Studies of upper limb pain in occupational medicine, in general practice, and among computer operators
Diagnostic contribution from manual muscle testing and assessment of cutaneous sensibility and nerve trunk mechanosensitivity

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ORIGINAL PAPERS
This thesis is based on the following papers, which will be referred to by their Roman numerals:
IV. Jepsen JR. Can testing of six individual muscles represent a screening approach to upper limb neuropathic conditions? BMC Neurology 2014;14:90 [4].
VI. Jepsen JR, Thomsen G. A cross-sectional study of the relation between symptoms and physical findings in computer operators. BMC Neurology 2006;6:40 [6].

Les affections du système nerveux sont, parmi toutes les maladies, celles qui obéissent le plus aux caprices des préoccupations scientifiques. C. Lasègue 1864 [9].

INTRODUCTION
In spite of high incidence [10], persisting symptoms and serious effects on life quality and work capacity [10-17], the ability to diagnose, manage and prevent work-related upper limb disorders has progressed only slowly.

During the last decennials I have noticed the high number of upper limb patients in clinical occupational medicine and the diagnostic challenge that they represent. The diagnostic difficulties are reflected by frequent consultations in various medical specialties with different diagnostic traditions and preferences and consequently diverse diagnostic outcomes. The management and advice given to these patients are not always helpful. It is obvious that many patients suffer from serious pain and functional limitation that threaten their future work-life. This situation is clearly unsatisfactory.

In addition to upper limb pain, many patients complain of symptoms such as muscular weakness and/or numbness and tingling that suggest an involvement of the nervous system. According to general consensus, a sufficient neurological examination should be included in the examination of patients presenting with such symptoms, but this is not always done.

To better understand the pathophysiology and diagnostic features of work-related upper limb conditions, I conducted a literature study on the issue with an emphasis on disorders that are not covered by diagnostic case definitions and on the potential involvement of the peripheral nerves in these conditions. I found that many of the symptoms and signs reported for these “non-specific” disorders could represent nerve afflictions. Equally important, I updated my knowledge with regard to upper limb anatomy with particular emphasis on the mechanical function of the muscles, and on nerve topography and innervation patterns. All three samples of study subjects in the subsequent empirical studies underwent a physical neurological upper limb examination developed by the Swedish professor in hand surgery Carl-Göran Hagert with the aim to identify and locate upper limb nerve afflictions.

BACKGROUND
Impact and challenges of upper limb disorders
Management of any disorder will benefit from a precise identification of the injured tissue and the character of the involved pathology. In the absence of such insight, the intervention may...
target healthy tissues or even worsen the condition. Prevention may also miss its goal.

Upper limb conditions occurring secondary to obvious injury or to inflammation following acute trauma or systemic disease may be straightforward to diagnose. However, if there are no confirmatory physical findings, the type of involved tissue, the specific structure, and the implicated pathology cannot be identified. This diagnostic challenge applies in many upper limb patients.

Upper limb disorders are common in general practice and in medical specialties such as rheumatology, orthopedic surgery, neurology, and occupational medicine. They have a substantial impact on physical function and use of health care. The high frequency of consultations of chronic cases in the secondary health sector reflects the limited success of prevention and poor responses to established treatments. Hagberg has pointed out the limited scientific evidence for clinical prognostic assessments and for successful procedures for returning to work despite the large number of these conditions. For the individual as well as for the community, there are serious consequences and major financial burdens of sick leave, early retirement, and compensation issues.

In a sample from general practice, the incidence density was calculated to 97.4/1000 person-years with persisting complaints after 6 months in about 50%. In the general population, 3.152 out of 6.038 subjects reported upper limb symptoms. Among 1,960 physically examined subjects, 44.8% had one or more specific soft-tissue disorder.

The role of occupational exposures is not clear. Epidemiologic surveillance has classified a high proportion of upper limb disorders as probably work-related (95% in men and 89% in women of age <50, and 87% in men and 69% in women of age >50) in one study. Seven percent of 827 workers reported work-related upper limb symptoms during three years of observation, and 12%/3% had persistent and 27%/8% fluctuating symptoms/work limitations, respectively. Systematic reviews have indicated highly repetitive work, forceful exertions, and awkward postures as risk factors for shoulder and elbow disorders and demonstrated a modestly increased risk with low-force repetition and rapidly increased risk for high-force repetition. However, the level of evidence for work-relatedness is low.

A systematic review of recent longitudinal studies found no strong evidence of work-relatedness, and only reasonable relations regarding mechanical exposures to heavy physical work, awkward postures, repetitive work, and computer work. A Swedish review found only limited scientific evidence for the etiological role of mechanical risk factors. The diagnostic constraints are illustrated in a study of epicondylitis. Whether blinded or not there was a low inter-examiner reliability of the examination, and palpation tenderness was present in many non-symptomatic subjects but only in few subjects with at least moderate elbow pain. Consequently, the authors suggested that the diagnosis of epicondylitis should be restricted to patients with severe pain and classical signs of inflammation, and that epidemiological research should deal with pain, clinical signs and disability as separate outcomes.

Diagnostic consensus criteria for “specific” upper limb disorders can be based on clinical experiences, analyses and discussions on the available information by work groups of experts representing various specialties. The criteria should cover at least the majority of conditions, and should be validated and redefined in case of low diagnostic power. There is no international consensus over appropriate diagnostic terminology, and major divergences characterize 27 sets of diagnostic criteria for work-related upper limb disorders. Katz et al. have called for valid classification methods. Nørregaard et al. have described serious validity problems with regard to generally accepted terminologies of four common diagnoses.

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Such logic has been applied in many analytical studies of associations between exposures and outcomes such as regional pain rather than to well-defined diseases. However, a non-specific symptom such as elbow pain may be caused by various conditions of different etiology that cannot be addressed individually. Factor analyses have shown that symptom-based case definitions, which localize upper limb musculoskeletal conditions to specific anatomical areas, may be incomplete, and that studies should rely on both signs and symptoms.

