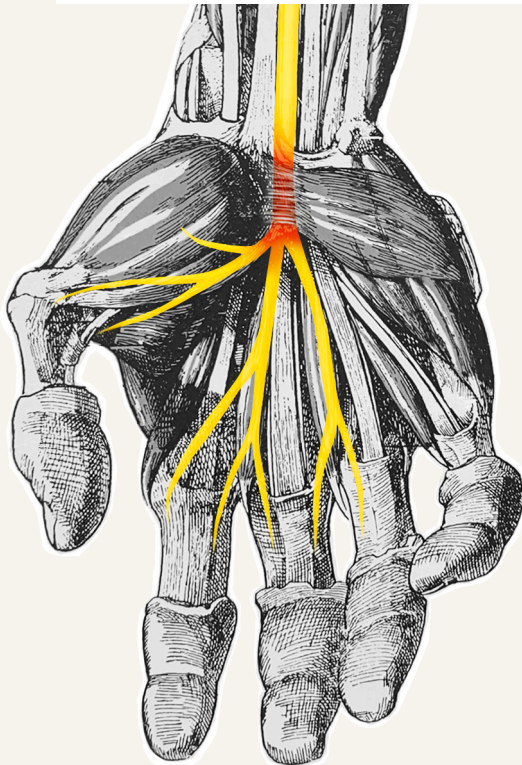
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Carpal tunnel syndrome

Diagnosis and treatment

MAGNUS FLONDELL | FACULTY OF MEDICINE | LUND UNIVERSITY





Carpal tunnel syndrome

This thesis focuses on how to diagnose CTS and the importance of preoperative electroneurography for outcome after surgery. It also focuses on how CTS affects sensory areas in the brain and the possibility of using guided plasticity to treat patients with CTS.

Carpal tunnel syndrome

Carpal tunnel syndrome

Diagnosis and treatment

Magnus Flondell



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DOCTORAL DISSERTATION

By permission of the Faculty of Medicine, Lund University, Sweden.
To be defended in CRC Aula (Agardh salen),
Skåne University Hospital, Malmö
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Title and subtitle Carpal tunnel syndrome - Diagnosis and treatment		
Abstract <p>Carpal Tunnel Syndrome (CTS) is the most common compression neuropathy causing pain, impaired hand function and sick leave. CTS is usually diagnosed based on patient history and clinical tests. In some patients an additional ENeG is done to support the diagnosis. However, ENeG can show pathology in healthy people and show normal values in patients with overwhelming clinical signs of CTS. Traditionally CTS is treated with CTR, however it is well known that a number of patients do not improve after surgery. The understanding of the human nervous system has increased dramatically during the last few decades. This has made it possible to better understand symptoms seen in patients with nerve injuries and to design treatment strategies where the dynamic capacity of the brain, i.e. brain plasticity is guided for therapeutic purposes. The aim of this thesis was to assess cerebral changes following CTS, and evaluate treatment using guided plasticity for patients with CTS. A further aim was to evaluate whether analysis of vibration perception thresholds at multiple frequencies can detect CTS, and if ENeG results are important for post-operative outcome following CTR.</p> <p>The first two studies evaluated the clinical and cerebral effects of treatment using guided plasticity in the form of cutaneous forearm anesthesia over 8 weeks. The results show that cutaneous stimulation of the hand with CTS causes activation of fewer neurons in the S1 compared to stimulation of a healthy hand. The concept of guided plasticity works, and treatment using guided plasticity results in recruitment of more neurons in the S1. However, it does not result in improved sensory function in the affected hand. Study III shows that patients with clinical and ENeG-verified CTS have increased vibration perception thresholds at multiple frequencies in all fingers. This suggests that analysis of vibration perception thresholds using multi-frequency vibrometry can serve as a diagnostic tool for CTS. Study IV showed that the outcome after endoscopic CTR is beneficial. This study also shows that the subjective outcome after endoscopic CTR is better if the patient, in addition to a typical history and positive diagnostic tests also has an ENeG indicating CTS as compared to a normal ENeG.</p>		
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Carpal tunnel syndrome

Diagnosis and treatment

Magnus Flondell



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The brain is the organ of destiny. It holds within its humming mechanism secrets that will determine the future of the human race.

Wilder Penfield

List of papers

The thesis is based on the following papers, which will be referred to in the text by their Roman numerals. Permission to reprint the published articles has been granted by the publishers.

Paper I

Carpal tunnel syndrome treated with guided brain plasticity: a randomized, controlled study

Magnus Flondell, Birgitta Rosén, Gert Andersson & Anders Björkman

Journal of Plastic Surgery and Hand Surgery, 2017, 51, No 3, 159–64

Paper II

Cerebral changes following carpal tunnel syndrome treated with guided plasticity – A prospective, randomized, placebo-controlled study

Magnus Flondell, Peter Manfolk, Birgitta Rosén, Isabella Björkman-Burtscher, Anders Björkman

Manuscript

Paper III

Vibration thresholds in carpal tunnel syndrome assessed by multiple frequency vibrometry: A case-control study

Magnus Flondell, Birgitta Rosén, Gert Andersson, Tommy Schyman, Lars B. Dahlin and Anders Björkman

Journal of Occupational Medicine and Toxicology, 2017, 12:34

Paper IV

Outcome of carpal tunnel release in patients with normal nerve conduction studies

*Peter Jørgsholm *Magnus Flondell, Anders Björkman, Niels O.B. Thomsen (*shared first authorship)

Journal of Orthopaedic Science <https://doi.org/10.1016/j.jos.2020.08.009>

Abbreviations and definitions

The following abbreviations, listed in alphabetical order, are used in this thesis:

BCTQ	Boston Carpal Tunnel Questionnaire
BOLD	Blood oxygen level dependent imaging(fMRI)
CNS	Central nervous system
CTR	Carpal tunnel release
CTS	Carpal tunnel syndrome
CTS6	Carpal tunnel syndrome 6 items evaluation tool for clinical diagnosis
DASH	Disabilities of the Arm, Shoulder and Hand questionnaire
ECTR	Endoscopic carpal tunnel release
EMLA[®]	Eutectic Mixture of Local Anesthetics
ENeG	Electroneurography
fMRI	Functional Magnetic Resonance Imaging
HAVS	Hand Arm Vibration Syndrome
MCD	Minimal clinical difference
PNS	Peripheral nervous system
PROM	Patient-rated outcomes measure
RCT	Randomized controlled trial
SSS	Symptom severity scale (part of BCTQ)
VAS	Visual Analogue Scale
VPT	Vibration perception thresholds.
QuickDASH	Short form of Disabilities of the Arm, Shoulder and Hand questionnaire

Thesis at a glance

I. Carpal tunnel syndrome treated with guided brain plasticity: a randomized, controlled study

Aim: To evaluate whether patients with CTS improve following an 8-week treatment protocol with sensory training in combination with guided plasticity compared to sensory training and placebo[®]

Background: Guided plasticity, induced by cutaneous forearm anesthesia, improves hand sensibility in patients with nerve injury and vibration-induced neuropathy.

Patients: 70 patients with ENeG-verified CTS were randomized to an 8-week treatment protocol of sensibility training, combined with either an anesthetizing cream (EMLA[®]), or a placebo-cream applied to the forearm.

Methods: The patients were examined using the Symptom Severity Scale (part of BCTQ), QuickDASH, nerve conduction studies, and clinical examination.

Conclusion: An 8-week treatment protocol with cutaneous forearm anesthesia to guide brain plasticity resulted in no significant subjective or objective improvements in hand function compared to placebo.

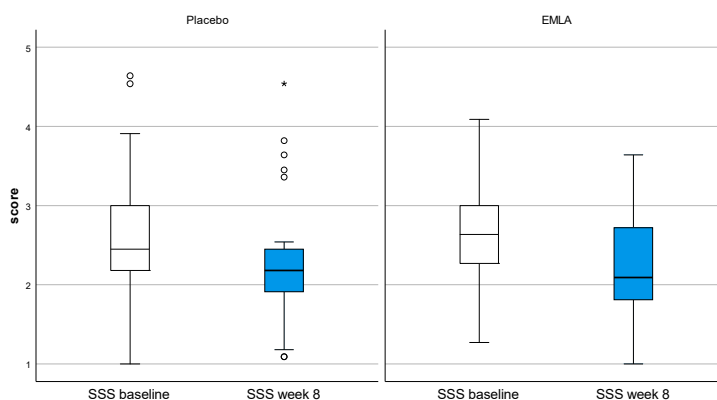


Figure 1 SSS scores at baseline and 8 weeks.
Boxplots depict median and quartiles of group SSS score (1 mildest–5 most severe)

II. Cerebral changes following carpal tunnel syndrome treated with guided plasticity – A prospective, randomized, placebo-controlled study

Aim: To assess cerebral changes following unilateral CTS. To evaluate short- and long-term cerebral effects of guided plasticity treatment. Ipsilateral cutaneous forearm anesthesia was compared to placebo treatment in patients with CTS.

Background: Surgical decompression generally relieves CTS symptoms in most patients. A possible cause of poor restitution of symptoms in patients operated on for CTS could be a combination of changes in somatosensory areas in the brain and peripheral nerve damage.

Patients: Twenty-four patients with mild to moderate ENeG-verified unilateral CTS were assessed at baseline, after 90 min, and after 8 weeks.

Methods: Cortical activation was evaluated using fMRI at 3T, to investigate activation changes in the somatosensory cortex (S1) of the brain. Short- and long-term effects of guided plasticity (EMLA[®]) compared to placebo, were evaluated with fMRI, PROMs and clinical examination.

Conclusion: fMRI showed that sensory stimulation of the hand with CTS resulted in smaller cortical activation in the S1 than stimulation of the healthy hand. Treatment with cutaneous forearm anesthesia on the side with CTS resulted in increased cortical activation in the S1 after initial treatment and after 8 weeks of treatment compared to the placebo group. Tactile discrimination improved in the EMLA[®] group over time.

III. Vibration thresholds in carpal tunnel syndrome assessed by multiple frequency vibrometry: a case control study

Aim: To investigate vibration thresholds in patients with CTS, using multi-frequency vibrometry.

Background: VPT is the lowest intensity that can be felt at a specific frequency. This threshold is higher, even at an early stage, in various neuropathies.

Patients: 66 patients with clinical and ENeG-verified CTS were compared to 66 age-matched healthy controls.

Methods: VPTs were assessed at seven frequencies (8, 16, 32, 64, 125, 250, and 500 Hz) in finger pulps of the 2nd and 5th digits bilaterally. VPTs were compared to ENeG. Severity of CTS was graded according to the Padua scale.

Conclusion: Patients with CTS had impaired VPTs at all frequencies compared to age-matched controls. Since the VPTs are dependent on function in peripheral receptors and their afferent nerves, multi-frequency vibrometry could possibly lead to diagnosis of CTS.

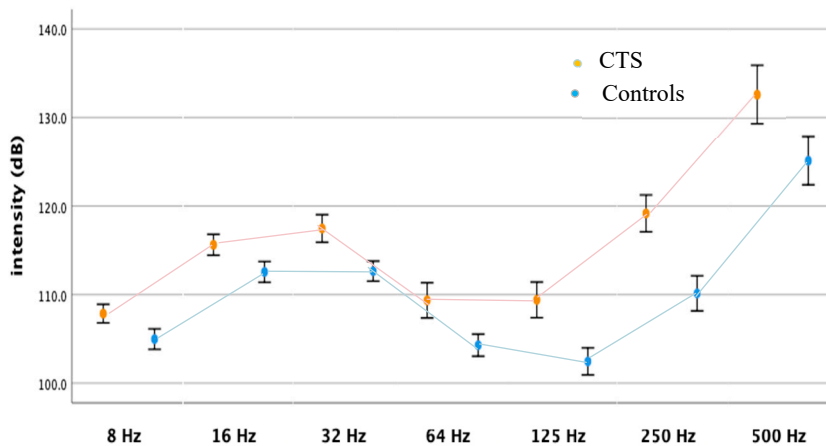


Figure 2 Vibration perception thresholds at 7 frequencies.

IV. Outcome of carpal tunnel release in patients with normal nerve conduction studies

Aim:

To evaluate outcome after ECTR in patients with clinically diagnosed CTS but normal ENeG, compared with a prospective group of patients with ENeG-verified CTS.

Background: Diagnosis of CTS is based on clinical findings and history, supported by ENeG which is an objective measure of large nerve fiber dysfunction but its usefulness as a reference diagnostic tool for CTS is debated.

Patients: 103 patients with clinically diagnosed CTS were operated on using ECTR, 94 completed a 4-month follow-up (47 were ENeG positive, 47 ENeG negative).

Methods: Patients were evaluated at baseline and at four months, using QuickDASH and patient satisfaction.

Conclusion: Patients with clinically diagnosed CTS and normal ENeG can expect a favorable clinical outcome, similar to that obtained in patients with ENeG verified CTS. Nonetheless, patients with a normal ENeG result had a lower satisfaction score.

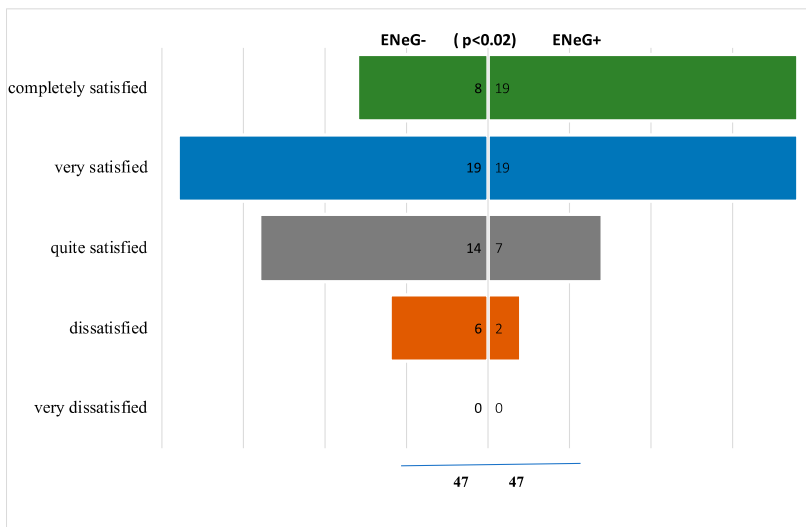


Figure 3 Satisfaction score 4 months after surgery.

Populärvetenskaplig sammanfattning

Karpaltunnelsyndrom (CTS) –en nervinklämning vid handledsnivån– är en mycket vanlig neuropati. Neuropati kommer från det grekiska ordet neuropathia (νευροπάθεια), som betyder nervsjukdom. Detta tillstånd kan medföra smärta och nedsatt känsel. Symtomen vid CTS är domningar och stickningar i de fingrar som försörjs av medianusnerven (tumme, pek-lång och halva ringfingret). CTS medför dessutom stora problem för den drabbade med nedsatt handfunktion och sjukskrivning. Diagnosen karpaltunnelsyndrom ställs oftast med hjälp av sjukhistorien och läkarundersökningen av handen. I tveksamma fall har man i Sverige av tradition undersökt nervfunktionen genom att mäta nervens förmåga att leda elektriska signaler, s.k. neurografi. Man brukar inleda behandlingen av CTS med att låta patienten använda en skena, som håller handleden rak på natten och ibland även komplettera med en kortisoninjektion i karpaltunneln. Om inte de behandlingarna fungerar, kan man överväga en operation, där ett ledband, som utgör taket i karpaltunneln, klyvs vid en operation, med karpalligamentsklyvning för att minska på trycket på nerven. Ca 13000 personer opereras varje år med karpaltunnelklyvning i Sverige.

Hjärnans förmåga att anpassa sig efter förändrade förhållanden kallas plasticitet. Till exempel så leder ofta en sjukdom eller skada i en nerv i armen till förändringar i hjärnan. Hjärnans förmåga till anpassning –plasticitet– kan användas i behandling, s.k. guidad plasticitet. Ett exempel på behandling med guidad plasticitet är att bedöva underarmen med en bedövningskräm. Detta leder till att nervcellerna i hjärnan, som normalt tolkar impulser från underarmen övergår till att tolka impulser från handen. Det i sin tur leder till att känseln i handen förbättras.

Syftet med avhandlingen var att undersöka om karpaltunnelsyndrom även påverkar hjärnans förmåga att tolka känsel impulser och om CTS kan behandlas med guidad plasticitet. Ett annat mål var att utforska nya sätt att bedöma om en patient har CTS och om resultatet av neurografi hos patienter som har kliniska tecken till CTS påverkar slutresultatet efter operation.

I den första delstudien undersöktes om 8 veckors behandling med underarmsbedövning (totalt 15 omgångar) kan förbättra symtomen hos patienter med CTS, jämfört med om en vanlig hudkräm smörjdes på underarmen. Subjektivt förbättrades båda grupper, men det var ingen skillnad mellan grupperna.