With the exception of carpal tunnel syndrome, most diagnostic classification systems for work-related upper limb disorders have a limited coverage of nerve afflictions. On this background it is not surprising that work-related upper limb nerve entrapment represents a relatively unexplored field in clinical practice and in research such as field studies of workers in occupation.

Since the description by B. Ramazzini three centuries ago of writers suffering from prolonged upper limb pain, similar subjective histories of upper limb ache, discomfort, muscle weakness, vague numbness, and the absence of confirmative objective findings have been described in workers of many trades and among artists. Though the following decennials, the interpretations have changed from initially attributing symptoms to disorders of muscle and nerve to the designation as neuroses understood as conditions for which no underlying lesions of the nervous system could be demonstrated.
Since then many pathophysiological mechanisms for NSAP have been proposed, ranging from disturbance in muscle function [39] to psychosocial features [40]. Explaining symptoms as psychosocial [41], somatization [42], or even as iatrogenic [43] is, however, hardly justified from a critical point of view [37,40,44,45]. In the absence of confirmatory physical findings, a standard physical examination may still conclude that tissue damage is absent and that symptoms reflect psychosocial constructs. Such interpretations have neither contributed to the treatment nor to the prevention of work-related upper limb conditions, and patients with chronic pain may be stigmatized. Cohen et al. argued that a principal reason for “negative empathy” is the failure of health professionals to appreciate their own clinical reasoning and behavior [46].

Diagnostic shortcomings may result in descriptive or tautological diagnostic terms that can neither characterize the involved tissue nor its location or pathology. These constraints are reflected by the application of various descriptions for painful “non-specific” work-related upper limb conditions: “Cumulative trauma disorders”, “occupational cervicobraclial disorder”, “refractive cervicobraclial pain syndrome” [47], and “repetitive strain injury” seem at least partially to cover the same conditions. These terms have been characterized as self-fulfilling prophecies [48] and researchers have warned against their use [18]. Discussions on the character of upper limb conditions that do not fit the criteria for defined clinical diagnoses [30] are ongoing in the scientific community. The use of diagnostic proxies that reflect the mere location of symptoms, e.g. “epicondylitis” with elbow symptoms or “rotator cuff syndrome” with shoulder symptoms, is another common practice that is not appropriate, but still applied in spite of the absence of signs suggestive of tendinopathy or enthesopathy.

Conditions regarded as NSAP may be either a “diagnosis” by exclusion [25] or as a condition with upper limb symptoms without specified criteria [26]. Harrington et al. characterized pain in the forearm in the absence of a specific diagnosis or pathology as NSAP [25]. Hellwell et al. required the presence of pain in hand or wrist, pain in neck, discomfort and/or pain, weakness in arms or hands, dropping things, or clumsiness in the absence of painful arch at the shoulder, pain at lateral epicondyle on loading muscle, finger joint pain or swelling, sleep disturbance, or fibromyalgia tender points [27]. Sluiter et al. characterized NSAP as pain in muscles, tendons, nerves, or joints without evidence of a combination of symptoms and signs typical for one of the “specific” disorders [26]. A clinical overlap has been described between NSAP and fibromyalgia [49], in which peripheral nerve inflammation contributes to the symptoms [50]. NSAP may cover brachial plexopathy [28], or this diagnosis may be excluded from classification [26], e.g. due to lack of consensus [25].

NSAP is regarded as a common chronic upper limb pain condition [25-29,51], the proportion of which depends on the sample, the setting, and the applied criteria for “specific” disorders. NSAP has been suggested to constitute up to ¾ of work-related upper limb disorders [52]. One study classified 458 out of 1382 upper limb cases as NSAP (and 124 as fibromyalgia) [27]. In other studies, more than half of the examined subjects with upper quadrant pain could not be diagnosed with a specific disorder [11,53]. Unlike “specific” conditions, the view of most researchers is that NSAP does not have any apparent signs of tissue injury. When performed, the normal results of nerve conduction studies are interpreted as the absence of frank nerve injury [25-29].

There are scant available data on the psychological characteristics of NSAP. Depressive symptoms or anxiety accompany somatic symptoms to the same extent as with “specific” upper limb disorders [44,54], and consequently has no diagnostic value. A comparison with age-matched controls of subjects with work-related dominant forearm and hand pain, out of which half had electrophysiological signs of median neuropathy at the wrist and the other half was without such signs resulted in identical health perception, depressive symptoms, and work satisfaction in the two pain groups, both of which had significantly more pain, extensor muscle tenderness, depressive symptoms, poorer physical functioning, reduced grip strength (significant in the electrophysiological positives), and wrist extension force (significant in the electrophysiological negatives) than the controls. Overall, both pain groups shared similar characteristics, with the exception of electrophysiologi- cal outcomes [54].

NSAP is commonly reported in workers who perform intensive and/or rapid work such as with computers [55,56]. Other described risk factors include shoulder hyper-abduction and overhead work [57], and repetitive use of the arm and wrist [58]. A similar controversy regarding the work-relatedness of NSAP [59]. The prognosis is poor. In a study of computer operators with NSAP, only 9% of computer operators with NSAP recovered and 77% worsened at follow-up [60].

**Symptoms characteristic to NSAP**

According to Cohen et al. referred pain of shooting, pulling, penetrating or burning/electrical quality, paresthesia and dysesthesia are typical features of NSAP [47]. Greening reported burning pain, aching, stiffness, cramp, numbness, heaviness, fatigue, and paresthesia [61]. Quinlter described diffuse pain with characteristics such as tingling, aching, burning, or electrical shock-like sensations [62]. Low typing endurance, more resting pain, and increased pain after a standardized typing test was demonstrated in keyboard operators with NSAP. Pain was worse in the right hands and tends to cluster more commonly at multiple locations in the neck and upper limb than would be expected if pain at each site occurred statistically independently [63]. Many clinicians have noted the tendency to contralateral spread, which was already described among scriveners by B. Ramazzini 300 years ago: “A friend of mine works as a notary. He spent all his time with writing and earned big money on it. Gradually, he began to complain of a strong pain in the right arm. Nothing helped, and eventually the entire arm became paralyzed. To get over this, he practiced to write with his left hand, but it was not long before the same problems hit the left arm” [35].

It is a challenge to understand the transition from acute to chronic pain, which may also be central of origin. Chronic musculoskeletal pain patients are characterized by spread of pain and sensitization that correlates to the intensity and duration of pain. The spread of pain may not only seriously contribute to the patient’s suffering and level of functioning. It also complicates the diagnostic process and the management of the condition. It should therefore be a priority to reduce the intensity as well as the duration of pain [64]. Curato et al. demonstrated generalized central hypersensitivity with pressure algometry in up to 35.3% of chronic pain patients. It was more frequent in patients with atypical pain that complicates classification and clinical management [65]. A very high frequency of hypersensitivity to electrical stimulation with chronic pain (71.2%) was recently shown. Spinal nociceptive hypersen-
Postural deviations from normal are frequent in NSAP. Forward displacement of the head and inwards rotation of the shoulder are typical examples [39,72]. Interestingly, restricted cervical range of motion and increased forward head posture is also associated to carpal tunnel syndrome [73].

Other characteristic features of NSAP include motor disturbances such as reduced muscle function [74,75]. Compared with controls, patients with forearm and hand pain have reduced peak torque [76], grip [54,74,77], pinch, and wrist extension force [54]. Weaknesses are related to the character of work and to perceived physical exertion [77]. Compared with healthy controls, patients with pain had significantly lower endurance in spite of identical oxygen consumption, meaning that muscle oxygenation and hemodynamics cannot explain early fatigue in pain patients [78].

Disturbed motor control [79-81], recruitment pattern [82], and movement strategies have been demonstrated in asymptomatic office workers. Neuromotor noise disturbs task performance, and pen pressure with writing is increased and pen pressure with writing is increased and range of motion and increased forward head posture is also disturbed [57].

Abnormal findings in NSAP

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Disturbed motor control [79-81], recruitment pattern [82], and movement strategies have been demonstrated in asymptomatic office workers. Neuromotor noise disturbs task performance, and pen pressure with writing is increased and further elevated with additional memory load [83]. Office workers with chronic neck-shoulder pain display increased muscle activity in various computer tasks [82,84,85], and similar findings have been found in other patient populations. In analogy, an insufficient scaling of forces increases the maximum and mean forces during lifting and holding [86]. Surface electromyography has showed changing spike shape measures with increasing contraction level [87], and can differentiate symptomatic from healthy computer workers [88]. Compared to patients with lateral epicondylitis and controls, smaller surface detected motor unit potentials in patients with NSAP indicate muscle fiber atrophy and/or loss [89], which may rely on innervation. Surface electromyographic studies have also demonstrated altered motor control consisting of higher muscle activity in the cervical erector spinae and upper trapezius in people with neck-shoulder pain during texting on a smartphone and typing on a computer. Unilateral texting increased muscle loading more than bilateral texting especially in the forearm muscles. There was higher activity in neck extensor and thumb muscles during texting than during typing but lower activity in trapezius and wrist extensors [90]. Analysis of surface electromyographic findings showed lower normalized mutual information in between homonymous muscle pairs during smartphone texting and computer work in symptomatic versus non-symptomatic subjects [91]. Tracking performance was poorer in cases than controls and deteriorated as a function of the impairment level [92]. Asymptomatic subjects in risk jobs (repetitive or forceful tasks involving the hand or wrist > 5 h/day for > 5 years) had significantly more errors in tracking tasks than asymptomatic subjects that were not in risk jobs [93].

Sensory abnormalities include sensory gain as well as sensory loss. Greening & Lynn described hyperalgesia as a common feature of NSAP [61], and a recent study by Moloney et al. confirmed the widespread pressure and thermal hyperalgesia in addition to neural tissue sensitization [94]. Disturbed cutaneous sensation may also be displayed as abnormal algesia/aesthesia, non-dermatomal paresthesia [34,95-98], or alldynia, e.g. on exposure to touch [99] or cold [100]. Touch evoked alldynia has been identified in up to 58% of patients with NSAP [61]. Other features of NSAP include reduced sensitivity to vibration and alldynic responses to supra-threshold stimulation [101], which has been described in 82% of symptomatic computer users [61]. Compared to healthy controls, elevated vibration thresholds were found not only ipsilaterally but also contralaterally to the symptomatic limb [102,103]. Reduced perception of vibration in symptomatic as well as in non-symptomatic keyboard users [61,104,105] suggests the presence of a latent disorder in the latter. Similar findings have been described in other risk jobs [106]. Secondary hyperalgesia induced by electrocutaneous stimulation of affected limbs is accompanied by spread and persistence of dysesthesia [97]. Unilateral lateral epicondylalgia is associated with reduced pressure pain threshold corresponding to the extensor carpi radialis brevis muscle dorsally to the lateral epicondyle, while cold and heat pain hyperalgesia thresholds were also present contralaterally. This finding indicates sensitization of peripheral and central origin. Heat pain hyperalgesia suggests peripheral nociceptor sensitization while cold hyperalgesia is rather in accordance with neuropathic pain mechanisms [107]. A subsequent cadaver study has proposed that the cutaneous radial nerve has a role in lateral epicondylalgia in addition to the posterior interosseous nerve [108].