I den andra delstudien undersöktes dels hur CTS påverkar hjärnan och dels hur behandling med underarmsbedövning påverkar hjärnan. En speciell form av magnetkamerateknik användes där man kan se hur nervcellerna i hjärnan aktiveras, s.k. funktionell MR. Hos patienter med ensidigt CTS såg man en mindre aktivering i känselbarken då den sjuka sidans fingrar berördes jämför med då den friska sidans fingrar berördes. Behandling med underarmsbedövning under 8 veckor ledde till att ett större område, dvs fler nervceller aktiverades då de sjuka handen berördes medan behandling med en vanlig hudkräm inte ledde till några förändringar i känselbarken.

I den tredje delstudien, undersöktes förmågan att uppfatta vibrationer hos patienter med CTS. Vibrationsmätning vid flera frekvenser, jämfördes mellan individer med och utan CTS. Analys av förmågan att känna vibrationer i fingertopparna vid olika frekvenser s.k. multifrekvens vibrometri användes. Metoden speglar hur väl nerverna och känselkropparna i fingrarna fungerar. Vi fann att patienter med CTS hade sämre förmåga att känna vibrationer i fingrarna i den påverkade handen. Skillnaden sågs inom alla frekvenser i pekfingret och alla utom en i lillfingret, i jämförelse med friska individer.

Slutligen, i den fjärde delstudien undersöktes hur viktigt det är att mäta nervfunktionen i handen hos patienter som skall opereras för CTS. Patienter med typiska symtom på CTS deltog i studien. De i studiegruppen hade bara typiska symtom, medan de i kontrollgruppen dessutom hade nedsatt nervledningshastighet. Alla patienter opererades med karpaltunnelklyvning. Patienterna i de två grupperna fick samma, goda symtomlindring efter operationen, men de i kontrollgruppen med nedsatt nervledningshastighet var mer nöjda med behandlingen.

Förbättrad diagnostik av patienter med misstänkt CTS är väsentligt för att kunna optimera behandlingen. En ökad kunskap om de plastiska förändringar som sker i hjärnan vid en perifer neuropati, som CTS, kan utgöra en grund för nya behandlingsstrategier vid CTS.

Introduction

Carpal tunnel syndrome is the most common entrapment neuropathy and 2-4 % of the general population will undergo surgery for CTS. The diagnosis of carpal tunnel syndrome is usually made based on the patient's history and the clinical examination. In Sweden, in uncertain cases, neurography (ENeG) has traditionally been performed. The majority of the patients improve after surgery, but some do not. The enormous advances in the field of neurobiology over recent decades have increased our understanding on how the peripheral and central nervous systems work, both in healthy people, and in patients with diseases. In particular, we have learned that the brain is capable of making substantial functional as well as structural changes, due to its plasticity.

The current thesis focuses on using evolving concepts in brain plasticity in the treatment of patients with CTS. In addition, the thesis addresses how CTS can be diagnosed, and whether ENeG predicts the outcome of carpal tunnel release (CTR).

Background

Carpal tunnel syndrome

Epidemiology

CTS, where the median nerve is compressed at the wrist, is the most common entrapment neuropathy with an estimated prevalence of 2.7-5.8% in the general population (Atroshi 1999, Papanicolaou 2001). The incidence is higher in female and older patients and those with diabetes and increased BMI (Nathan 2002, Rydberg 2020). It is most commonly seen between ages 36-60 and has a female-to-male ratio of 2-5:1 (Ferry 1998).

Approximately 2-4 % of the general population undergo carpal tunnel release (Figure 4) during their lifetime (Andersen 2006, Graham 2016, Pourmemari 2018).

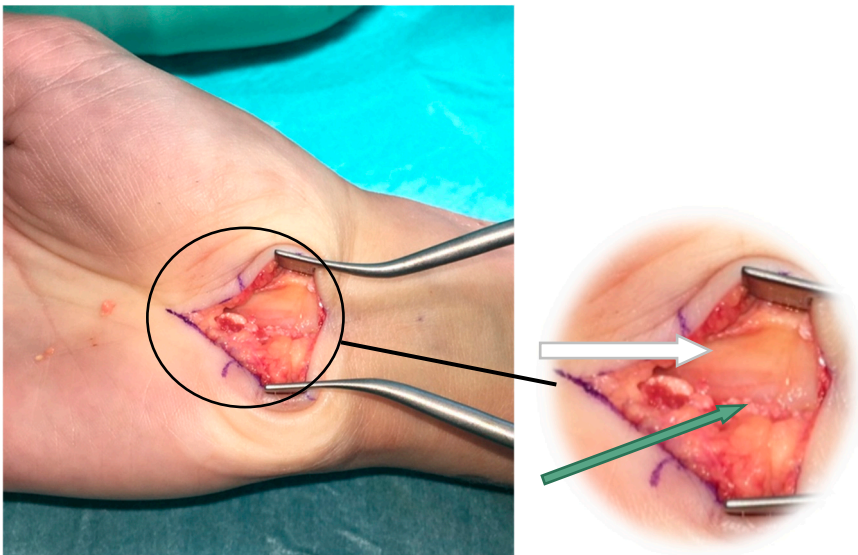


Figure 4 Carpal tunnel release, the white arrow shows the median nerve, the green arrow indicates the severed carpal ligament

Historical perspective

Though probably the most common disease operated on by modern day hand surgeons, CTS had been described as early as towards the end of the 17th century. J. Gensoul an otolaryngology pioneer working in Lyon, first reported on median nerve palsy in an autopsy performed in 1836. He noticed a direct injury to the median nerve from entrapment in an open distal radius fracture (Paget 2007). In 1854, Sir James Paget, an English surgeon and pathologist, reported median nerve compression at the wrist in two patients. An association between median nerve compression, and carpal ligament pathology was described by M. Bouilly in 1884 and cited by D. Lewis in 1922 (Lewis 1922). He reported on a young patient with median nerve compression, caused by a Colles' fracture, who was treated by excision of a palmar callus. Clinical symptoms of CTS were described by James Jackson Putnam in 1880 in a group of 31 patients with nocturnal paresthesia or burning pain at night. At that time he speculated that the symptoms were caused by vasodilation (Putnam 1880).

Decompression of the carpal tunnel was suggested as a potential treatment for a pseudoneuroma affecting the median nerve found during autopsy by Pierre Marie and Charles Foix in 1913 (Marie 1913). In 1946, B. Cannon and J. Love published a case series and introduced a technique for treating distal median neuropathy by decompression of the median nerve (Cannon 1946). Before this, CTS was possibly



Figure 5 George Phalen (1911-1998)

misdiagnosed as acroparesthesia and thenar neuritis. Russel Brain, a British neurologist, described these conditions as variable manifestations of median neuropathy, due only to entrapment of the median nerve, at the flexor retinaculum (Brain 1947). Inspired by Russel's work, George Phalen (Figure 5), an American orthopedic surgeon, published a series of papers in the 1950s and 60s on the outcome of carpal ligament releases (Phalen 1950, Phalen 1966). He described the diagnosis of CTS and its treatment with cortisone injection and operation with carpal tunnel release together with the results of the surgical treatment.

Anatomy

The median nerve originates in the lateral (spinal nerve roots C5-C7) and medial cords (spinal nerve roots C8-T1). It travels deep in the upper arm, slightly medial to the humerus. Thereafter entering the forearm and traveling deep under the flexor muscles down to a few centimeters proximal to the wrist, where it become more superficial, lying between the flexor tendons.

The carpal tunnel is situated slightly distal to the wrist joint on the volar aspect of the hand (Figure 6). It is a passage through which the median nerve, and all nine flexor tendons to the fingers and the thumb, pass from the forearm down into the hand (Figure 7). Inside the carpal tunnel the median nerve and all flexor tendons are suspended in a vacuolar synovium that promotes their gliding amplitude. The transverse carpal ligament is a fibrous structure, 3-4 cm wide, forming the roof of the carpal tunnel and functions as a pulley in the flexor retinaculum system. The floor is made up of the joint capsule, and the radiocarpal ligaments cover the underlying carpal bones (Kiss 1980).

The carpal ligament and the carpal bones form the boundaries of the carpal tunnel. The carpal ligament is inserted proximally to the tubercle of the scaphoid and the pisiform and distally to the hook of the hamate and the trapezium.

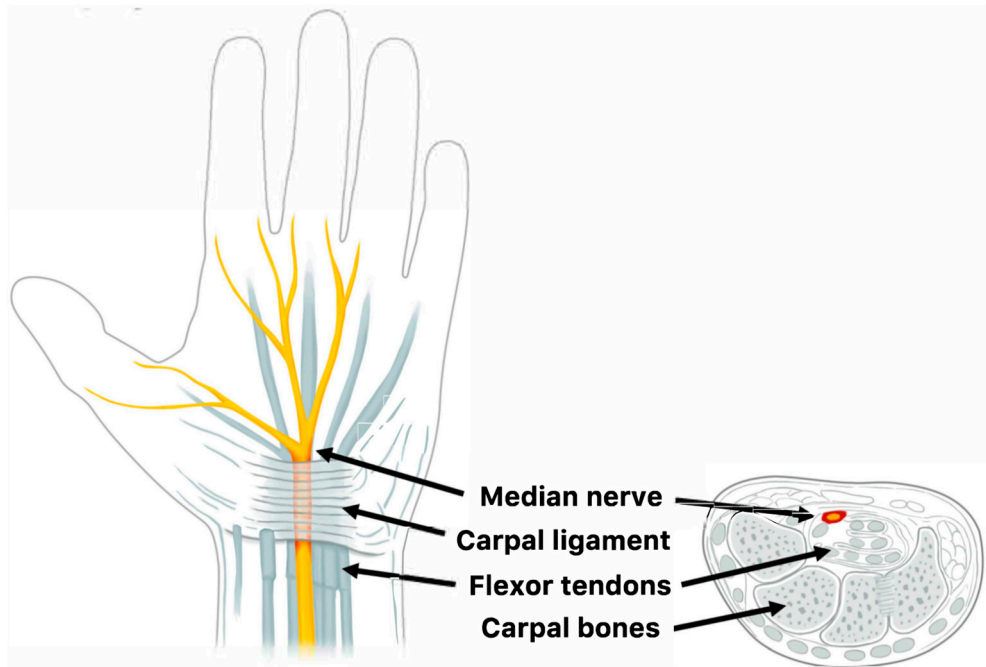


Fig. 6 The carpal tunnel and its boundaries
Frída Nilsson, Mediatryck, Lund

Some anatomical landmarks in relation to the median nerve can be detected on the skin surface; the tendons of the flexor carpi radialis and palmaris longus, the pisiform bone and the hook of the hamate, can be felt on the boundary of the carpal tunnel.

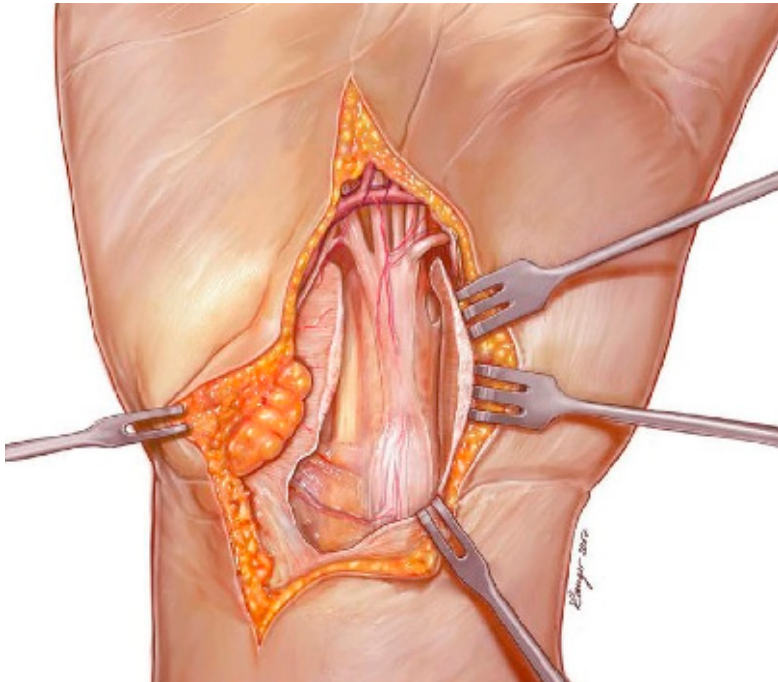


Figure 7 Opened carpal tunnel reveals the compressed median nerve causing carpal tunnel syndrome with permission of Martin Langer

Pathology and etiology

Entrapment of a peripheral nerve occurs when the nerve passes through an anatomical compartment that is too narrow. Normal pressure in the carpal tunnel is 2-10 mm Hg, increasing when the wrist is not in the neutral position. It is highest in extension, when it can reach 110 mm Hg (Gelberman 1981). In patients with carpal tunnel syndrome, the pressure within the carpal tunnel is much higher (30-90 mm Hg) both with the wrist in neutral position and higher when the wrist is flexed or extended (Bauman 1981, Gelberman 1981). The pathomechanism behind the symptoms seen in CTS involves combined compression and traction on the median nerve (Gelberman 1988).

Previous studies have shown that entrapment of a nerve leads to compromised intraneural microcirculation (Rydevik 1981, Lundborg 1988). This in turn causes changes in the axon, the Schwann cell with the myelin sheath and the synovial tissue (Dahlin 1986). Gradually the myelin sheath becomes thinner, the synovial tissue hypertrophies increasing the entrapment and nerve conduction become slower (Werner 2002, Guimberteau 2005). Increased pressure in the carpal tunnel leads to a reduced microcirculation in the epi- and perineurium. Reduction in microcirculation in this fashion is called backward failure. Backward failure causes alterations in the vascular permeability leading to edema (Rydevik 1977). It causes an accumulation of proteins and inflammatory cells and an edema within the fascicles of the nerve, much like a miniature compartment syndrome (Lundborg 1988).

CTS is known to affect large- and small diameter myelinated nerve fibers, but also, to a much lesser degree, unmyelinated nerve fibers (Arendt-Nielsen 1991, Schmid 2014), which are essentially resistant to compression (Dahlin 1989). The changes described in the peripheral nerve can cause permanent damage to axons in the median nerve in the carpal tunnel in patients with CTS. The axons distal to the injury may, depending on the magnitude and duration of the entrapment, undergo so-called Wallerian degeneration (Waller 1851). This is an active process in which the axon disintegrates and the myelin sheath degrades. The axons in the median nerve have their sensory cell bodies in the dorsal root ganglia adjacent to the spinal cord and when axons die some of the cell bodies also undergo programmed cell death (apoptosis) (Martin 1999, Wiberg 2001).

Usually, CTS is idiopathic, meaning that no specific cause can be identified. However, some medical conditions such as diabetes obesity, hyperthyreosis and rheumatoid arthritis, have been shown to increase the risk of developing CTS (Dyck 1993). In addition, CTS may be related to diseases that distort the anatomy of the carpal tunnel, such as a malunited fracture of the distal radius (Niver 2012). A dynamic CTS can also occur under pathological conditions relating to manual work (Bonfiglioli 2006) and long-term exposure to hand-held vibrating tools is known to be associated with CTS (van Rijn 2009).

The nervous system

Overview

The human nervous system is divided into the central nervous system (CNS) and the peripheral nervous system (PNS). The CNS comprises the brain and spinal cord and the PNS comprises the peripheral nerves and receptors (Figure 8). The everyday use of the hands is highly dependent on an interaction between the sensory and motor systems in the CNS and PNS. The complexity of this interaction becomes obvious when the individual contracts a disease of the nervous system.

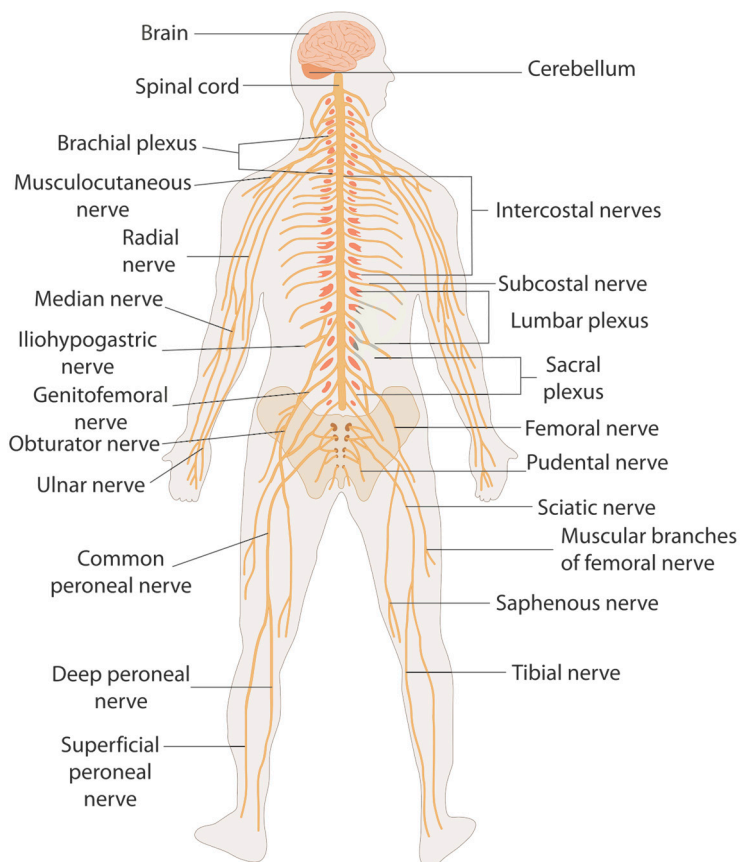


Fig 8 Nervous system of the human body.
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From 'Human Biology' by D. Wilkin and J. Brainard.

The central nervous system

The brain has a remarkable motor- and somatosensory-related capacity, controlling more than 600 different muscles in the body together with somatosensory information from these muscles and the entire skin surface. This is possible because of the large number of interacting neurons and nerve tracts in the brain. Anatomically the brain is divided into two symmetrical hemispheres which in turn are divided into different regions: prosencephalon (diencephalon and telencephalon), mesencephalon and rhombencephalon (medulla oblongata, pons, and cerebellum). The most caudal and in many respects the simplest part of the CNS, the spinal cord extends from the base of the skull to the first lumbar vertebra. The spinal cord is divided into a central core of gray matter containing the neurons, and an outer layer of white matter containing ascending and descending tracts of myelinated axons. Although the brain is often described in anatomical terms, its functional organization is much more complex and different anatomical brain areas contribute to various functional systems such as the somatosensory system and motor system.

The somatosensory system

The primary somatosensory cortex (S1) is situated in the postcentral gyrus. Based on its histological appearance it can be sub-divided into four separate areas, Brodmann area (BA) 1, 2, 3a and 3b (Merzenich 1978, Geyer 1999). Neurons in the S1 process sensory information from receptors in the skin, muscles and joints throughout the body. Neurons processing information from a specific body part are located together forming a distinct order, a somatotopy, in the S1.

In the first half of the twentieth century neuroscientists such as Wilder Penfield showed that the number of neurons processing sensory information is not related to the actual size of the skin area, muscle or joint. Instead a very large number of neurons are devoted to processing sensory information from the hands and face.

Using intra-operative electrical stimulation Penfield was able to describe the cerebral body map – the homunculus (Figure 9).

The secondary somatosensory cortex is located on the superior bank of the lateral fissure. Whereas the S1 is a unimodal area processing only sensory information, S2 is a multimodal area integrating information from the S1 with information from other areas. This integration is important, for example for the interpretation of complex sensory information as well as for planning motor acts.

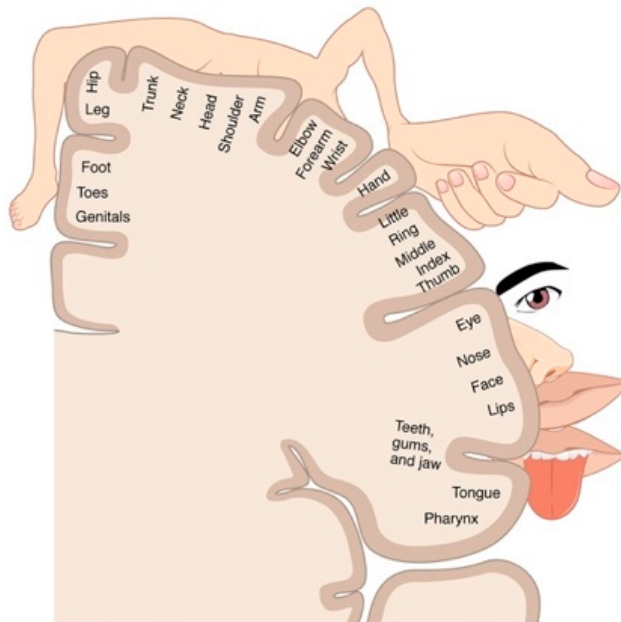


Figure 9 The sensory homunculus describes the proportions of neurons devoted to processing sensory information from specific skin areas, from *Anatomy & Physiology* by Lindsay M. Biga licensed under a Creative Commons Attribution-Share Alike 4.0

The motor system

Compared to the somatosensory system the motor system is more complex involving several brain areas. The primary motor cortex (M1) is located in the precentral gyrus of the frontal lobe. However, the M1 is only a part of a larger motor network. Voluntary motor acts can be divided into three stages; 1) purpose of movement, involving prefrontal areas; 2) forming a motor plan, involving S1, pre-motor areas, visual cortex, cerebellum and basal ganglia and 3) execution of the motor plan, involving mainly M1 (Kandel 2018).

The peripheral nervous system

The PNS is comprised of the peripheral receptors in the skin, the peripheral nerves and ganglia.

There are several groups of receptors in the PNS mediating various modalities of sensation. Sensory stimuli in the hands are managed by different types of mechanoreceptors (Johansson 1979) (Figure 10) divided into: a) Free nerve endings (dendrites) mediating pain and temperature, b) Merkel (discs) cells mediating low frequency vibration (5-15 Hz); c) Pacinian corpuscles mediating pressure and high frequency vibration (>250 Hz); d) Meissner's corpuscles mediating light touch and vibration (<50 Hz); e) Ruffini corpuscles mediating stretching of the skin (Iheanacho 2020).

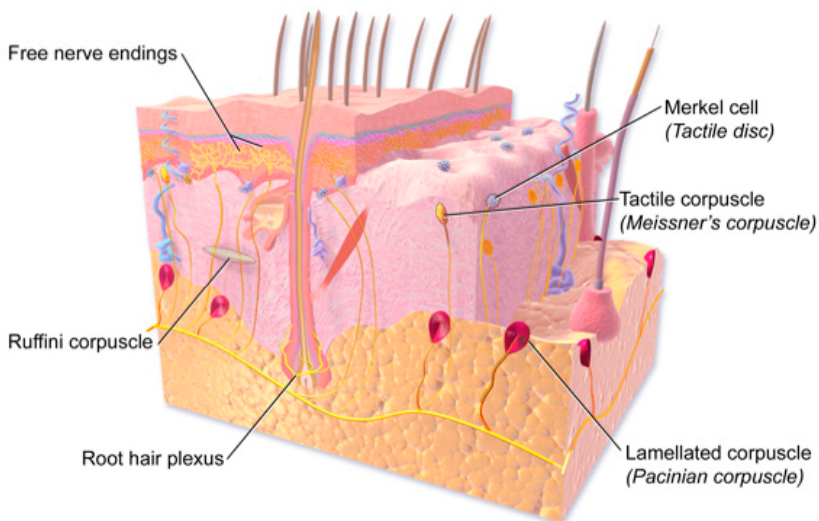


Figure 10 Mechanoreceptors of the skin
Blausen.com staff (2014). "Medical gallery of Blausen Medical 2014"

The peripheral nerve

The peripheral nerves comprise axons and connective tissue (Figure 11). Connective tissue surrounds the axon and endo- epi- and perineurium surrounds the nerve fibers. Nerves receive their blood supply from collateral arteries, vasa nervorum. Within the endoneurium, the axons are surrounded by myelin sheaths and Schwann cells. Myelin sheaths are present in some axons where they protect and isolate the them. Schwann cells promote a diversity of functions, such as nerve conduction, regeneration and antigen presentation. A majority of nerves, like the median nerve, are mixed nerves meaning that they contain both sensory and motor axons (Kandel 2018).

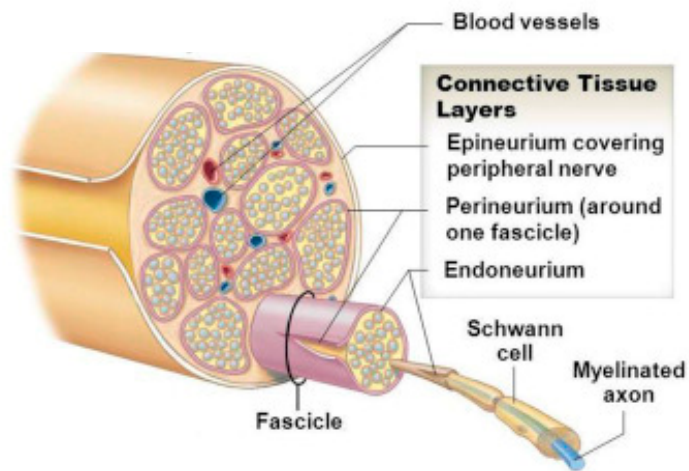


Figure 11 Anatomy of a peripheral nerve. Reproduced with permission, HUMAN ANATOMY, 8th ed. 2015, Martini, Reprinted with permission of Pearson Education, Inc., New York, New York.

The sense of touch

How precisely sensory stimulation is perceived in the upper extremity varies. Mechanoreceptors are much more densely distributed in the fingertips than in the palm, which in turn is more densely populated than the forearm. The receptive fields, i.e. the skin area supplied by a single neuron, are 1-2 mm in the fingertips, compared to 5-10 mm in the palm and several centimeters on the forearm. This is mirrored in the capacity to detect fine sensory stimuli, which is far better in the fingertip than in the forearm.

Sensory information from receptors in the index finger is sent along the median nerve to the dorsal root ganglia located adjacent to the spinal cord. From the dorsal root ganglia, the tactile nerve signals are sent in the dorsal column-medial lemniscal system, while information about pain and temperature are sent in the spinothalamic tract to the nucleus cuneatus, located in the medulla oblongata. From here the nerve tracts cross to the contralateral side of the body and continue to the thalamus. In the thalamus the nerve signal is processed before being sent on to the S1. At this stage, we become aware of the sensory stimuli. Some, but not all, sensory stimuli are sent on to S2, where the information is integrated with information from other centers in the brain.

Brain plasticity

Overview

For a long time, the brain was seen as a rather static organ without the potential to change. This view was mainly based on the fact that recovery following brain injury was rare. However, during the last half of the twentieth century our understanding of how the brain is capable of change, i.e. brain plasticity, has increased enormously. We now know that, the organization in the sensory and motor cortex is in a constant state of change (Kandel 2018).

Functional adaptation occurs in response to changes in the surrounding world, and plasticity is a dynamic force that links the internal world of the mind with the external world (Schwartz 2016). Changes such as environmental demands, training, activity and injury cause alteration in the afferent and efferent signals to the brain. Activity dependent plasticity describes how the brain adapts to normal demands and training, whereas injury-induced plasticity describes how the brain reacts to an injury to the nervous system. One example of activity dependent plasticity in violin players is that the cortical representation of the left hand (string hand, where the fingers are used independently) is greater than the bow hand (where the fingers are used as a unit) (Elbert 1995). Injury-induced brain plasticity plays an important role

in compensating for injury: This is exemplified by the changes that occur after an amputation or immobilization, where neurons in the cerebral areas deprived of afferent input, start processing afferent information from other areas. (Meinzer 2004, Taylor 2009, Davis 2011, Weibull 2011).

Cross modal plasticity describes plastic interaction between different sensory modalities, such as interaction between the visual and sensory system or between the auditory and the sensory system (Cohen 1997).

Plasticity can be an adequate response to a changed situation, an adaptive plasticity which is often seen as something positive. However, plasticity can also be maladaptive and cause problems such as phantom sensations and pain. Plasticity can be rapid; where functional changes in somatosensory areas have been seen within minutes after a median nerve injury. This rapid plasticity is thought to be mediated by reduced inhibition of existing neurons. Plasticity can also be a slower process, occurring over weeks and months. This slow plasticity is thought to be based on development of new connections between neurons.

Plasticity can be short- or long-term, mediated, for example, by rapid changes in the strength of the synapses and in the latter case mediated by new connections between neurons (Purves 2018). The absence of signals from an area with an injured nerve is rapidly compensated for by using this silent area for processing input from adjacent nerve areas (Merzenich 1983). An injury causes loss of inhibition and thus unmasking of the adjacent synapses. In the next phase (weeks) long-term plasticity mediates changes in the somatosensory map following a deafferentation. Later new axons grow to form connections for long-term plasticity (Kaas 1991).

Plasticity in the CNS following peripheral nerve injury

A peripheral nerve injury, for example a transection of the median nerve at the wrist causes a cascade of events both in the peripheral nerve and in the CNS (Lieberman 1971, Taylor 2009). Following suture of the nerve the nerve segment distal to the injury undergoes Wallerian degeneration and the axons die (Yu 2013, Purves 2018). This means that no nerve signals are sent to the neurons in S1 that usually respond to sensory information from the thumb, index, long and radial half of the ring finger, as well as the radial half of the palm. The neurons in S1 do not lie dormant, instead they start responding to sensory information from receptors in adjacent skin areas, innervated by the ulnar nerve. In this way more neurons become available to process information from the ulnar half of the ring finger, the little finger and the ulnar half of the hand and accordingly the sensibility here improves (Jones 2000). In addition, sensory and motor areas in the two hemispheres are also connected. In the case of a median nerve injury, this means that some of the neurons in the S1 deprived of input start processing input from the median nerve innervated areas of the contralateral hand (Clarey 1996).

Gradually the regenerating axons in the peripheral nerve cross the repair site and start reinnervating the peripheral receptors. However, there is a much misdirection during this regeneration process, meaning that axons destined for the thumb may reinnervate the index finger and so on (Brushart 1980). The result is a changed afferent nerve signal pattern from the hand to the brain. This change in afferent signal pattern from the injured nerve results in adaptations in the corresponding areas in the S1, where the normal somatotopy of neurons is broken down into more of a mosaic pattern (Taylor 2009, Davis 2011, Chemnitz 2015). The ability to adopt and interpret this new afferent signal pattern is crucial for the clinical outcome.

Plasticity in the CNS following neuropathy

A neuropathy, just like a traumatic nerve injury, changes afferent signaling to the brain, which leads to changes caused by plasticity in the CNS. However, while cerebral changes following a peripheral nerve injury are described rather well in the literature, cerebral changes following neuropathy are hardly described at all. Patients with neuropathy induced by long exposure to hand-held vibrating tools have been shown to display a changed somatotopy in S1 (Lundborg 2002, Björkman 2010).

Some authors (Napadow 2006, Dhond 2012, Maeda 2013) have found plasticity-induced cerebral changes, caused by CTS. Altered neural activity in patients with CTS has been linked to a reduced afferent sensory input. A previous study on patients with CTS, using somatosensory-evoked potentials (SEP), found changes in the somatosensory cortex and, to a lesser extent, in the spinal cord and brainstem structures (Tinazzi 1998). A change in the somatosensory cortical representation of all fingers in patients with CTS has also been detected by magnetoencephalography (MEG) (Tecchio 2002). In addition, studies using magnetoencephalography have suggested that the cortical hand representation in patients with CTS is related to the severity of the patient's symptoms (Tecchio 2002).

Using fMRI, Napadow and colleagues (Napadow 2006) found a positive correlation between ENeG and changes in the contralateral S1 in patients with CTS. Additional studies, using fMRI and MEG, have shown expansion, amplification, and a shift in somatosensory area S1 (Napadow 2006, Dhond 2012). In addition, a larger and stronger activation in BA 3b was seen following sensory stimulation of the index and long finger as well as a smaller separation distance between the two (Napadow 2006).

Interestingly, one study also showed structural changes with a reduction in gray matter volume in S1 in patients with CTS (Maeda 2013). When interpreting results from studies that use functional imaging to evaluate how the S1 reacts to sensory stimulation, it is important to know which type of sensory stimulation was employed and how it was administered.

Most earlier studies that evaluated cerebral response to CTS used electric stimulation. However, the receptors principally used when the hand explores a surface or an object are the mechanoreceptors, which respond mainly to pressure and vibration. Electrical stimulation will by-pass the mechanoreceptors and one might ask how representative an electrical stimulation of the hand is (Mizobuchi 2002). Furthermore, in some studies that used electrical stimulation (Maeda 2017) the strength of the electrical stimulation was adjusted in relation to the person's pain threshold (Napadow 2006). This was done in an attempt to "normalize" the sensory stimulation in order to be able to compare patients with different sensibility. For example, a stimulation up to three times the touch threshold was used in one study where somatosensory-evoked potentials (SEP) were used to assess cerebral response in patients with CTS (Tinazzi 1998). Given that the mechanoreceptors are by-passed and that the intensity of the stimuli is adjusted to the patients' pain thresholds, results from studies using electrical stimulation should be interpreted with care.

Guided Plasticity

The brain's plastic capacity opens up possibilities. Plasticity can be guided, for therapeutic purposes, to support functions that have been damaged or lost (Duffau 2006). The enormous advances over the last few decades in our understanding of how the brain works also enhance our possibilities for designing treatments using guided plasticity.