Increased nerve trunk mechanosensitivity was noted by early authors such as Poore [109,110] and Dana [111] as an almost defining feature, which is present in the majority of patients with NSAP [50,96,112] in which nerve-palpation elicits alldynic responses [113-115]. In addition to palpation of nerve trunks, neural tissue provocation tests in patients with NSAP can cause alldynic reactions, e.g. paraesthesia or pain, with active and passive movements such as arm elevation or elbow extension [71,112,115-118], and such movements, which apply strain to the brachial plexus and peripheral nerve trunks, are limited and painful [94,96,112,119]. Positive neurodynamic tests that reflect the abnormal neural mechanosensitivity have been demonstrated in 88% and 78% of patients with NSAP [71,94]. Similar responses in non-symptomatic keyboard users suggest a latent disorder [96]. Bilateral nerve trunk soreness of the radial and median nerve has been demonstrated in women with unilateral epicondylalgia or carpal tunnel syndrome, respectively [120]. Painful responses to limb movements and compressive forces in NSAP are not caused by restricted longitudinal nerve sliding with subsequent pathologically increased nerve strain, but is rather a consequence of increased mecha-
nossensitivity due to local nerve inflammation [116], which causes aberrant nociceptive firing in response to normal levels of nerve strain [121]. However, nerve slide may have some significance since transverse median nerve movement is reduced in carpal tunnel syndrome [115,122]. In addition, forearm median nerve longitudinal slide during maximal inspiration is reduced in NSAP, possibly related to a reduction of first rib excursion [112]. While median nerve sliding in response to wrist, elbow, shoulder and neck movements in healthy persons results in strain below the level that may impair blood flow or nerve conduction [123], protracted shoulder and slumped position in NSAP patients may reduce the median nerve excursion in response to moving joints to a level, which is sufficient for impeding neural blood supply and function [124]. Upper limb tension test 2 (radial nerve bias) has been reported as positive in patients with diagnosed lateral epicondylitis, which is surprising since this condition is regarded as a tendinopathy [125]. The lower cervical spine is also sensitized in epicondylitis [126].

**Autonomic functions** may be altered in NSAP. Stimulation of painful limbs with ice causes reflex vasoconstriction [127]. Reduced axonal flare response following stimulation with capsaicin [128,129] or iontophoresis of histamine [127] indicates an involvement of small dorsal root fibers. The severity of pain is inversely associated with the magnitude of flare [98,130]. The response is also increased in contralateral limbs without pain [98]. The cooler skin in symptomatic limbs after keyboarding but rarely in controls may be related to reduced blood flow caused by sympathetic activity [131,132]. In a sample of patients with various diagnoses, the skin temperature was lower in the most severely affected limbs [133]. The occurrence of plastic changes in the sensorimotor cortex in NSAP patients is suggested by disorganized or inappropriate cortical representation of proprioception and pathological pain [134].

The relation between inflammatory mediators and NSAP has been studied in patients with early-onset overuse-related NSAP that were stratified according to the severity of signs and symptoms and compared to asymptomatic subjects. C-reactive protein correlated strongly and TNF-α, IL-1β, and IL-6 moderately with upper-body musculoskeletal assessment scores. This illustrates the contribution in NSAP of systemic inflammatory mediators. Widespread effects may extend to tissues that are not directly involved in task-performance or exposure, e.g. contralaterally [135] with ensuing extensive and puzzling symptoms [136].

Schliessbach et al. found that widespread central hypersensitivity was more frequent in patients that due to the atypical character of their pain were difficult to classify and clinically manage [65]. A study of computer operators with mostly minor chronic musculoskeletal pain comparable to NSAP had normal excitability of the central pain system with low pain intensity, while higher pain intensity and lower pressure pain threshold were associated with reduced descending pain modulation. This is in accordance with chronicization of pain rather than with increased excitability of the pain system [137].

**Neuropathic arm pain**

Sensory input, integration of data and motor output are key functions of the nervous system but mechanisms within each of these are complicated, and symptoms and findings with neuropathic arm pain may be difficult to interpret. For example, sensory abnormalities in chronic pain patients may appear in non-dermatomal patterns or do not reflect a single peripheral nerve. These physical findings should not be regarded as non-organic and indicating a conversion disorder [138]. In any event we should wean ourselves from perceiving nerves as electrical cables between the tissues and the central nervous system [139].

Clinically, neuropathic pain is characterized by spontaneous ongoing or shooting pain and evoked amplified pain responses after noxious or non-noxious stimuli. Nerve lesions can cause spontaneous pain (deafferentation) due to ectopic activity [140]. Neuropathic pain following nerve injuries may appear as dysesthetic pain or nerve trunk pain [141] with frequent simultaneous presence of both qualities [117]. Dysesthetic pain may arise in damaged or regenerating nociceptive afferent C fibers and is mostly perceived as a burning or electrical sensation. Nerve trunk pain felt as a deep and aching pain that follows the nerve trunk is attributed to increased activity in mechanically or chemically sensitized nociceptors within the nerve sheaths. Neuropathic pain may also be described as dull, throbbing or heavy [142,143]. There is a limited effect of conventional analgesics such as paracetamol or non-steroid anti-inflammatory drugs [51] and consensus that first-line analgesics should rather include antiepileptics, tricyclic antidepressants, and topical lidocaine [144].

Key features of neuropathic pain include central sensitization, which is manifested as neurogenic hyperalgesia, and partial nociceptive deafferentation expressed as painful hypalgesia [99]. Alloodynia mediated by low-threshold Aβ fibers can occur consequent to central sensitization [145]. Increased central processing of high-threshold Aδ nociceptor-derived activity can cause pinprick hyperalgesia [146] predominantly in an area surrounding the zone of a primary injury (secondary hyperalgesia) [147]. A generalized hypersensitivity to different pain modalities suggests a disturbed descending pain control [148]. Widespread hypersensitivity demonstrated with, e.g. pressure and thermal thresholds is common with nerve entrapment such as carpal tunnel syndrome, but unrelated to the electrodagnostic severity [149].

The character of pain may be helpful in distinguishing neuropathic pain from nociceptive pain but in practice this may be difficult [150]. Questionnaires may be helpful for identifying neuropathic pain [151]. Haanpää et al. have suggested criteria for neuropathic pain to be evaluated for each patient [152]: 1) Pain with a distinct neuroanatomically plausible distribution; 2) A history suggesting a relevant lesion or disease affecting the peripheral (or central) somatosensory system; 3) At least one confirmatory test (clinical or laboratory) supporting a distinct neuroanatomically plausible distribution; 4) At least one confirmatory test demonstrating the relevant lesion or disease. Definite neuropathic pain requires all 4 criteria, probable 1 and 2 plus either 3 or 4, and possible 1 and 2.