Several treatment routines exist that use guided plasticity to improve function. Controlled stimuli and absence of stimuli can be applied, to evoke brain plasticity. For example, stroke patients with impaired motor function in one hand can be injected with an anaesthetic agent anaesthetizing the muscles around the shoulder. This results in a rapid transfer of neural resources to facilitate function in the ipsilateral hand (Muellbacher 2002). Another example is constrained-induced therapy, where the uninjured arm and hand is immobilized, forcing the patient to use the injured arm. This results in transfer of neural resources focusing on the injured hand and arm, which improves function (Weibull 2011). Action observation and motor imaginary are two further methods where a person observes someone else doing a motor task or imagines doing it themselves. This results in adaptations in the motor network and improved motor function (Ehrsson 2003, Mulder 2007, Bassolino 2014). Also, Mirror visual feedback (MVF) is a rehabilitation technique that also uses observation of action to trigger guided plasticity. In this method the injured hand is hidden behind a vertical mirror, and the mirror reflection of the uninjured hand, in place of the injured hands, gives an illusion that the injured hand moves or touches an object. Recent studies have used observation of touch and mirror visual feedback in sensory re-learning following nerve repair with good long-term results (Rosen 2015, Vikstrom 2018). Another guided plasticity method is

cutaneous forearm anesthesia. The neurons in S1 that process sensory information from the forearm are located next to the neurons processing sensory information from the hand (Penfield 1958). If an anesthetic cream is applied to the volar aspect of the forearm, no nerve signals are sent to S1. The neurons in S1 responsible for processing sensory information from the forearm immediately start processing sensory information from the hand (Björkman 2009). This results in improved sensory function in the hand in both healthy people and patients with a median nerve injury (Rosen 2012), a possible mechanism being rapid plasticity and recruitment of nearby cortical areas (Björkman 2004, Björkman 2009). Repeated treatments with cutaneous anesthesia can cause a long-term improvement in patients operated on for a median or ulnar nerve transection (Rosen 2006) and in patients with diabetic and vibration-induced neuropathy (Lundborg 2010, Rosen 2011). In addition, it is possible to combine sensory training with cutaneous forearm anesthesia in order to enhance the effects of the training (Rosen 2006, Rosen 2011).

Guided plasticity has not been applied in patients with CTS. However, in one study acupuncture was used to evoke plasticity in patients with CTS (Maeda 2017). It is not entirely clear how acupuncture works, but some modulation of neural functions is probably part of the mechanism. Acupuncture in patients with CTS showed both structural and functional adaptations within several areas in the brain, including sensory areas, as well as improved function in the hands (Maeda 2017).

Diagnosis of Carpal Tunnel Syndrome

Many other diseases can mimic CTS and these must be ruled out in order to arrive at a diagnosis. Detailed patient history and physical examination are necessary, sometimes in conjunction with ENeG and imaging studies.

Clinical diagnosis

There is no “gold standard” for how to determine a CTS diagnosis. It is usually based on a medical history of typical sensory symptoms with pain, numbness and a “tingling” sensation in median-nerve innervated fingers, combined with positive clinical tests, such as Phalen’s test and the Hoffman-Tinel sign (Schmid 2014).

Clinical symptoms and signs of CTS were originally described by Phalen as pain at night, brachialgia paraesthetica nocturna, which is one of the classic symptoms, the others being numbness and a tingling sensation mostly affecting the radial fingers. Pain may be referred to the affected arm and shoulder. The symptoms are often exacerbated by physical activity.

Provocative tests are often positive:

Hoffman-Tinel test: paresthesia elicited by gently tapping the median nerve by the proximal wrist crease with the wrist in slight extension (Mossman 1987, Tinel 2005).

Phalen’s test: paresthesia caused by wrist flexion over 30-60° (Phalen 1950).

Durkan’s compression test: paresthesia by wrist flexion and gentle compression of the median nerve over the wrist (Durkan 1991).

The symptoms are relieved by carpal tunnel release but differential diagnoses must be ruled out for a reliable clinical diagnosis. These include: radiating symptoms from a root compression in the lower cervical spine, drug effects or interactions causing sensory phenomena. The most frequent drug families are: SSRI, antihypertensives and thyroxine. Other peripheral nerve entrapments that simulate CTS, for instance pronator teres syndrome, might be considered as well.

Electroneurography

While electrophysiological assessment is the most reliable examination for confirming a clinical CTS diagnosis, both false positive and negative results occur (Nathan 1993, Atroshi 2003). The sensitivity of the assessment is high but specificity is lower. To improve sensitivity, comparative analyses of sensory nerve conduction have been used (Jablecki 1993). Additionally, up to 15% in the general population have an asymptomatic median mononeuropathy. (Bingham 1996). Another concern is that ENeG mainly measures the function of large myelinated nerve fibers. For small fiber sensory neuropathy, as in diabetes and nerve ischemia, electrophysiological assessment is inadequate (Werner 2002). Furthermore, a representative local reference group must be used to establish reliable reference values.

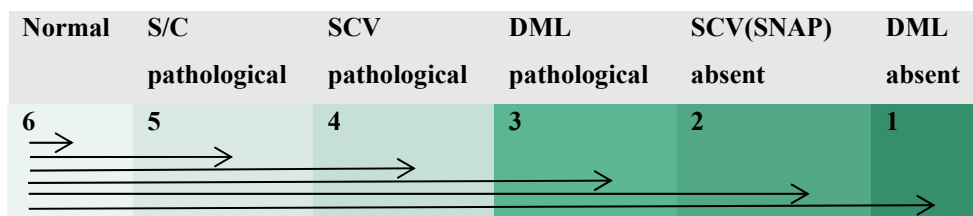


Figure 12 Padua classification (Padua 1997) S/C: segmental/comparative, SCV: sensory conduction velocity, DML: distal motor latency, SNAP: sensory nerve action potential
Cases can be classified according to their severity of ENG parameters.

ENeG is used before surgery to support the clinical CTS diagnosis in many countries (Graham 2016). Others have argued that in cases with certain clinical CTS, ENeG does not change the probability of diagnosis (Graham 2008). In a large review by the American Association of Electrodiagnostic Medicine, comparative analysis digit 3-palm-wrist has been recommended as a solution to the lower sensitivity of ENeG. The main weaknesses are the selection of a control group in studies and neurophysiological examinations that are difficult in clinical practice (Padua 1996). There are conflicting results in outcome following clinically diagnosed CTS with a normal ENeG. However, there are no studies in larger groups of clinically diagnosed CTS, compared in subgroups according to ENeG pathology (Figure 12).

Ultrasound

Ultrasound has been used recently to examine CTS and some typical ultrasound findings can be found in patients with classical CTS. In a group of ENG-confirmed CTS, a 2 mm² difference in median nerve cross-section between the level of the pronator quadratus and the carpal tunnel has a 99% sensitivity and 100% specificity for CTS (Wong 2004).

The typical ultrasonographic parameters described are:

palmar bowing of the flexor retinaculum >2 mm between the pisiform and the scaphoid.

enlargement of the nerve proximal to the carpal ligament (cross-sectional area 9-11 mm²).

flattening of the median nerve midway in the carpal ligament.

However, the method is currently only used in some countries for diagnosis in standard clinical settings. Clinical use of ultrasound needs reliable reference values that signify a pathological finding but cutoffs are still debated (Klauser 2009). In mild CTS the sensitivity is 64% and 67% respectively for ultrasound and nerve conduction velocity in relation to a clinical diagnosis (Wong 2004).

MRI

MRI can demonstrate morphological signs similar to ultrasounds including:

Palmar bowing of the carpal ligament (Tsujii 2009).

Enlargement and flattening of the median nerve (Mesgarzadeh 1989).

Other changes can be detected by MRI such as *edema* or *loss of fat* within the carpal tunnel, and *increased size* or edema of the nerve on fluid-sensitive sequences and, in some cases, contrast enhancement of the nerve (Miller 2010, Campagna 200).

Nevertheless, the sensitivity and specificity of MRI in CTS should be considered with caution. It varies depending on which morphological sign that is evaluated (Pasternack 2003) Even when grading multiple morphological signs on MRI and thus reaching a 96% sensitivity compared to ENG-verified CTS, the specificity was low at 33% (Fleckenstein 2002).

fMRI

fMRI is a functional imaging technique to assess function in specific parts of the brain. Images can be obtained with both high spatial and temporal resolution. Making it possible to analyze the effects of a multitude of diseases and treatments on the brain.

BOLD contrast in fMRI

Blood oxygen level dependent (BOLD) imaging means that the oxygenation level of hemoglobin can be used as a contrast in fMRI. The blood transverse relaxation rate of protons is blood oxygen level dependent, i.e. increased firing of cortical neurons in a specific area increases the blood flow to that area. Hemoglobin acts differently to magnetic fields. When oxygenated, it is diamagnetic and when deoxygenated, it is paramagnetic. Since oxygenated hemoglobin is present in areas with a high blood flow, fMRI can be used to indirectly detect active areas with a high metabolic rate (Ogawa 1990).

The MR signal varies with blood oxygenation as deoxyhemoglobin distorts the magnetic fields; therefore, hemoglobin acts as an endogenous contrast. In this fashion, fMRI makes it possible to measure human brain activity over time in various areas (Thulborn 1982).

fMRI techniques have been used to evaluate contralateral cerebral changes following CTS (Napadow 2006, Maeda 2014). Contra- and ipsilateral BOLD responses can be analyzed in CTS patients to assess cerebral changes. In a similar fashion as in Paper II in this thesis, brain activation can be analyzed in correlation to clinical data.

Treatment of CTS

Orthosis

Splints have been used successfully to treat CTS. The pressure in the carpal tunnel is reduced when the wrist is supported in neutral position by a splint. Various types of wrist-splints have been tested and found effective, measured by validated outcome instruments (Brininger 2007). A neutral wrist splint can alleviate symptoms as well as improve ENeG parameters in CTS patients, unfortunately this study was not controlled using placebo treatment (Walker 2000).

Cortisone

Cortisone injections are effective in treating CTS, but they only provide long-term relief in some patients (Atroshi 2013, Graham 2016). Cortisone is injected proximally into the carpal tunnel, deeper than the level of the median nerve. Most patients require surgery when the symptoms return although a subgroup of patients experiences a long-term alleviating effect from cortisone (Armstrong 2004).

Surgery

Carpal tunnel release is an effective and a commonly performed procedure. Since the incidence rate of CTS is 1–4%, one can estimate that the procedure is performed millions of times/year throughout the world. Phalen originally described a large series of CTS patients treated during the 1950s and 60s. Carpal tunnel release was described as almost always curative regarding numbness and pain and often also cures the thenar atrophy accompanying the CTS (Phalen 1966).

There is some discrepancy in the long-term results of carpal tunnel release. Long-term success rates of between 75-90% have been described (Louie 2013). The range of the success rate could be due to the preoperative ENG grade, where the success rate is below 50% in severe cases (Figure 13). Additionally, incorrect diagnosis of CTS and selection bias in surveys may lead to inappropriate conclusions (Bland 2001). Furthermore, there are some biomechanical concerns regarding widening of the carpal arch causing pillar pains as well as reduced grip strength (Gartsman 1986, Thomsen 2009, Morrell 2014, Thomsen 2014).

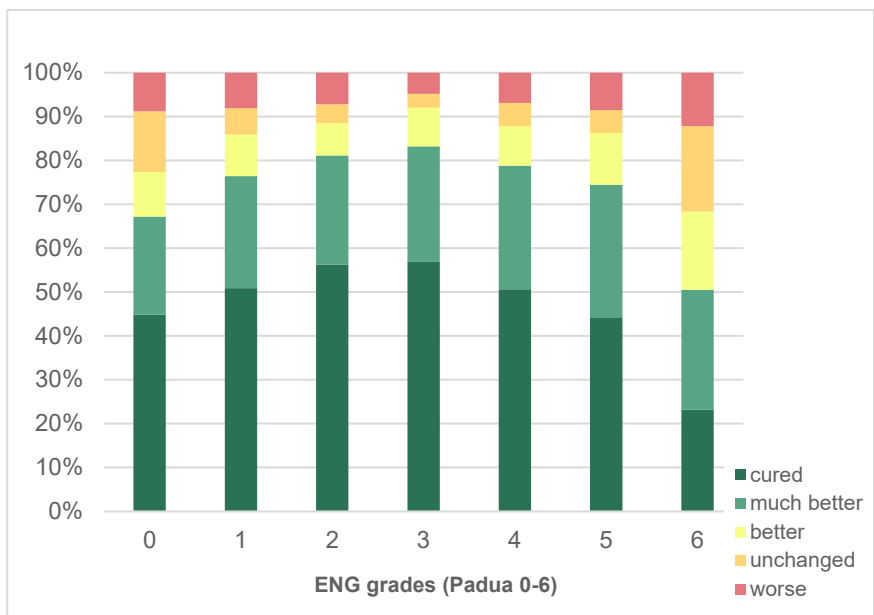


Figure 13 Relationship between pre-operative neurophysiological grade and surgical outcome groups. Outcome after surgery – segmented barchart From Bland (2000a),

Aims of the thesis

General aims

The general aim was to study the diagnosis and treatment of CTS. Specifically it was to evaluate cerebral changes in CTS, before and after treatment with guided plasticity, and in addition to study the role of vibrometry in diagnosis in CTS and outcome after CTR in patient with clinical diagnosis of CTS.

Specific aims were:

- To evaluate clinical outcomes following an eight-week treatment with guided plasticity using a randomized controlled study design, where cutaneous forearm anesthesia was compared to placebo in patients with CTS (Paper I).
- To investigate whether a unilateral CTS, results in cerebral changes in somatosensory areas in the brain (Paper II).
- To evaluate cerebral changes in somatosensory areas from a short- and long-term perspective following treatment with cutaneous forearm anesthesia compared to placebo (Paper II).
- To investigate VPTs using multifrequency vibrometry in patients with CTS (Paper III).
- To evaluate the outcome following ECTR in patients with clinical signs of CTS, but with normal ENeG, compared to abnormal ENeG (Paper IV).

“A correct diagnosis is three-fourths the remedy”

Mahatma Gandhi

Patients and Methods

Patients

During the years 2009 to 2015, patients referred to the Department of Hand Surgery with suspected CTS were screened for inclusion (Figure 14).

Inclusion criteria were: subjective symptoms for more than 3 months, clinical signs of CTS (Katz 1990); an electroneurography (ENeG) , with a fractionated sensory nerve conduction speed across the wrist of 40 m/s or less (10% below the rate for normality which has been set at 44 m/s or above). 72 Patients with both unilateral and bilateral CTS were included in total (Paper I, II or III).

Exclusion criteria were; the presence of rheumatoid arthritis, diabetes, a history of neurologic disease, multiple systemic diseases, vibration-induced neuropathy; a complete nerve conduction block on ENeG; allergy to local anesthetic agents; and an inability to complete patient-rated outcome measures (PROMs). (Table 2,3)

Paper I: A total of 70 consecutive patients were included, 16 men and 54 women with a mean age of 49, SD 9, with clinically and ENeG-verified CTS. One surgeon interviewed all the patients and established the clinical diagnosis.

Paper II: Included 24 patients, 22 from those in Paper I, with unilateral CTS.

Paper III: 66 patients from Paper I were recruited and examined at inclusion using vibrometry.

Paper IV: A total of 103 patients were recruited and treated at the Department of Hand Surgery, Mølholms private hospital, Vejle, Denmark by one senior hand surgeon (Table 1).

Table 1 Participants in the Papers in the thesis.