The symptoms in neuropathic arm pain are comparable to those of NSAP and include pain, which is frequently described as burning or electrical [47,61,62], subjective motor disturbances [47,61,71] and abnormal sensory perceptions [47,61,70]. The examination of patients with NSAP has showed many abnormal findings in accordance with neuropathic upper limb conditions. Among these are postural deviations [39,72] that may be primary by contributing to compromised nerve function or develop secondary to a nerve affliction. Muscle strength may be reduced [54,74-77] and motor control disturbed [79,80]. Sensory abnormalities [34,95-98], including allodynia [61,99,100] and altered perception of vibration, are other characteristic features [61,101-106,153]. Additional characteristics of NSAP include increased nerve trunk mecha-
The shared features of NSAP and focal upper limb nerve afflictions suggest an overlap in between the two constructs. Hutson has suggested “neuropathic arm pain” as an umbrella term for NSAP [154]. However, the International Association for the Study of Pain (IASP) defines neuropathic pain by as caused by a lesion or disease of the peripheral somatosensory nervous system. This definition challenges the presence of neuropathic pain in NSAP when no lesion or disease is obvious. Moloney et al. have found evidence for the existence and indeed coexistence in NSAP of peripheral neuropathic pain, nociceptive pain, and central sensitization [155]. The role of peripheral nerve afflictions in NSAP is increasingly recognized [45,51,72,156-162] and features of minor neuropathy in patients with NSAP acknowledged. There are clear signs of nerve trunk mechanosensitivity and changes that may be subtle to the function of large myelinated sensory nerve fibers, small dorsal root fibers and sympathetic fibers [51,127].

Confronted with a patient who displays features of NSAP and/or neuropathic pain most clinicians will consider a number of responsible conditions some of which are briefly reviewed.

Myofascial pain syndrome is a poorly defined condition, which according to the prevailing concepts in occupational medicine explains the pain by muscular dysfunction with associated tender (trigger) points in muscles [163]. The understanding of the pathology of myofascial pain remains limited, and controversy remains as to whether this is a true diagnosis or merely a term used to describe clinical conditions. Myofascial pain and fibromyalgia may overlap and central sensitization seems to be a common denominator. The role of peripheral nociception is under debate [164]. In a critical analysis of the constructs on which the concept of myofascial disorder are based, Quintner et al. refuted the theory of myofascial pain syndrome caused by trigger points [165] and argued that symptoms are better explained by neuropathy [166]. Based on the lack of demonstrable pathology, Pearce also dismissed this term as a distinct disease entity and suggested that the complaints are rather related to neural dysfunction [167]. In a significant proportion of patients with cervical myofascial pain syndrome careful electrophysiological assessment has shown axonal degeneration in the spinal accessory nerve with disturbed neuromuscular transmission [168]. The relation of interscapular pain of a myofascial character to dorsal scapular nerve affection has also been demonstrated by electrophysiology [169]. Depending on the applied case definitions, the same patients can be diagnosed as myofascial pain syndrome and as brachial plexopathy [170].

Complex regional pain syndrome (CRPS) may be evidenced by a combination of reduced movement, sensory (e.g. hyperalgesia or allodynia), vasomotor, sudomotor/edema and/or motor/ trophic changes. Pain may develop disproportionately in time and severity relative to a previous lesion and exhibits various progression over time. Minor nerve inflammation is regarded as essential in CRPS [171]. Type I (reflex sympathetic dystrophy) occurs in the absence of any known nerve injury. Type II (causalgia) occurs following a known peripheral nerve injury with damaged nerve function. While the contribution of cortical pain mechanisms in type I is suggested by increased pain and measurable swelling in patients who just thought of but did not move the affected limb [172], peripheral input appears to be equally influential. Positive effects of nerve decompression on complex regional pain syndrome type II [173] is not surprising since a nerve affliction is implicated. However, splitting up CRPS into two types may be arbitrary as surgical decompression following a careful history and physical examination including neurosensory testing and nerve blocks in a series of type I patients has relieved the symptoms in 80% [174]. The majority of patients with CRPS I, CRPS II, or peripheral nerve injury displayed a combination of sensory loss and gain. Small fiber deficits were less frequent than large fiber deficits. Sensory gain was highly prevalent in peripheral nerve injuries. The almost identical sensory profiles of both types of CRPS suggest that they represent one disease continuum [175]. The IASP criteria for diagnosing CRPS have been criticized for poor specificity [176] and internal validity [177].

Although neuralgic amyotrophy (Parsonage-Turner syndrome) has been estimated to be a common cause of brachial plexopathy [178] it is mostly regarded as a rare idiopathic or hereditary condition. Following initial acute and very severe, continuous shoulder pain in particular on the dominant side that lasts approximately four weeks, pareses and atrophy develop, and minor sensory involvement is also common. The brachial plexus, in particular the upper and middle trunk, is reported to be mostly involved together with an impaired function of the suprascapular and the long thoracic nerve. Recurrent attacks may occur and pain and paresis may persist in the majority of patients [179].

Neuropathic pain may move and spread from one location to another and occur distant to an afflicted nerve portion [156,180]. Bilateral upper limb conditions have been observed with a higher frequency than would be expected by random variation. This means that patients with a unilateral work-related upper limb condition are more likely to develop similar symptoms on the other side. Contralateral spread of an upper limb disorder may follow consequent to identical bilateral exposure, e.g. keyboarding, or by sparing the painful limb and substituting with the other arm to perform the job. Such contralateral spread may be even more likely when the subject is not accustomed to use the non-dominant limb arm for purposes that are normally done with the dominant arm, or when using tools or a workstation designed for use by the right (typically dominant) arm. Peripheral sensitization and central processing of sensory inputs following plastic alterations in the central nervous system can also explain this “mirror pain” phenomenon [181]. Experimentally, small fiber loss has been demonstrated in the upper limb nerves contralateral to limbs with nerve compression [182]. In carpal tunnel syndrome, widespread bilateral hypersensitivity extends beyond the innervated territory. It may involve the ulnar and radial territory and even spread to other parts of the body [149].

The inflammation accompanying painful neuropathy causes release of pro-inflammatory cytokines, which circulate in the body and sensitize nerves elsewhere, such as in the contralateral limb. In addition, neuroplastic changes may take place in, e.g. the cerebral cortex, the brainstem, the dorsal horns of the spinal cord or the sensory ganglia – not only in the primarily affected side, but also contralaterally. It is well-known that phantom pain can develop after severing a nerve and subsequently even worsen. Neuropathy contralaterally to the amputation is not unusual [183]. Bilateral hyperalgesia has also been seen in many other conditions such as lateral epicondylalgia [107]. It is in line with these observations that postoperative recovery in bilateral carpal tunnel syndrome may also occur in the non-operated hand [184]. These features of bilateralism are in accordance with studies of the outcome of vibrometry. Uni-lateral upper limb disorders may also have vibrometric abnor-
Peripheral neuropathy has many etiologies including metabolic, genetic, infectious, inflammatory and medication-related factors. Other locations of focal nerve entrapment are less implicated. This limited scope may be due to tradition, to an assumption that other nerve afflictions are rare, or to the spectrum of disorders with defined diagnostic criteria. With unfamiliarity with upper limb nerve topography and innervation it may be perceived as difficult to identify and interpret patterns of pareses, sensory abnormalities, and mechanical nerve trunk allodynia that do not reflect an affliction of a single root or a single peripheral nerve. In addition, viewing the outcome of electrophysiology as gold standard for the diagnosis of nerve afflictions, a clinical diagnostic conclusion based on an integration of symptoms and neurological findings may be rejected if the electrodiagnosis is negative. Confidence to any clinical assessment, e.g. the clinical neurological examination, is a prerequisite for its application.

Some authors regard neuropathic dysfunction as very common in patients with neck/shoulder problems and encourage neurological screening [162]. According to two recent sets of diagnostic criteria for work-related upper limb disorders, neuropathic conditions were indeed found to be very common in a sample of patients in the primary health sector [170]. The criteria of Sluiter et al. [26] and Laursen et al. [170] assigned neuropathic diagnoses in 76.2% and 89%, respectively, of 194 symptomatic upper limbs with agreement between the two sets of criteria with regard to the presence of neuropathy in 75% of limbs [170]. However, according to the criteria of Sluiter et al. [26], carpal tunnel syndrome was diagnosed in 117 and ulnar nerve compression at elbow and wrist level in 35 and 79 limbs, respectively [170]. In contrast, the diagnostic criteria by Laursen et al., which covered a range of additional locations of upper limb neuropathy, located most nerve afflictions proximally, in particular to the brachial plexus, and rarely identified isolated carpal tunnel syndrome and ulnar neuropathy [170]. The perception of vibratory stimulation in relation to the two sets of diagnostic criteria showed better agreement with the criteria by Laursen et al. [170].

COMPRESSION NEUROPATHY

Pathophysiology of nerve compression

Peripheral neuropathy has many etiologies including metabolic, systemic, genetic, infectious, inflammatory and medication-related factors. The following text deals with nerve compression/entrapment, which may be superimposed on any other of the mentioned etiologies that may render the nerve particularly vulnerable to external compromise.

Several mechanisms of nerve affliction from compressive forces have been hypothesized after repetitive use and recurrent static postures of the upper limb. Muscular imbalance with some muscles shortened and others weakened may affect nerves in the vicinity [157]. Other demonstrated mechanisms include chronic compartment syndrome [186]. “Minature compartment syndromes” have been suggested several decades ago [187]. Nerves are particularly at risk on their passage through fibrous or osseous tunnels, below tight fibrous structures, fascial edges or vessels [188] or through a compartment in which the tissue pressure is elevated for any reason. Any local pathology or structural change causing a disproportionate between the nerve volume and the available surrounding space such as hypertrophied or shortened muscles may compromise adjacent nerve tissue. A pressure that is applied to the surface of a nerve decreases gradually more profoundly. Consequently, the superficial fascicles are more in risk relative to the deeper ones [189].

Clinical, experimental and epidemiological studies indicate that microtrauma from repetitive and/or forceful tasks may lead to the onset and progression of NSAP and cause local and even systemic inflammation, pain and dysfunction. Still, there is a need of further understanding of the pathophysiological mechanisms leading to tissue responses in the early stages of disease and tissue structural changes such as fibrotic scarring and reorganization in the peripheral and central nervous system during subsequent repair [135,190].

Animal studies have contributed to the understanding of the pathogenesis of entrapment neuropathy and neuropathic symptoms following sustained minor nerve injury or inflammation [191]. The inflammatory response in chronic or recurring tissue injury consequent to cumulative repetitive and/or forceful upper limb movements is related to behavioral indicators of discomfort and movement dysfunction [192] consistent with NSAP. Motor performance degraded at high exposure levels [193]. Involuntary repetitive fingertip loading for 6 h per week for 4 weeks caused slowed nerve function at the wrist [188]. Peripheral nerve injury with localized inflammation following repetitive, forceful tasks leads to neuroplastic changes at multiple levels of the somatosensory pathways including decreased substance P in the dorsal horn, increased neurokinin-1 receptor, and expression of the excitatory neuropeptide Y in the dorsal root ganglion [194]. There is evidence of activity-induced synaptic modification of central neuronal networks [195]. Animal studies of neural mechanosensitivity following nerve inflammation demonstrate C-fiber firing in response to nerve stretch within the physiological range [121,196].

Acute nerve injuries such as transsections and crush injuries following trauma are characterized by Wallerian degeneration, which involves both the axon and the surrounding myelin [197]. External compression of 20 mm Hg reduces the venous blood flow. Delayed nerve injury may occur after 2 hours with 30 mm Hg compression. Initial capillary leakage is followed by accumulation of intra- and extraneurial edema and increased intraneurial pressure. The next month a brief inflammatory reaction may be followed by fibrosis, demyelination, and axonal loss [188].