Participants	Paper I	Paper II	Paper III	Paper IV
Malmö cohort (n=72)	70/72	24/72	66/72	-
-Malmö controls	-	-	66	-
Mølholm cohort	-	-	-	103

Patients from Malmö cohort have participated in more than one study

Screening

Table 2 Inclusion and exclusion criteria Papers I and III

Inclusion criteria	Exclusion criteria
subjective symptoms > 3 months clinical signs of CTS ENeG <41 m/s	rheumatoid arthritis diabetes neurologic disease multiple systemic disease HAVS ENeG nerve conduction block allergy to EMLA® inability to fill out PROMs

Paper II

Additional inclusion criterium: unilateral ENeG-verified CTS

Table 3 Inclusion and exclusion criteria Paper IV

Inclusion criteria	Exclusion criteria
subjective symptoms > 3 months clinical signs of CTS	rheumatoid arthritis diabetes neurologic disease multiple systemic disease HAVS ENeG nerve conduction block inability to fill out PROMs

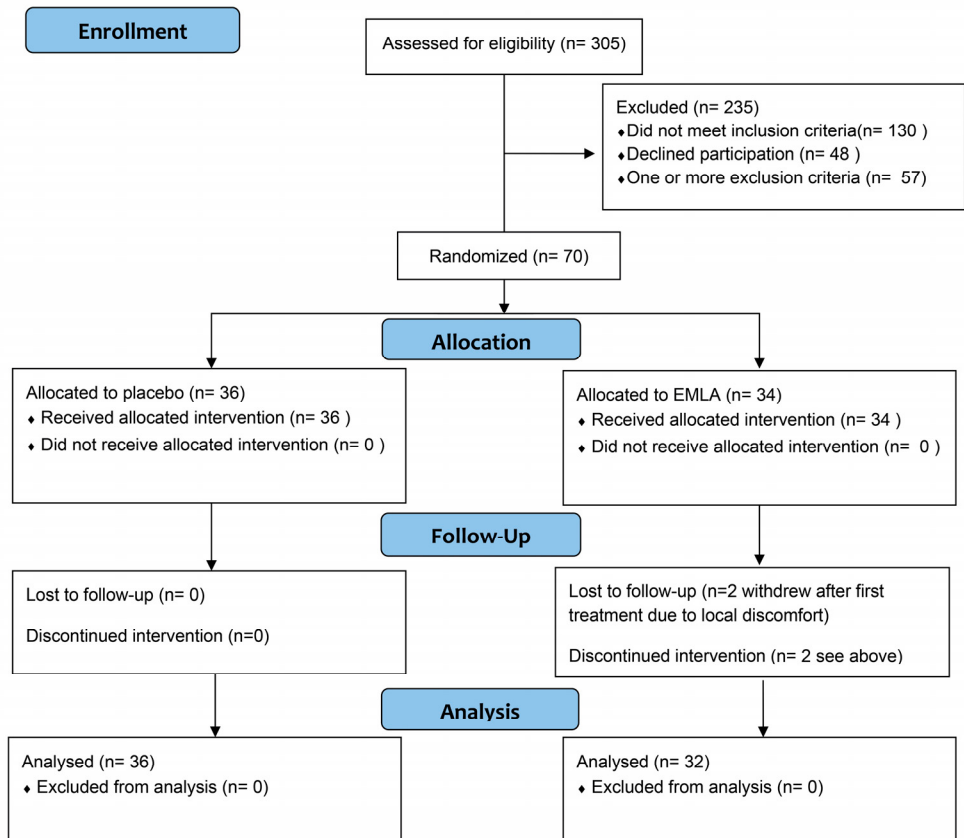


Figure 14 CONSORT flow chart from Paper I

Methods

Tests and examinations

All patients were thoroughly examined regarding inclusion and exclusion criteria. The diagnosis was established according to subjective symptoms that were assessed using Katz's hand diagram (Katz 1990). A clinical evaluation was performed where the patients were assessed for weakness in thumb abduction and for signs of atrophy in the thenar muscles. Provocation tests were also carried out.

Provocation tests

All provocative tests are largely examiner-dependent. To reach the precision described in the literature, provocative tests must be performed exactly as originally set out. Sensitivity and specificity graphs are selected from studies considered most relevant by the author, and do not represent all opinions (Gunnarsson 1997).

Hoffmann-Tinel's test



This test is performed by tapping over the volar wrist distal to the wrist crease above the median nerve. Hoffmann-Tinel's sign is positive if the patient perceives paresthesia that radiates in the projection of the median nerve sensory area. Percussion should be performed with slight wrist extension (Mossman 1987, Tinel 2005). Hoffmann-Tinel's sign ranges in sensitivity from 28-73% and specificity from 44-95%.

Phalen's sign



Phalen's test is done by applying maximum flexion of the wrists. It is positive if paresthesia is felt in the hand within one minute. As with the Hoffmann-Tinel's sign, the wrist flexion test is not only positive for CTS (Phalen 1950)

Durkan's test



A carpal compression test is performed by applying pressure directly over the carpal tunnel and the underlying median nerve while flexing the wrist maximally. It is considered to be more sensitive or specific than Phalen's test (Durkan 1991).

APB strength



The strength of thenar muscles should be tested to determine motor loss. Abductor pollicis brevis (APB) can be examined by palmar abduction of the thumb. The thumb is abducted against resistance to the side of the finger pulp. The strength is graded according to the MRC scale (Magee 2020).

Electrophysiology



In this thesis a standard electrophysiological assessment (ENeG) was performed on both arms (Figure 15). Orthodromic sensory ENeG was performed by stimulating the thumb, the index finger and the long finger for the median nerve and the little finger for assessment of the ulnar nerve. The stimulation ring electrodes were placed at the proximal interphalangeal and distal interphalangeal joints for the index, long, and little finger and just proximal and distal to the interphalangeal joint of the thumb. Recording electrodes were placed over the respective nerves at the proximal wrist crease and three cm more proximal. For motor conduction studies, recordings were made from the abductor pollicis brevis muscle (innervated by the median nerve) and abductor digiti minimi muscle (innervated by the ulnar nerve) with stimulation of the respective nerves 80 mm proximal to the electrode placed over the muscle. The patient's skin temperature was kept above 30°C during the ENeG examination. The ENeG was carried out using a Nicolet™ Viking Select Electromyograph (Nicolet Brand Products, Middleton, WI, USA), and the examination includes assessment of sensory conduction velocity (SCV), sensory nerve action potential (SNAP), and distal motor latency (DML).

All examinations were performed by the same technician and evaluated independently by the same neurophysiologist.

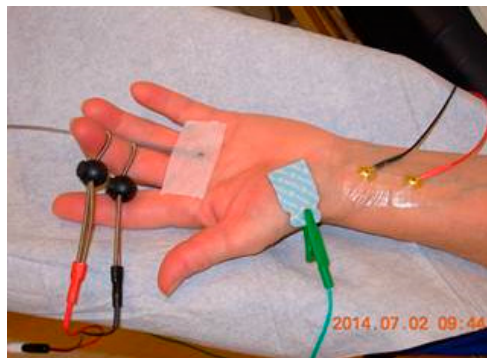


Figure 15 sensory neurography with stimulation of the long finger and registration of the median nerve. Reprinted with permission of Gert Andersson

Intervention

The patients in Papers I and II, were randomized to treatment either with 15g of a local anaesthetic cream containing 2.5% lidocain and 2.5% prilocain (EMLA[®]; AstraZeneca, Södertälje, Sweden) or with a placebo cream. The placebo cream was visually and cosmetically identical to the EMLA[®]. Either EMLA[®] or placebo was applied to the volar aspect of the forearm, in an area from the wrist and 15 cm proximal on the same side as the CTS. In patients with bilateral CTS, EMLA[®] or placebo was applied on the side where the patient experienced most symptoms. After 90minutes, the cream was washed off. Thirty-four patients were randomized to EMLA[®] treatment and 36 patients to treatment with the placebo. The initial treatment was carried out at the hospital, and the patients were observed for any adverse events. They were thoroughly informed about how to administer the treatment at home, and given information on the sensory re-education technique (Rosen 2006). They were given advice on how to integrate the sensory re-education into their activities of daily living.

An 8-week treatment program was used (three treatments in the first week, two treatments in weeks 2–6, and one treatment in weeks 7–8). This treatment has previously proved successful in improving sensory function in the hands of patients with nerve repair and vibration-induced neuropathy (Rosen 2006, Rosen 2011). After completing the 8-week treatment (Rosen 2011), all participants were offered a surgical decompression of the median nerve.

Blinding

To ensure blinding of the investigators performing direct assessments, the application and subsequent removal of EMLA[®] or placebo was performed by the same researcher, who randomized and informed the participants in a standardized manner about treatment and follow-up. The researcher also instructed the study patients not to comment on the treatment to the investigator performing the direct assessments. Two therapists – who were blinded regarding the treatment and who were experienced in the assessment of nerve function – carried out all the direct assessments and administered the PROMs.

All electrophysiological examinations were performed by the same technician and were evaluated independently by the same neurophysiologist.

Measures must be taken to ensure standardized performance of the sensory test. The test person was seated in a quiet environment with the tested hand comfortably resting in a supine position. Sensory testing was done with a screen in place to obscure the hand, and was performed by an experienced occupational therapist.

Surgery

CTR

After completion of EMLA/placebo treatment all participants in study I, II and III were offered a CTR. Local anesthesia was injected and a lower arm tourniquet was applied. A curved incision was made from a point radial to a longitudinal axis of the ring finger and proximal to Kaplan's cardinal line to the proximal wrist crease (Arian 1977, Nigst 1992). Subcutaneous fat was retracted with hooks and palmar fascia and transverse carpal ligament were divided using a scalpel in a proximal to distal direction. Distally, the incision was extended until the volar fat pad was visualized. The antebrachial fascia was then divided a further 2.5 cm proximal to the wrist crease using scissors keeping the nerve in direct sight. Wound closure with sutures and a soft compressing dressing was applied. Patients were advised to do a range of motion exercises and use the hand for lighter activities as much as they could.

ECTR (Paper IV)

Single proximal portal endoscopic carpal tunnel release (Agee 1992) (Micro-Aire Surgical Instruments, Charlottesville, VA, USA) was used for all operations in Paper IV. Anesthesia was achieved by a local or regional nerve block and a forearm tourniquet. A small transverse incision was made 1.5 cm proximal to the wrist crease. The transverse carpal ligament was prepared with a synovium elevator radial to a longitudinal axis from the ring finger and proximal to a horizontal line from the maximally radially abducted thumb to the hook of the hamate (Kaplans line). Dilatators were used to create a path for the endoscope. After identification of the median nerve, transection of the carpal ligament and distal antebrachial fascia was carried out under visual control in a distal to proximal direction.

After the procedure, the wound was closed with wound tape only and a soft compressing dressing was applied. The patients were advised to do range of motion exercises and use the hand for lighter activities as much as they could. The dressing was reduced after 3 days and an adhesive bandage was applied to cover the wound tape for 10–12 days after surgery. The same senior consultant hand surgeon performed all operations.

Outcome measures

PROMs (Papers I,IV)

Patient-reported outcomes measure (PROM) is an indirect assessment and a way of recording symptoms or signs in a standardized manner, collected in the form of an ordinal scale of intensity (e.g. 1-5 from 1="no pain" to 5="constant pain"). Often these symptoms make up a score. The score is related to the mean symptom severity in the specific PROM.

BCTQ

The Symptom Severity Scale (SSS) from the Boston carpal tunnel syndrome questionnaire (BCTQ) was used (Levine 1993). The questions target symptoms caused primarily by CTS.

QuickDASH

Activity limitations caused by disease in the upper extremity were evaluated using the short version of the DASH form "Disability of Arm, Shoulder and Hand Questionnaire" (QuickDASH) (Gummeson 2006).

Satisfaction

The patients indicated their level of "satisfaction with the treatment" after the treatment period on a visual analogue scale (VAS), where the endpoints represented "not satisfied at all" (0) and "completely satisfied" (100) (Wewers 1990). In one study the Likert satisfaction score was graded in only five steps from 1 "very unsatisfied" to 5 "totally satisfied" (1-5).

Assessment of touch threshold (Paper I)

Assessments were performed at baseline, directly after the first treatment, and at the 8-week follow-up. Assessment of cutaneous touch/pressure thresholds was made on the tip of the index and little fingers on both hands in patients with CTS, and on the index finger of the dominant hand in controls, using a set of 20 Semmes–Weinstein monofilaments (SWM) (North Coast Medical Inc., Gilroy, CA, USA). Assessment was started with SWM no. 2.83 (representing a pressure of 70 mg) and thereafter continued in an ascending or descending order, depending on the answer for the first filament. Each filament was applied three times according to a standardized procedure (Bell-Krotoski 1993). Results were quantified from 0 to 20, representing the 20 monofilaments, with 20 corresponding to the lowest threshold.

Assessment of tactile discrimination (tactile gnosis) (Papers I, II)

Assessments were performed at baseline, directly after the first treatment, and at the 8-week follow-up. Tactile discrimination denotes sensory function based on active touch and enables recognition of shapes and textures without using vision. Two-point discrimination (2PD) was used at fingertip level of the index finger for assessment of tactile discrimination (tactile gnosis). The instrument used for 2PD was a single and pairs of blunted stainless-steel pins, with a diameter of 300 μ m, mounted on two separate discs to allow easy switching between the distances. The pins were separated by 0.7, 1.0, 1.3, 1.6, 1.9, 2.2, 2.5, 2.8, 3.1, 3.4, 4.0, 4.3, 4.6 and 5.0 mm. 2PD testing was done according to the ‘Moberg Method’ in a descending order with enough pressure to cause skin blanching. A score of at least 7 out of 10 correct answers was required to permit testing with pins with a smaller gap between them. To familiarize the test person with the test procedure and to eliminate biased results due to learning effects, testing of 2PD and touch threshold on the long finger was performed prior to the baseline testing (Figure 16).

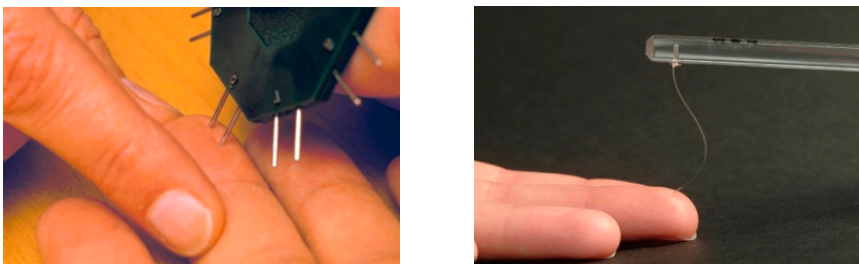


Figure 16 2PD and SWM measurements. Reprinted by permission of Birgitta Rosén

Assessment of dexterity (Paper II)

Assessments were performed at baseline and at the 8-week follow-up. The Purdue pegboard test for finger dexterity and speed was done using the right hand or left hand subtest and calculating the mean score of three consecutive trials. The pegboard is a board with two parallel rows of 25 holes, into which cylindrical metal pegs are placed by the patient. The score is the number of pins placed in 30 seconds (Tiffin 1948).

Multi-frequency vibrometry (Paper III)

Assessments were performed at baseline and at the 8-week follow-up. Vibration perception thresholds were measured at multiple frequencies using a VibroSense Meter[®] (Vibrosense Dynamics, Malmö, Sweden) in accordance with a previously described technique (Dahlin 2015). Before the examination, the operator explained the examination procedure to the patients. Essentially, the median and ulnar nerves were evaluated by recording vibration thresholds at the finger pulps of the index finger (innervated by the median nerve) and little finger (innervated by the ulnar nerve) bilaterally. The patients wore acoustic earmuffs to avoid bias from sound emitted by the vibration pin of the measurement unit. Since sensibility varies with temperature (Lele 1954), the finger temperature was monitored and was kept above 30°C during the examination. The examination started with the patient placing the finger to be examined on the vibration pin (Figure 17). When the patient perceived vibration, he or she indicated this by pressing a switch and by holding it depressed until vibrations were no longer felt. The VibroSense Meter[®] administers vibration at seven different frequencies (8, 16, 32, 64, 125, 250, and 500 Hz), and a median threshold value was recorded for each frequency from the index and little fingers of both hands. The patients and controls were examined in the same way, except that the controls were only assessed in the dominant index finger and little fingers.

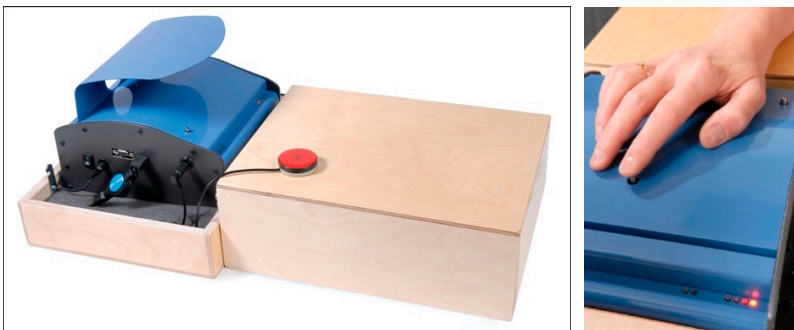


Figure 17 Vibrometry setup for examination Reprinted by permission of Vibrosense Dynamics AB.

Functional magnetic resonance imaging (Paper II)

In study II, fMRI was performed at baseline, after 90 minutes, and at the 8-week follow-up. fMRI was carried out to investigate cortical activation during tactile stimulation of the fingers using a whole body 3T scanner (MAGNETOM Skyra, Siemens Healthineers, Erlangen, Germany) equipped with a 20-channel head coil (Figure 18). A previously designed device for tactile finger stimulation was used in the MR camera (Weibull 2008). This device included eight easily attachable plastic membranes which deliver tactile stimulation using pressurized air. In addition, eight electronically controlled pneumatic valves, managing the air pressure delivery, made it possible to individually vary stimulation frequency, amplitude and duration.



Figure 18 3T whole body MR scanner.
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The stimulation device had six individually controlled channels, each consisting of a pneumatic valve (Festo, Germany) connected by a plastic tube (0.8 cm^2) to a chamber with a membrane (4-D Neuroimaging, San Diego, CA). The chambers were applied to the finger pulps of the thumb, index finger and little finger of both hands (Figure 19).

Stimulus was applied in a randomized fashion in order to avoid habituation. Cutaneous stimulation was administered to both the median nerve (thumb and index finger) and ulnar nerve (little finger). During the fMRI examination patients were told to rest both arms comfortably on cushions to prevent errors caused by motion or fatigue. Tactile stimulation of the fingers was performed in random order in a block design, alternating between stimulation and resting condition (100 ms pulse, 1 Hz pulse frequency, 2.5 bars pressure), resulting in four blocks of stimulation for each finger. Sequence parameters are provided in Paper II.

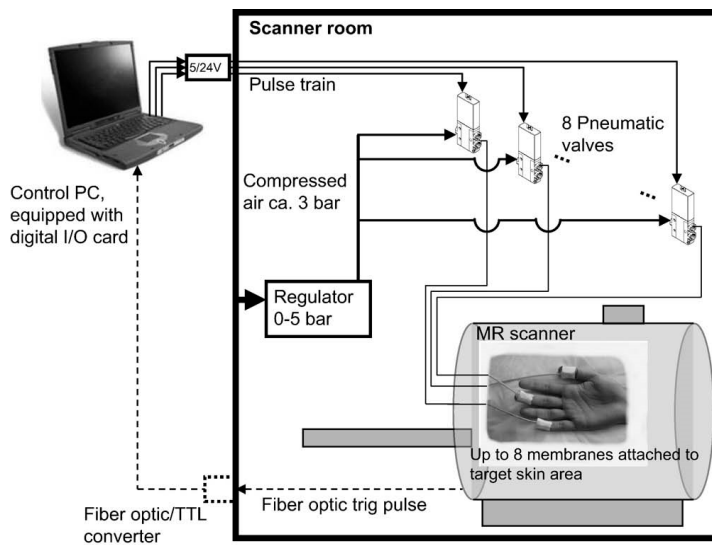


Figure 19 Schematic view of the stimuli system setup. Illustration from (Weibull 2008).
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Statistical methods

IBM SPSS statistics (Statistical Package for the Social Sciences, Version 22-25 for Mac, Armonk, NY, USA) was used for the statistical assessment of data obtained from the testing.

Paper I

Results for each group are presented with means and SD. The t-test was used and differences within and between groups are presented with means and a 95% confidence interval (CI). When the results were examined, they were normally distributed and the variability was small (standard deviation). Ordinal values are often tested using a non-parametric method. However, results were much the same when compared to parametric methods. For ease of interpretation, we then used uniform analyses of all variables, in cooperation with an experienced biostatistician.

Effect size of the mean difference in symptoms and specific sensory functions was calculated. A p-value below 0.05 was considered significant. The longitudinal changes between baseline and after eight weeks of treatment was calculated within groups. Bonferroni correction was made because of multiple pairwise comparisons. Consequently, p-values below 0.004 were considered significant.

Paper II

Brain imaging data sequences were analyzed of using SPM software package (FIL Methods Group, UCL 12 Queen Square, London) for Matlab (MathWorks, Natick, Massachusetts, USA). Results for each group are presented with medians and interquartile range. The Wilcoxon signed rank test (touch thresholds) and Mann-Whitney U test (tactile discrimination, dexterity and grip strength) were used for significance testing of the clinical assessments of hand function. These tests were used since the sample size of the groups were below 20. Fishers exact test was used for hypothesis testing of categorical data.

Paper III

Values are presented as median and interquartile range (IQR). As this was a matched-control study, the Wilcoxon signed rank test was used to evaluate any statistical differences between patients with CTS and the control group. This was done in cooperation with a biostatistician. The same method was used to evaluate whether there were any differences between hands in the same patient. When comparing subgroups according to Padua, the Mann-Whitney U-test was used for hypothesis testing of continuous and ordinal variables. Fisher's exact test was used for hypothesis testing of categorical variables. Spearman's correlation for non-parametric testing was used for investigation of correlations. Any p-value less than 0.05 was considered significant.

Paper IV

Values are presented as median and interquartile range (Q1–Q3). Comparison between groups was done using the Mann-Whitney U-test for unpaired continuous and ordinal variables. Comparison within groups was done using the Wilcoxon signed rank test for paired continuous and ordinal variables. Hypothesis testing of categorical data was made using Fisher's exact test. Any p-value less than 0.05 was considered significant. Correlations were calculated using Spearman's rank sum test. Odds ratio for the satisfaction score was calculated using logistic regression analysis. Patient satisfaction was dichotomized according to whether the satisfaction score was a higher (score 4 or 5) or lower (score 2 or 3). The logistic regression was carried out in collaboration with a biostatistician.

Sample size

Paper I

The primary outcome was the result of the Symptom Severity Scale (SSS) from the Boston carpal tunnel syndrome questionnaire (BCTQ) (Levine 1993). A change of 0.8 has been suggested to represent a significant clinical change (Leite 2006, Atroshi 2013). According to the sample size estimation for SSS (0.9 power and 0.05 significance level), the trial was able to detect a minimum difference of 0.8 (SD 1.0) in the SSS between the EMLA[®] and the placebo group when 66 patients were randomly assigned.

Paper II

Sample size calculation was not performed in voxel analysis of fMRI studies in 2010. The methods available at that time were statistically very demanding. The currently used fMRI power program for Matlab was first developed in 2011.

Paper III

Here there was no reliable way of calculating sample size, since there were no earlier studies to predict the difference between medians and there was no known minimal clinically relevant difference in VPTs between a healthy individual and a CTS patient.

Paper IV

A change of 10 points is considered a clinically relevant change in QuickDASH score between the groups (Kazmers 2019). The pre-study sample size estimation assumed a QuickDASH standard deviation of 17 points. To achieve a significance level of 0.05 and a power of 0.8, a total of 92 patients should be included.

Ethics

Papers I, II and III were approved by the Regional Ethical Review Board in Lund (DNr 1062–03, DNr 386–2007, 269–2008, and amendment 23–2011). Paper IV was approved by the Regional Ethical Committee of Region Syddanmark, Denmark (S–20110157).

All studies were carried out in accordance with the tenets of the Helsinki Declaration. All patients gave written informed consent prior to participation in the studies.

Results

For detailed information, about individual papers, please see the section where they are reprinted. Below is a summary of the findings, with additional information, not emphasized in the papers.

Paper I

We investigated whether patients with CTS (Table 4) would benefit from sensory training and guided plasticity using cutaneous forearm anesthesia.

Results

Primary outcome

There was no significant difference (mean difference = 0.05 units, $p = 0.78$, 95% CI = -0.3–0.4) in the results of the BCTQ symptom severity scale between the EMLA[®] group and the placebo group when comparing baseline and 8-weeks follow-up.

Secondary outcome

There were no significant differences observed regarding improvement in activity limitations (SSS), sensory functions (SWM and 2PD) or nerve conduction (SCV) between the groups. The BCTQ symptom severity scale ratings had improved significantly in the EMLA[®] group after 8 weeks ($p < 0.001$). However, in absolute numbers (Table 5), the improvement was 0.5 units on the BCTQ symptom severity scale, which ranges from 1 to 5, where 0.8 units is considered a clinically important change (Leite 2006).

Comments

Patients treated with EMLA[®] only showed improvement in tactile discrimination within the group ($p=0.001$) over eight weeks. The significance level was ($p<0.004$) after correction for multiple comparisons. There was however, a tendency towards improvement in all PROMs of both groups, with an improvement of 6.3-9.6 units in QuickDASH (Table 9). QuickDASH Minimal clinical difference (MCD) is about 10 units (Kazmers 2019). The difference between groups is illustrated by the carpal tunnel release frequency within 12 months. It was 47% in the EMLA[®] and 61% in the placebo group.

No treatment-related adverse events were observed in any of the groups. Comparisons by t-test at baseline did not show any significant differences between the groups for any of the outcome parameters (Table 5).

Table 4 Demographic data.

	EMLA [®] group	Placebo group
Gender (male: female)	7:27	9:27
Treated hand (right: left)	27:7	31:5
Age, mean (SD)	51.0 (9.1)	46.8 (8.5)

Table 5 Raw data at baseline, 90 minutes, and 8 weeks after treatment with EMLA or placebo.

		Baseline Mean (SD)	90 min Mean (SD)	8 weeks Mean (SD)
Symptom Severity Scale (SSS, 0–5)	EMLA [®]	2.7(0.73)		2.2(0.69)*
	Placebo	2.5(0.87)		2.2(0.85)
Activity Limitation (QuickDASH, 0–100)	EMLA [®]	30(17.50)		24(17.91)
	Placebo	35(21.52)		28(19.20)
Touch threshold digit II (SWM, 0–20)	EMLA [®]	18(1.24)	18(1.15)	18(1.05)
	Placebo	18(1.32)	18(1.43)	18(1.29)
Tactile discrimination digit II (2PD, mm)	EMLA [®]	3.4(0.77)	3.2(0.68)	3.1(0.68)
	Placebo	3.6(1.53)	3.4(1.12)	3.3(1.06)
ENeG nerve conduction (m/s)	EMLA [®]	30(5.3)		31(6.5)
	Placebo	31(6.8)		32(7.8)

* $p<0.001$ and effect size 0.63. Significant p -values <0.004 after correction for multiple comparisons. Effect size interpretation: trivial (ES <0.20), small (ES $0.20<0.50$), moderate (ES $0.50<0.80$), or large (ES >0.80).

Paper II

Cerebral changes were assessed in patients with unilateral CTS. An additional aim was to evaluate the short- and long-term cerebral effects of guided plasticity treatment using ipsilateral cutaneous forearm anesthesia in these patients.

Results

fMRI showed that sensory stimulation of the hand with CTS led to less cortical activation in the primary somatosensory cortex (S1) than stimulation of the hand without CTS (Figure 20).

Treatment with cutaneous forearm anesthesia on the side with CTS resulted in increased cortical activation in S1 both after the initial treatment and after 8 weeks of treatment, compared to the placebo group. Meanwhile, tactile discrimination improved in the EMLA[®] group, over time (Table 6).

Comments

Tactile discrimination (2PD) improved significantly for the hand with CTS in both the index and little fingers following the first EMLA[®] treatment. A significant improvement compared to baseline remained in the index finger following 8 weeks of treatment. Dexterity assessed using the Purdue Pegboard improved significantly on the affected side following 8 weeks of treatment. Neither patient-reported outcome, BCTQ, QuickDASH, distal motor latency (ms) nor sensory conduction velocity (m/s) did change between baseline and the follow-up clinical evaluation after 8 weeks of treatment in any group, except for BCTQ in the placebo group (Table 6).

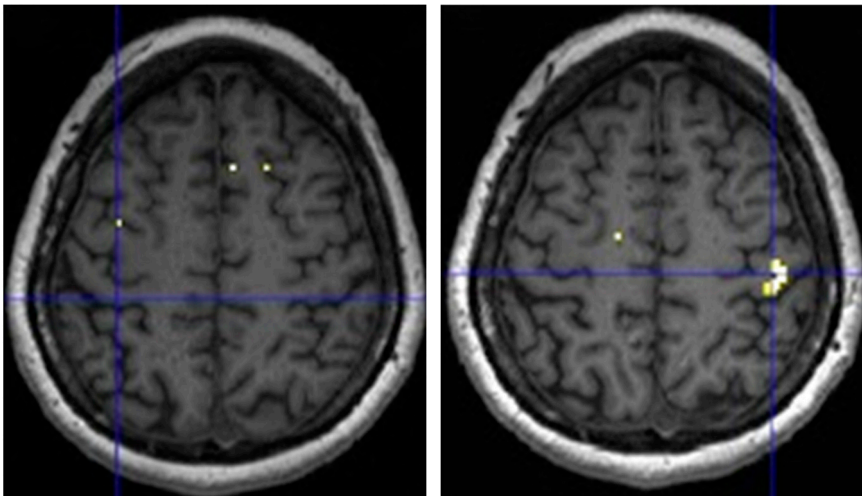


Figure 20 Activation clusters at baseline related to stimulation of median nerve innervated fingers

Activation clusters at baseline ($n = 24$), related to stimulation of median nerve innervated fingers (thumb and index finger) affected by unilateral CTS (left image) compared to stimulation of healthy median nerve innervated fingers (right image); extent threshold $k = 0$ voxels, $p < 0.001$ (uncorrected). (Neurological presentation with right hemisphere to the right). Activation clusters are related to statistical threshold levels. Threshold levels in the pictures are set as described in the method section.

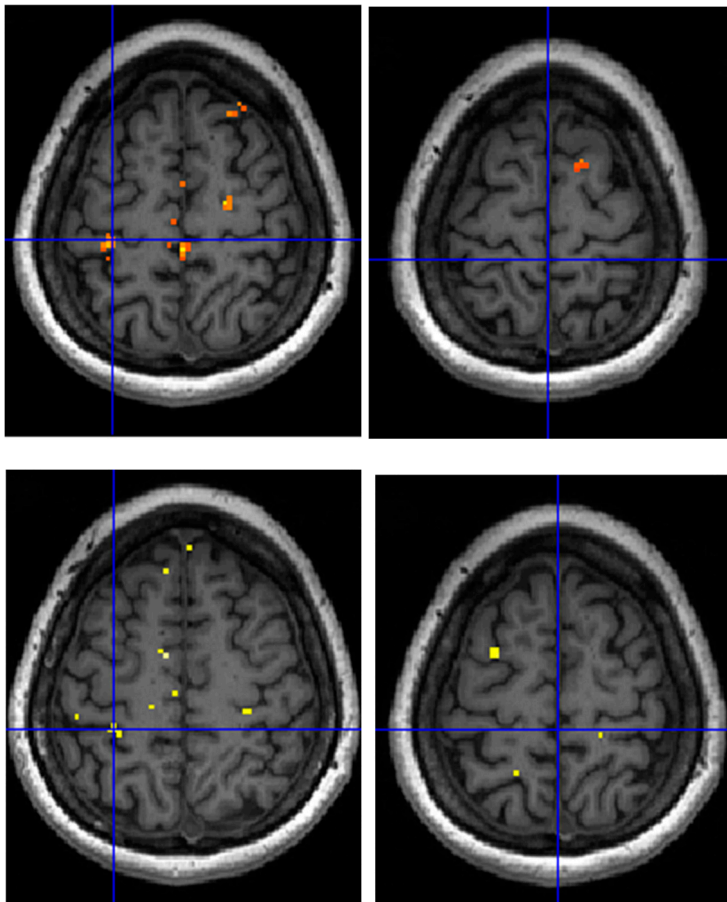


Figure 21 Mean activation related to stimulation of thumb and index finger

Mean activation related to stimulation of thumb and index finger of the affected hand compared to the healthy hand increase after short-term treatment (MR 2) with EMLA[®] (upper row) compared to baseline (MR 1) (left) while no increase is seen related to stimulation of thumb and index finger of the healthy hand compared to the affected hand (right). Similar, but less pronounced effects are seen when

comparing long-term follow-up (MR 3) to baseline (MR 1) (lower row). Paired t-test, extent threshold $k = 0$ voxels, $p < 0.01$ (uncorrected). (Neurological presentation with right hemisphere to the right).

Table 6 Outcomes in EMLA® and placebo group

Evaluated parameter		Cohort	Clinical evaluation (CE)			Statistical analysis (Wilcoxon sign)	
Digit	Side		CE 1	CE 2	CE 3	CE 1 vs CE 2	CE 1 vs CE 3
BCTQ (Boston carpal tunnel syndrome questionnaire), median SSS (symptom severity scale) 0-5 (range)							
		EMLA®	2.3 (1.5-3.9) ^a	-	2.3 (1.2-2.8) ^a	-	n.s.
		Placebo	2.7 (1.5-4.5)	-	2.4 (1.2-4.5)	-	$p \leq 0.05$
Activity Limitation, median QuickDASH (disability of arm, shoulder and hand questionnaire) 0-100 (range)							
		EMLA®	22.7 (4.5-54.5) ^a	-	11.4 (2.3-45.5) ^a	-	n.s.
		Placebo	34.1(0-86.4)	-	27.3 (0-86.4)	-	n.s.
Tactile discrimination, median 2PD (two-point discrimination) mm (range)							
II	IL	EMLA®	4 (2.5-5)	2.8 (2.2-4.3)	3.7 (2.2-4.3) ^a	$p \leq 0.05$	$p \leq 0.05$
II	CL		2.8 (2.5-4)	3.1 (2.2-4.3)	2.5 (2.5-4) ^a	n.s.	n.s.
V	IL		4 (3-4.6)	3.1 (2.8-4.3)	4 (2.8-5) ^a	$p \leq 0.05$	n.s.
V	CL		4 (2.2-5)	3.4 (2.8-5)	3.4 (2.8-6) ^a	n.s.	n.s.
II	IL	Placebo	3.4 (2.2-7)	3.4 (2.2-7)	3.1 (2.5-4)	n.s.	n.s.
II	CL		3.4 (2.2-4)	3.1 (2.2-4)	2.8 (2.2-4)	n.s.	n.s.
V	IL		4 (2.8-8)	4 (2.8-9)	3.7 (2.5-5)	n.s.	n.s.
V	CL		4 (2.8-5)	3.7 (2.8-6)	3.7 (2.5-4.6)	n.s.	n.s.
Purdue pegboard, median mean score							
	IL	EMLA®	14 (9-16) ^a	-	16 (10-15) ^b	-	$p \leq 0.05$
	CL		13 (10-16) ^a	-	12 (10-15) ^b	-	n.s.
	IL	Placebo	13 (11-18)	-	14 (12-17)	-	n.s.
	CL		14 (12-16)	-	13 (10-15)	-	n.s.

a, missing n = 2; b, missing n = 3; CL, contralateral to carpal tunnel syndrome; EMLA® (EMLA®; AstraZeneca AB, Södertälje, Sweden); n.s., not statistically significant vs; QuickDASH, disability of arm, shoulder and hand questionnaire; IL, ipsilateral to carpal tunnel syndrome.