In vivo and in vitro models have improved the understanding of the cellular mechanisms underlying chronic nerve compression [197]. The pathophysiology of chronic nerve compression depends on the level and duration of the compressive or tensile forces. Several mechanisms may work together in the development of symptoms. Tubes or balloons placed around or adjacent to the nerve and inflated to low pressures cause delayed onset chronic pain and morphologic nerve changes including sprouting, endoneurial edema, a persistently increased intraneurial pressure, and long-term changes such as demyelination and fibrosis. The applied pressure causes a dose-dependent decrement in nerve function and abnormal morphology linked to the amount of endoneurial edema [188]. The increased pressure may also compromise the capillary supply to the nerve and lead to epineurial ischemia. At lower pressures, reduced venous return can lead to venous stasis, which in turn can cause extraneurial edema. Over time,
this process may result in demyelination, perineural fibrosis and scar tissue formation [18]. The appearance in chronically compressed human nerve segments of new thinner myelin following injury [198] is linked to the remyelination by proliferating Schwann cells that follows demyelination. The demyelination of the compressed nerve fibers happens immediately adjacent to the node of Ranvier and proceeds toward the internode. Swann cell proliferation occurs in areas with thinner myelin typical of remyelinating axons and decreased internodal length. In contrast to the axonal degradation seen in acute injuries, the morphology of the axons in chronically compressed nerves is not changed [199,200], and the neuromuscular junction lacks the morphological changes seen in acute crush injuries [201]. In vitro studies have demonstrated that mechanical forces such as shear stress can induce Schwann cell proliferation following chronic nerve compression. The myelinated neurons are consequently particularly sensitive to mechanical impact. The mechanosensitivity of Swann cells is regarded as a key pathophysiological feature of chronic peripheral nerve afflictions [197]. While macrophages invade nerves following acute crush injuries one to four days after injury in an effort to clean up axonal debris, the macrophage infiltration and the Schwann cell proliferation involved in remyelination takes weeks in chronic compression. Chronic compression leads to an up-regulation of intraneurial inflammatory cytokines, and results in fibrosis, Schwann cell death, axonal demyelization, and reduced electrophysiological function [202] in a dose-response manner [203]. The increased mechanosensitivity of nerve trunks resulting from local inflammation causes local tenderness and painful responses to nerve stretch during joint movements with dysfunction in both intact and damaged fibers [121] due to disrupted axonal transport [204]. Recruitment and activation of immune cells such as T-lymphocytes may take place, and antibodies to neuronal antigens develop. Mediators released by immune cells, such as pro-inflammatory cytokines, cause further sensitization and nociceptive signaling in the peripheral and central nervous systems [205]. In addition to peripheral sensitization, the activation of glia cells during peripheral inflammation is regarded as important for the transition from acute to chronic pain [206]. Continued task performance superimposed upon injured and inflamed tissues results in a vicious circle of injury, inflammation and motor dysfunction [207].

Following experimental nerve injuries that extensively disrupt axons, such as chronic constriction injury, the invasion of immune cells in the nerve, related dorsal root ganglia, and spinal cord will lead to hyperexcitability, reduced sensitivity, and pain. To understand the underlying pathology, a tube was placed around the sciatic nerve in 8-week-old rats, leading to progressive mild compression as the animals grew. Immunofluorescence was used to examine myelin and axonal integrity, glia, macrophages, and T-lymphocytes in the nerve, L5 dorsal root ganglia, and spinal cord after 12 weeks. The constricting tubes caused extensive and ongoing loss of myelin, together with compromise of small-, but not large-, diameter axons. Macrophages and T-lymphocytes infiltrated the nerve and dorsal root ganglia. Activated glia proliferated in dorsal root ganglia but not in the spinal cord. Histologic findings were supported by clinical hyperalgesia to blunt pressure and cold allodynia. Tubes that did not compress the nerve induced only minor local inflammation. Thus, progressive mild nerve compression resulted in chronic local and remote immune-mediated inflammation depending on the degree of compression. The results from animal models are comparable to findings in patients with entrapment neuropathies in which such neuroinflammation may contribute to explain the widespread symptoms [208]. Persistent neuropathic pain may develop consequent to injuries to the peripheral or central nervous system that activates the pain system so that the patient becomes more pain sensitive [209]. Therefore, on examination of patients, the elicited pain response may seem to exceed the expected intensity. This, regrettable, may be interpreted by clinicians as “symptom amplification” connoting a psychological basis for symptoms. The involved pathophysiological mechanisms in the peripheral and central nervous systems include inflammatory reactions that trigger the nociceptive neurons, which become abnormally sensitive and can induce ectopic nociceptor activity with spontaneous pain. In addition, hyperactivity in nociceptors may induce secondary changes in processing neurons in the central pain modulatory systems, so that input from mechanoreceptive A-fibers causes further hyperexcitability and pain [210].

The earliest histopathological changes in human entrapped nerve are described in the endoneurial microvessels and perineurium with presence of Renault bodies. Subsequent connective tissue changes include epineurial and perineurial fibrosis, and variable nerve fiber pathology in between fascicles. In the myelinated fiber population, the myelin undergoes marked thinning. Among the unmyelinated fibers, a shift to a new population of very small fibers indicates their degeneration and subsequent regeneration [198]. The histopathology of brachial plexopathy revealed similar epineurial and perineurial fibrosis, vascular hyalinization, mucinous degeneration and frequent intraneurial collagenous nodules. However, the relation of these findings to clinical symptoms during life is not known [211].

In 1973 Upton and McComas suggested a cumulative effect of compression at multiple levels along the nerve, each of which in isolation is insufficient for causing clinically overt symptoms [212]. Since then the “double crush” hypothesis has been supported by experimental [213,214], clinical, and laboratory observations [180,213,215-218] including electrophysiology and imaging [219]. According to the “double crush” theory, a proximal affliction renders the nerve more vulnerable distally due to disturbed perineurial transport of substances produced in the nerve cell body. The health of the nerve cell body is also dependent on retrograde axonal transport of neurotrophic substances synthesized in the axonal endings [215]. “Reverse double crush” reflects compromised axonal transport due to vulnerability of proximal nerve segments consequent to a peripheral nerve affliction. Clinically, upper limb multilevel nerve compression occurs with simultaneous involvement of several nerve-ports, which may include the brachial plexus [158]. One study found distal neuropathy in 44% out of 165 cases of brachial plexopathy [220], and Hooper assumes this combination to be present in about 50% [221]. A review of cases with concurrent brachial plexopathy and distal focal neuropathy (median, ulnar or radial nerves) suggests the former to precede the distal afflictions [222]. With simultaneous brachial plexopathy and carpal tunnel syndrome, distal surgery will rarely relieve symptoms caused by the proximal neuropathy while brachial plexus release relieves the distal symptoms in half of the cases [215,222]. These observations support the double crush theory and the importance of identifying proximal afflictions. The involvement of proximal structures in carpal tunnel syndrome may reflect restricted cervical range of motion, which was
independent of the electrodiagnostic severity [223], as well as the frequent protracted neck position [73].