Paper III

We investigated vibration thresholds in patients in different stages of CTS, compared to a matched control group using multi-frequency vibrometry.

Results

CTS patients were tested and compared to individually matched controls. Vibration thresholds were higher at all frequencies in the index finger (Table 7), as well as at nearly all frequencies in the little fingers.

In patients with unilateral CTS (n=38), the vibration thresholds were higher in the affected hand. A greater proportion of patients had bilateral symptoms at a higher Padua stage, i.e. more severe CTS. There was a correlation between a decrease in the sensory conduction amplitude of neurography and an increase in the VPTs of vibrometry.

Comments

We stratified patients according to their CTS severity grade. Compared to their individual controls, patients with mild CTS had significantly higher VPTs in the index finger at all frequencies except at 500 Hz. The patients with moderate CTS had significantly higher VPTs at all seven frequencies (Table 8).

Table 7 VPTs in patients with CTS and in healthy controls

Index finger	8 Hz	16 Hz	32 Hz	64 Hz	125 Hz	250 Hz	500 Hz
CTS (n=66)	108.6[4.9]	115.9[5.1]	117.5[7.8]	109.0[11.7]	110.3[10.3]	120.0[11.3]	133.4[13.1]
Controls (n=66)	105.0[6.6]	112.5[7.7]	113.1[6.1]	103.1[7.0]	102.0[9.7]	110.1[12.7]	125.9[13.2]
P-value	<i>< 0.001</i>	<i>0.001</i>	<i>< 0.001</i>	<i>< 0.001</i>	<i>< 0.001</i>	<i>< 0.001</i>	<i>< 0.001</i>

VPTs are expressed in dB. Data are median [IQR]. P-values are based on Wilcoxon's signed rank test
 Values in italics represent statistically significant differences

Table 8 VPTs in patients with CTS sub-divided according to Padua

Index finger	8 Hz	16 Hz	32 Hz	64 Hz	125 Hz	250 Hz	500 Hz
Mild CTS (n=11)	108.5[4.5]	116.2[10.0]	119.1[9.1]	109.0[11.9]	109.8[8.2]	117.8[10.2]	132.4[9.5]
Controls (n=11)	99.4[6.3]	108.2 [8.5]	107.8[7.3]	101.0[3.9]	97.2[9.6]	108.3[14.3]	125.3[17.1]
P-value	<i>0.011</i>	<i>0.041</i>	<i>0.006</i>	<i>0.008</i>	<i>0.016</i>	<i>0.050</i>	0.062
Moderate CTS (n=55)	108.9[5.3]	115.6 [4.3]	117.3[7.8]	109.0[11.6]	110.5[10.7]	120.4[12.3]	133.9[15.4]
Controls (n=55)	105.8[6.0]	113.3 [7.5]	113.6[5.0]	104.9[7.4]	102.8[9.8]	110.2[11.3]	125.9[12.7]
P-values	<i>0.009</i>	<i>0.010</i>	<i>0.001</i>	<i>0.001</i>	<i><0.001</i>	<i><0.001</i>	0.003

VPTs are expressed in dB. Data are median [IQR]. P-values with Wilcoxon's signed rank test
 Values in italics represent statistically significant differences

Paper IV

The subjective outcome after ECTR was evaluated in patients with clinical signs of CTS but normal ENeG.

Results

QuickDASH score was significantly improved in both groups (18 and 20 points respectively, $p < 0.001$) (Figure 22). Satisfaction score was significantly higher in the group with ENeG-verified CTS, odds ratio 3 (CI 1-8; $p < 0.02$) Nevertheless, satisfaction rates were high overall; 41/47 in the normal ENeG group and 45/47 in the group with abnormal ENeG.

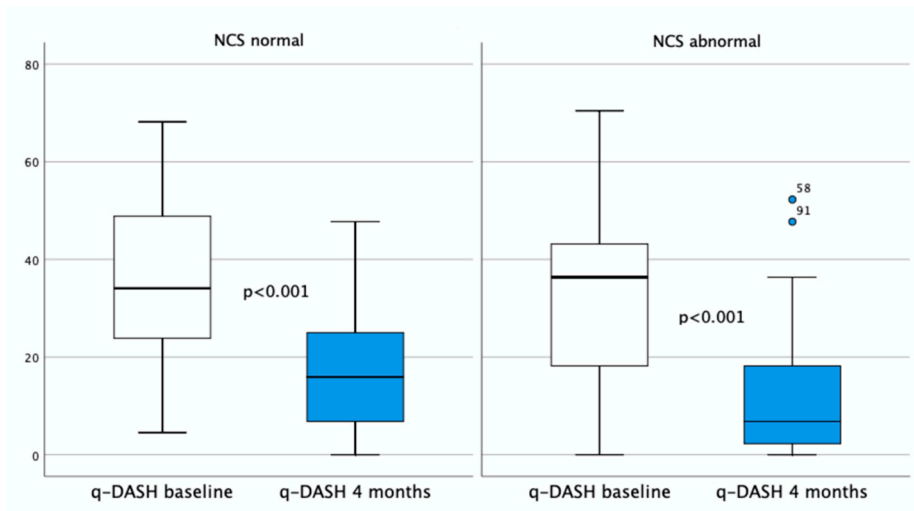


Figure 22 QuickDASH. The box plots represent ENeG groups (white-baseline, blue-four months) preoperatively and four months after surgery (median, IQR, range).

Comments

To adjust for age, both patient groups were divided into those younger and older respectively than the median age (42 years) for the study group. There was no significant difference between the old and young patient groups, independent of the ENeG result.

General discussion

This thesis focuses on how to diagnose CTS and the importance of preoperative electroneurography for outcome after surgery. It also focuses on how CTS affects sensory areas in the brain and the possibility of using guided plasticity to treat patients with CTS.

Research during the last few decades has increased our understanding of how the CNS and PNS react to nerve injury and how plasticity mechanisms can be used for therapeutic purposes. This thesis furthers our knowledge of how the CNS reacts to a nerve compression. This knowledge is essential for a better understanding of the symptoms seen in patients with CTS, and also for the ability to design treatment strategies using guided plasticity to treat CTS. Such treatments have become an integrated part of the treatment following peripheral nerve repair in the upper extremity. However, to our knowledge no prior study has evaluated the effects of guided plasticity on patients with CTS.

It is well known that patients with no clinical signs of CTS can display ENeG results suggesting the presence of CTS; it is also known that patients with clinical signs of CTS supported by pathological ENeG who, despite improving clinically after surgery, continue to display abnormal ENeG. This indicates a need for improved diagnostics for patients with suspected CTS.

Diagnosis of CTS

Accurate diagnosis of CTS is fundamental, both in clinical practice and in clinical studies of CTS. A thorough anamnesis and clinical examination is the cornerstone in the diagnostic work-up of patients suspected of having CTS. Patients who display a typical anamnesis and have positive clinical tests are often easily diagnosed with a CTS, and most of them indeed have a CTS. However, a certain number of patients with typical anamnesis and clinical findings do not have CTS, which becomes obvious when they do not improve after CTR. In addition, many patients have a vague anamnesis and ambiguous clinical findings. There is no consensus about the relative importance of symptoms, signs, and tests in patients with suspected CTS. Graham (Graham 2006, Graham 2008) has explored the effects of a standardization of clinical criteria without reaching a general conclusion. This points to the need for

more advanced tests to establish or exclude the diagnosis of CTS. It has been suggested that combining anamnesis, clinical tests, including specific sensory tests, and ENeG provides the most reliable diagnosis (Rempel 1998, Graham 2016). This has led some countries to recommend using ENeG for a secure diagnosis in all patients with suspected CTS, before deciding on operative treatment (Katz 2002, Bland 2007).

Our findings in Paper IV, reinforce the importance of an accurate clinical diagnosis, possibly supported by ENeG, for a satisfactory outcome, but also that ENeG-verified patients have statistically higher satisfaction. However, even the non-ENeG-verified patients have a high grade of satisfaction. ENeG also adds time and cost in establishing the CTS diagnosis.

Diagnostic tests in CTS

The American Academy of Orthopaedic Surgeons (AAOS) has assembled clinical practice guidelines for CTS. The latest version supports the use of ENeG or PROMs to establish the diagnosis of CTS. However, according to the AAOS, there is limited evidence to support routine use of ultrasound in the diagnosis of CTS; the use of multi-frequency vibrometry in the diagnosis of CTS is not mentioned at all (Graham 2016). Clinical signs of CTS with a normal ENeG is often considered a “false negative” result (Bland 2001). This view implies that the use of some variant of ENeG is a gold standard for diagnosis of CTS; an idea supported in former versions of the AAOS guidelines, but not in the current one (Graham 2016). Many Swedish practitioners use ENeG as a supplement in unclear cases. However, it has been shown that as many as 30% of patients with clinical symptoms of CTS have a normal ENeG (Witt 2004, Atroshi 2011). Some argue that ENeG measures median neuropathy at the wrist which may not correspond to the underlying pathology causing the symptoms of CTS (Sonoo 2018). Furthermore, ENeG measures the function of large myelinated nerve fibers, but small nerve fibers that mediate pain are not assessed (Werner 2002). These facts indicate a need for additional diagnostic modalities in patients with CTS.

Assessment of vibrations thresholds, at one frequency, has been used as a screening instrument in a working population, to detect hand arm vibration syndrome (HAVS) but studies were unable to detect a correlation between ENeG parameters and vibration thresholds (Werner 1995). The technique to assess vibration thresholds has been developed further, including assessments at multiple frequencies (Lundborg 1986). Assessment of vibration perception thresholds at multiple frequencies evaluates function both in the peripheral receptors and in the peripheral nerve (Dahlin 2015). Earlier studies also indicate that vibrometry can detect HAVS (Lundborg 1987, Stromberg 1998). Patients with HAVS can have symptoms that

mimic those of CTS, or even have coexisting CTS and HAVS. Furthermore, patients with diabetes and CTS have been shown to have an increased vibration perception threshold in median nerve innervated fingers (Thomsen 2011). Paper III corroborated these findings in patients with clinical and ENeG-verified CTS, showing a significant difference between vibration thresholds in CTS patients and healthy controls. However, we were not able to show any correlation between vibrometry and ENeG.

Patients with CTS are likely to have normal peripheral receptors in the fingers and the pathological vibration perception thresholds shown in Paper III probably indicate pathology in the median nerve. Given the results in Paper III, where vibration perception thresholds were increased at all frequencies, multi-frequency vibrometry may have a role in the diagnostic work-up in patients with suspected CTS. Furthermore, it may also have a role in patients who have had a CTR operation but do not experience symptom relief. In such cases, increased vibration perception thresholds may indicate impaired function in the peripheral receptors, delay in the recovery process or an intrinsic scar formation in the median nerve which is not amenable to further surgery (Konchalard 2011).

Vibrometry, like all examination tools, has shortcomings. Detection of vibration thresholds requires the patients to pay close attention for accurate data to be obtained. Both ENeG and vibrometry measurements are temperature sensitive, and in the case of vibrometry, and according to some, it is more pronounced in higher than in lower frequencies (Harazin 2007). In our study the examiner took care to measure the temperature of the subject's fingers to avoid any temperature variability. In addition, HAVS, which mimics the symptoms seen in patients with CTS or even co-exists with CTS, was one of the exclusion criteria in the study. Most patients with CTS are upper middle aged and thus display greater variability in their vibrometry, making detection of small differences difficult (Bloom 1984).

Ultrasound examination of the median nerve is another potential method for complementing clinical diagnosis. The studies in this thesis did not use ultrasound, but the method has shown promising results as one tool to use in diagnosing CTS (Padua 2008, Cartwright 2012). While ultrasound is quick and painless and can be specific and sensitive, it requires expensive equipment and specially trained staff. In some patients with normal ENeG, it would be a valuable supplement in the diagnosis of CTS. In such patients, an additional diagnostic test—the cross-sectional area of the median nerve proximal to the level of the pisiform measured by ultrasound—has been found to have greater specificity for CTS (94%) than ENeG (specificity for CTS: 83%) (Fowler 2015).

Clinical Outcomes of CTS

Standards for the outcome of CTS treatment constitute another key detail in a clinical CTS study. The outcome measures used are standardized, with SSS of BCTQ (Leite 2006), QuickDASH, SWM, and 2PD (Jerosch-Herold 2011). Minimal clinical difference (MCD) is the smallest difference deemed to be important. Nevertheless, a minimal clinical difference can vary in different populations (Jerosch-Herold 2011, De Kleermaeker 2019, Kazmers 2019). In Paper I, tactile discrimination improved after 90 minutes in patients treated with EMLA[®]. The improvement was not statistically significant after application of the Bonferroni adjustment for multiple comparisons ($p < 0.02$), but came close to the MCD for tactile discrimination.

Bonferroni correction reduces the risk of getting any false positive result from statistical tests (type 1 error). Such correction for multiple comparisons gives a corrected, lower p-value level for significance; in Paper I it was 0.004.

An alternative way of considering the clinical effect of the intervention in Paper I is that all patients were offered CTR, without delay, after the study. However only 47% in the experimental group, compared to 61% in the control group, were operated on within a year.

Cerebral effects of nerve injury and neuropathy

Central and peripheral effects of a median nerve injury are fairly well described in the literature. A median nerve injury that has been repaired is known to result in a cascade of events, both in the CNS and PNS, resulting in both functional and structural changes (Kaas 1983, Taylor 2009, Chemnitz 2015). Following transection of a peripheral nerve some axons and their corresponding cell-bodies die. A number of those axons that regenerate, navigate incorrectly and reinnervate the wrong targets (Brushart 2011). This is shown in impaired sensory and motor function and a pathological result of ENeG (Chemnitz 2013). The change in afferent nerve signaling shapes the S1 and the motor-network, which adapts. Earlier studies have shown that those operated on for median nerve injuries in childhood have excellent sensory function (Chemnitz 2013, Rosen 2015) even though they have a changed afferent nerve signal in the injured nerve, evident as a pathological ENeG. Interestingly, these people showed a completely normal activation in somatosensory areas in the brain if they had sustained their injury before 12 years of age. This suggests that the young brain can adapt and interpret the changed afferent nerve signal from the injured nerve whereas the older brain find this difficult, as shown in the impaired restitution of sensory function in the injured nerve.

Central and peripheral effects of neuropathy are less studied; studies on central effects are scarce. Changes in S1 and motor network are often driven by a change in afferent nerve signaling. Patients with a neuropathy often display a pathological ENeG, indicating a change in afferent signaling. However, this change is probably different in patients with neuropathy than the changed afferent signaling in nerve-injured patients. Therefore, the cerebral changes seen in patients with neuropathy may differ from those seen in nerve-injured patients. One previous study, using fMRI has shown deranged somatotopy in S1 in patients with neuropathy due to long-term exposure to hand-held vibrating tools (Björkman 2010). Paper II, showed a smaller cortical activation following cutaneous stimulation of the affected hand. These findings seem logical given the reduction in velocity and amplitude of the nerve signal in these patients with CTS. However, the results from Paper II contrast with those in a previous study that addressed cerebral changes in CTS, where a larger and stronger activation, with a smaller separation distance between index and long finger was found in the somatosensory area following stimulation of the index- and long fingers. The separation distance between index- and long fingers was statistically significant (Napadow 2006); however, the distance was below the smoothing distance of 4 mm, and may cause a spatial shift of the activations, meaning that the significance could be an artefact (Mikl 2008). Another difference is that Napadow et al found a correlation between ENG to fMRI, whereas we could not reproduce this correlation. One important factor that may explain the differences between study II and Napadow et al is that Napadow used electric stimulation to stimulate the fingers. We on the other hand used a hydraulic system to apply pressure to the fingertips, at a standard intensity. Our stimulation equipment applies an equal amount of pressure stimulation to the fingers.

The electric stimulus intensity was set relative to the pain threshold (Napadow 2006). This is a method used in studies assessing cerebral changes following nerve injuries to standardize the perception of stimulus in patients. Thus, Napadow et al used a higher stimulus intensity in CTS patients, with poor sensibility compared to those with good sensibility. Furthermore, mechanoreceptors mainly respond to pressure and vibration, such as that administered in study II. A higher sensory threshold in a patient with neuropathy may be missed using electrical stimulation (Mizobuchi 2002).

CTS may also lower the pain threshold and therefore a strong electrical stimulation could potentially lead to a coactivation of pain pathways (Fernández-de-las-Peñas 2009). If this happens, some activation changes might be due to activation of the pain pathways, as opposed to the sensory pathways, especially with stronger stimulation. Furthermore, extraterritorial sensitization resulting in hyperalgesia has been described in unilateral CTS (Zanette 2010). Sensitization could potentially lead to a coactivation of pain pathways, thus increasing the area or strength of activation.

In study II, cutaneous stimulation of the median nerve innervated fingers on the healthy side resulted in a larger activation than stimulation of the fingers on the

affected hand. This was not the case in the earlier comparison between CTS and healthy individuals (Maeda 2013). The size difference between affected and non-affected sides was smaller than between CTS and healthy controls (Napadow 2006). This could also be due to the stimulation paradigm choosing not to compensate for the strength of stimulation.

In analogy with the findings in nerve injured patients (Chemnitz 2013), plasticity caused by a CTS could also result in changes in the ipsilateral S1. However, no such changes were detected. Given that the sensory areas in the two brain hemispheres are heavily interconnected, a change in activation in the hemisphere ipsilateral to the affected hand might be expected. Such activation may be below the detection threshold used in study II and thus was not detected. Further studies are needed to evaluate the role of the ipsilateral S1 in patients with CTS.

Guided plasticity in CTS

Plasticity can be guided to promote the recovery of functions lost in a nerve injury (Duffau 2006). Several different types of rehabilitation strategies, where guided plasticity is used, have proved beneficial in patients operated on for a median and/or ulnar nerve injury (Merzenich 2014, Rosen 2015). One such technique, cutaneous forearm anesthesia, using an anesthetic cream applied at gradually increasing intervals, has been shown to improve sensory function in patients operated on due to a median and/or ulnar nerve injury. The neurobiological basis for the improvement is thought to be recruitment of more neurons able to process afferent signals from the injured hand (Bjorkman 2005, Rosen 2015). The challenge when using guided plasticity in the rehabilitation is to achieve a prolonged or permanent improvement. One solution is to combine cutaneous anesthesia with a sensory re-education program, in order to consolidate the cerebral adaptation (Vikstrom 2018). Guided plasticity has not previously been applied to patients with CTS.

The hypothesis was that patients with CTS might benefit from sensory training in combination with cutaneous forearm anesthesia. Participants in Papers I and II had mild or moderate CTS, which are the most common grades of CTS in clinical practice. These patients have a measurably reduced sensory and motor nerve conduction but a near normal to normal tactile discrimination and perception of touch. Both studies I and II showed improvement within the group treated with cutaneous forearm anesthesia. However, there were no statistical improvements compared to placebo treatment over 8 weeks. Interestingly, study II showed an increased activation in the S1 following the first cutaneous forearm anesthesia treatment, and in the subsequent 8 weeks of treatment. This indicates that the concept behind cutaneous forearm anesthesia works, with potentially more neurons being recruited. However, this did not result in significantly improved sensory

function compared to a placebo group. There are several possible explanations for these findings;

One feasible explanation for less improvement in sensibility in CTS cases with normal sensibility is that sensory information transmitted in the median nerve is delayed but still provides sufficient afferent input to the S1. When the afferent input is normal or near normal, an increased processing capability cannot be expected to significantly increase the sensibility. Another explanation could be that SWM and 2PD are not sensitive enough for this purpose. There was a clear ceiling effect in the improvement of touch thresholds. The improvement in both the treatment and the placebo group could be attributed to the effect of sensory awareness after the sensory training. Furthermore, in studies of CTS some improvement is common, possibly attributable to the normal clinical course of CTS.

Earlier studies have established that a median nerve that has been damaged and repaired, results in functional and structural changes in the brain (Merzenich 1983, Chemnitz 2015). At present it is not known how a unilateral CTS changes the task-related cortical activation. In line with clinical studies (Björkman 2009, Taylor 2009) the hypothesis was that patients with CTS might benefit from guided plasticity with sensory training. This effect would be enhanced if supplemented by EMLA[®] treatment. It is supposed that the improved sensory function after guided plasticity aided by cutaneous anesthesia is the result of more nerve cells in the cortical region supplying the anesthetized area are being made available for processing sensory information from the hand.

In some CTS patients there is a marked decrease in nerve conduction speed or a complete conduction block. Severely reduced sensory function is a late sign of CTS (Schmid 2014). The most common median nerve entrapment of Padua CTS grade 3-4 (mild and moderate), however causes a measurably reduced sensory and motor nerve conduction (Padua 1997). Our group of patients with Padua grade 3-4 have near normal to normal tactile discrimination and perception of touch. This is not the case after a median nerve transection or severe neuropathy after long-term exposure to hand-held vibrating tools. Consequently, it could be argued that guided plasticity would be more effective in more severe CTS.

However, in our group of mild to moderate CTS, there were measurable effects from treatment with guided plasticity. Differences could be measured, both in activation of the sensory cortex and in short-term tactile discrimination. Guided plasticity could be attributed to the effect of sensory awareness after sensory training, in this way causing an improvement in outcome scores in both groups. Improvement in both study groups is common in studies of CTS and can perhaps be attributed to the normal clinical course of CTS (Dammers 1999, Armstrong 2004, Burton 2016).

The effects on clinical outcome of guided plasticity, although statistically significant in some cases, had only a minor clinical effect. The improvement was subclinical, with 0.5 units in BCTQ and 6.3 units in QuickDASH. It should, however, be pointed

out that around 47% of the patients in the experimental group had not been operated on after one year, since they experienced improvement in CTS symptoms.

Internal and external validity

Internal and external validity should always be considered in a scientific study. Are the conclusions of this research reliable? Are the results applicable to my patients? There are a number of factors that affect the internal validity of a study. Selection of eligible patients for inclusion in a study is based on inclusion criteria and preferably a control group is included.

To be regarded as a valid sample of the population a cohort study should include a consecutive sample from the entire/general population. A typical selection bias would be not to include all eligible patients, in order to produce a result that fits the hypothesis. The investigator is responsible for preventing such flaws in clinical studies.

This thesis includes two randomized prospective studies, one of them blinded. All available patients were included to avoid selection bias. One way of checking for selection bias is to compare the baseline characteristics. However, in smaller clinical studies there is a higher risk of non-identical baseline data between groups (Hernán 2004). In Paper IV there was a small difference in age between the severity groups. Theoretically, this might reflect the smaller sample size, but more than 100 patients were included. Another explanation for the 6-year age difference in baseline data could be that one group had both clinical and ENeG findings, and older patients usually have a more severe disease. To reduce this, age correction was added to our analysis.

The correlation between the independent variable and the dependent variable may be hard to verify. In Papers I-III, the inclusion criterion was only Padua stage 3 and 4 and we selected a narrow span of ENeG severity, thus making correlations more difficult to detect. In addition, the sensibility tests and PROMs have ceiling effects (Gelberman 1983) which could prevent the outcome instruments and examinations from detecting any differences in the dependent variable. Yet another factor that is important for internal validity is whether the treatment (independent variable) precedes the change in the PROMs, sensibility and ENeG (dependent variables). It seems self-evident, but it may be complicated in a disease such as CTS, which has a variable course of progression. In Papers I-III, the inclusion criterion of having had symptoms for more than three months may reduce the symptom variability. Gender, age, or profession, for example, could be confounding factors (Burton 2016). We have recorded demographic data for many of these confounders in the group comparisons in the papers. The age correction and comparison of professions between groups in Paper IV was done to compensate for confounders in our analysis.

Can we apply the papers of this thesis to other groups of patients with CTS? Patients in Papers I-III are graded as having the two most common forms of CTS severity grades which probably apply to CTS patients. The male/female ratio was lower than in some studies, but the inclusion criteria for severity were narrow, which reduces gender differences in CTS severity. Males have a more severe CTS, when they seek medical attention (Padua 2001). The Mølholm cohort represents CTS patients in private practice and this also conceivably applies to them and probably to outpatients in the public setting.

Drop-out bias should also be taken into account. It can be seen when healthier patients drop out, reducing the likelihood of detecting any difference between groups. For example, CTS patients who are not feeling ill, and may not want to fill out forms and be contacted after eight weeks, may be more likely not to stay with the studies (Chin 2008). In our papers, the drop-out frequency was low (below 5%) and should have little consequence for the results. Patients in private care may also be less inclined to join a clinical study, particularly if it means they must wait for an extra ENeG investigation. This is called volunteer bias, and in this manner, many clinical studies suffer a lower inclusion rate (Chin 2008). A selection of appropriate individuals for studies is always a challenge. Selection bias could also arise from the inclusion criteria. Patients in a more severe ENeG group will be older and have other physical problems. We also noted an overrepresentation of manual labor in the group with more severe CTS.

Volunteer bias is present in all studies, it means that the sample is restricted to those who volunteered or elected to participate. Historically, women have been underrepresented in clinical trials (Schiebinger 2003), partly because of legislation regarding fertile females, but also because of the inclusion criteria for studies in the past and societal restraints. Recent overviews presented on musculoskeletal disease, show that female gender predisposes for inclusion, and that women are more likely to give informed consent (Feldman 2019). We recruited more women than men in our studies, even taking into considering the female dominance of CTS.

Observation bias can arise from employing different ENeG methods for verification of CTS. When we use a sensitive, comparative ENeG method, with a higher sensitivity but lower specificity, patients with less nerve affection are more often classified as ENeG positive more often. The ENeG method must be standardized and fully disclosed to allow the reader to compare results (Stalberg 2019).

Strengths and limitations

This thesis has strengths and limitations. A major strength was the prospective design of the studies and very strict inclusion criteria, including subjective symptoms, objective clinical status and ENeG. Furthermore, in the study assessing cerebral changes only patients with unilateral, ENeG-verified CTS were included. This was important since it is well known that sensory and motor areas in the two brain hemispheres interact and thus if patients with bilateral CTS would have been included it would have been difficult to assess if cerebral changes were attributed to the investigated hand or secondary to the not examined hand. In addition, all examinations were done by examiners blinded to the intervention.

Limitations were the sample size, and rate of inclusion. We made sample size calculations prior to study start for the clinical studies in paper I and IV to provide general validity to our conclusions. Given that CTS is very common we were surprised by the slow inclusion rate. This was partly due to the strict inclusion and exclusion criteria, and also due to logistical problems in a large clinical setting over a long period of time which rendered some patients could not available for inclusion.

Conclusions

The papers in this thesis support the following conclusions:

- Guided plasticity, using cutaneous forearm anesthesia, resulted in no improvement in hand function in CTS (Paper I).
- Patients with unilateral CTS showed smaller activated S1 volume contralateral to the affected hand (Paper II).
- Cutaneous forearm anesthesia for eight weeks resulted in a larger activation in the contralateral S1 and improved sensory function in the hand with CTS (Paper II).
- Patients with CTS had impaired VPTs at all frequencies compared to the controls (Paper III).
- Outcome after ECTR was favorable, regardless of the ENeG result (Paper IV).
- However, patients with a normal ENeG result had a lower result in satisfaction score after ECTR than patients with ENeG verified CTS (Paper IV).

Future perspectives

Guided plasticity could be beneficial in patients who have not improved after CTR. Further studies should focus on how to achieve clinical outcomes after surgical treatment of CTS that are generally favorable. However, there is potential for improvement in both diagnosis and treatment.

Selecting the right patients for surgery is always a challenge and a cornerstone in this process is a correct diagnosis. In many countries ENeG is considered the golden standard for diagnosing CTS. However, ENeG has shortcomings and future studies should address alternative diagnostic methods such as multi-frequency vibrometry. This technique has the advantages that it assesses function in both the peripheral receptor and the nerve. Future studies should address outcomes following CTR in patients where the diagnosis has been made using multi-frequency vibrometry.

This thesis shows the presence of cerebral changes in the sensory area in the brain in patients with CTS. The role of these cerebral changes is not clear and should be studied further. Are the cerebral changes reversible following CTR? Do patients with residual symptoms following CTR show more pronounced cerebral changes? These are important questions which additional research needs to answer.

As understanding of basic neurophysiology in health and disease increases, so too does the possibility of using guided plasticity for treatment. In patients with CTS some of the symptoms are related to a local compression of the median nerve at the carpal tunnel. Thus, alleviating this pressure is an important part of treatment. However, we do not know why some patients, including those that are ENeG-verified, do not improve after decompression. A better understanding of the local processes in the median nerve following decompression is important, as are the long-term effects of treatment, and ideally, permanent improvement when guided plasticity treatment is used.

Summary

Carpal Tunnel Syndrome (CTS) is the most common compression neuropathy causing pain, impaired hand function and sick leave. CTS is usually diagnosed based on patient history and clinical tests. In some patients an additional ENeG is done to support the diagnosis. However, ENeG can show pathology in healthy people and show normal values in patients with overwhelming clinical signs of CTS. Traditionally CTS is treated with CTR, however it is well known that a number of patients do not improve after surgery.

The understanding of the human nervous system has increased dramatically during the last few decades. This has made it possible to better understand symptoms seen in patients with nerve injuries and to design treatment strategies where the dynamic capacity of the brain, i.e. brain plasticity is guided for therapeutic purposes.

The aim of this thesis was to assess cerebral changes following CTS, and evaluate treatment using guided plasticity for patients with CTS. A further aim was to evaluate whether analysis of vibration perception thresholds at multiple frequencies can detect CTS, and if ENeG results are important for post-operative outcome following CTR.

The first two studies evaluated the clinical and cerebral effects of treatment using guided plasticity in the form of cutaneous forearm anesthesia over 8 weeks. The results show that cutaneous stimulation of the hand with CTS causes activation of fewer neurons in the S1 compared to stimulation of a healthy hand. The concept of guided plasticity works, and treatment using guided plasticity results in recruitment of more neurons in the S1. However, it does not result in improved sensory function in the affected hand.

Study III shows that patients with clinical and ENeG-verified CTS have increased vibration perception thresholds at multiple frequencies in all fingers. This suggests that analysis of vibration perception thresholds using multi-frequency vibrometry can serve as a diagnostic tool for CTS.

The last study, Study IV, showed that the outcome after endoscopic CTR is beneficial. This study also shows that the subjective outcome after endoscopic CRT is better if the patient, in addition to a typical history and positive diagnostic tests also has an ENeG indicating CTS as compared to a normal ENeG.

Future studies should focus on evaluating the role of treatment using guided plasticity in patients with residual symptoms after CTR. In addition, the role of multi-frequency vibrometry in the diagnostic work-up in patients with suspected CTS should be studied.

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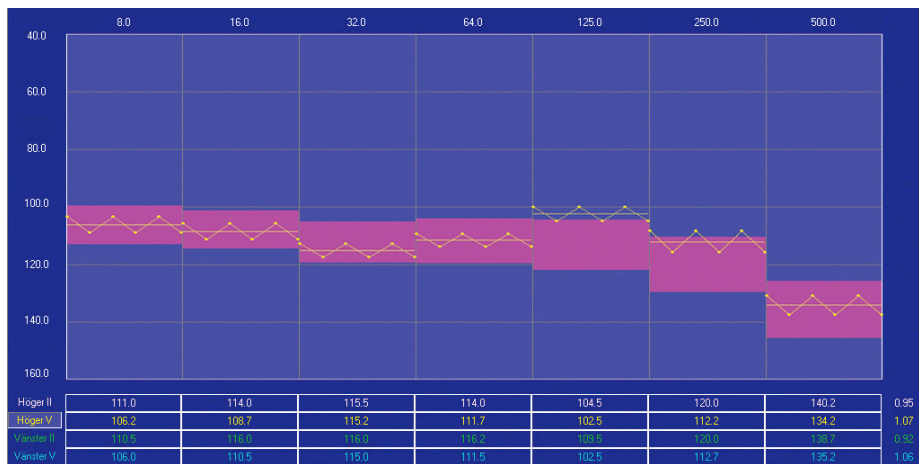
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Appendix

Vibrogram

Normal



Normal Vibrogram. Reprinted by permission of Vibrosense Dynamics AB.

Pathological



Pathological Vibrogram. Reprinted by permission of Vibrosense Dynamics AB.

*“There are known knowns; there are things we know we know.
We also know there are known unknowns; that is to say
we know there are some things we do not know.
But there are also unknown unknowns — there are
things we do not know we don't know”*

Donald Rumsfeld