An increased pressure gradient in the vicinity of two or more nerves (“multiple entrapment”) may develop following a constrained limb posture for an extended period of time [217,218].

One example may be forced forearm pronation causing passive tension in the supinator muscle and consequently reduced space in the radial tunnel, which causes compression of the posterior interosseous nerve. At the same time, the median nerve may be impinged on its passage through the two heads of the pronator teres muscle.

A recent Delphi study found four plausible mechanisms for the development of dual/multiple nerve disorders: impaired axonal transport, ion channel up- or downregulation, inflammation in the dorsal root ganglia and neuroma-in-continuity. Eight additional mechanisms may render the nervous system more vulnerable to multiple nerve disorders, such as systemic diseases and neurotoxic exposures. The experts indicated a range of mechanisms to be considered to better understand dual nerve disorders, and warned against discarding previously listed theories, which, however, may be insufficient to explain the high prevalence of double or multiple crush [224].

Workers exposed to awkward postures, forceful or repetitive movements, and vibrations have a high prevalence of neurological signs [225,226]. In a study of 137 male industrial and office workers tested at baseline and after 5 years, the cumulated incidence of neurological signs was 2/100 person-years. Factors related to work-conditions, constitution, disease, and neck trauma were associated with the neurological signs. The abduction external rotation test predicted future neck and upper extremity symptoms and signs of nerve compression [225]. This study supported the double or multiple crush theory of nerve compression, which has also been related to repetitive work by others [72,157,161,227,228]. Prevention, evaluation, and management of neck and upper extremity nerve compression should therefore pay attention to the potential locations of double or multiple crush lesions – even when a specific location of nerve afflictions is in focus [225]. A recent review has again emphasized the awareness of clinicians of the possibility of concomitant nerve afflictions at several levels as well as of a potential underlying systemic neuropathy that renders nerves more vulnerable to external compression [229]. Still, “double crush” remains controversial [229,230].

**Classification of nerve injuries**
The classification of nerve injuries into three stages by Seddon [231] and five according to Sunderland [232] has been further extended by Lundborg with a preceding early stage [233] (Table 1). Several stages are likely to coexist in entrapment neuropathies in which partial and mixed lesions are typical features.

**The assessment of focal peripheral nerve afflictions**
Any situation with symptoms such as pain, weakness, and/or numbness/tingling may potentially reflect compressive neuropathy. Depending of the clinical situation, the classical neurological examination addresses a number of individual representative neurological items, which are regarded as sufficient for diagnosing or excluding a neurological condition. The neurological upper limb examination should be systematic and sufficiently detailed by incorporating an appraisal of representative muscles in terms of individual strength, of sensibility in representative homonymous innervated territories of the skin, and of allodynic reactions to nerve trunk palpation at relevant locations or to provocative maneuvers [228,231,234].

Representing a rational and classical paradigm, the neurological upper limb examination should include a search for patterns that reflect potential locations of focal neuropathies [228,231] including “double and reverse double crush”, “multiple entrapment” and brachial plexopathy. The interpretation of patterns in a neurological context is based on anatomical facts relating to the course of nerves and their motor and sensory innervation. The actual capability to do so depends of examiner skills and familiarity with anatomy, and of the content, execution and quantification of the examination [235,236]. The patterns may permit the identification and location of nerve entrapment. Some may be “specific” conditions covered by case definitions that are relatively easy to recognize such as carpal tunnel syndrome and ulnar neuropathy at elbow level. However, a physical examination only reveals what is looked for, and even with a careful physical examination, conditions with less obvious signs may be difficult to interpret: The sensibility may be entirely normal – such as with entrapment of a motor nerve, e.g. the posterior interosseous nerve. Sensibility may be disturbed in a non-dermatomal pattern or abnormal sensibility may cover several peripheral nerve-territories. Weaknesses suggesting motor involvement may neither reflect a single root nor a single peripheral nerve. The presence of “multiple entrapment” or brachial plexopathy may well appear in confusing neurological patterns. One particularly complicating issue when looking for patterns of anatomical relevance is the frequent presence of variations such as

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<td>Seddon [231]</td>
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<td>Sunderland [232]</td>
<td>I. Conduction block</td>
<td>III. Transection of axon and nerve sheath inside an intact perineurium</td>
<td>V. Transection of the entire nerve trunk</td>
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<td>Lundborg [233]</td>
<td>Short-term circulatory stop</td>
<td>II. Transection of axon</td>
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| Damaged structure | Myelin | Myelin, axon (including perineural tissues) | Myelin, axon, neural tube, surrounding connective tissue |

**Table 1. Classification of nerve injuries**
anastomoses between nerves [237,238]. One to five variations were found in 91% of upper limbs in 90 cadaveric upper limbs [237].

The neurological examination is not straightforward and it has been shown that neurologists perform better with regard to observable neurological signs than to elicitable signs [239]. As practiced, the neurological examination has been shown to need improvement and it has been suggested that evidence should be applied to update and qualify the exam [240].

In the clinical setting, the patient’s history is known and can guide the physical examination. This knowledge may increase the prevalence of positive findings [162].

Muscle function. Classical adverse postures induced by muscular imbalance due to anatomically strictly outlined pareses include the waiter’s tip position (paretic spinati, deltoid, biceps, brachialis and supinator muscles) from an upper trunk injury, drop hand (paretic wrist, thumb and finger extensors) from an upper arm radial neuropathy, and “claw hand” (intrinsic paresis) from an ulnar neuropathy. These examples illustrate the diagnostic potential of the identification of abnormal postures induced by specific and severe nerve afflictions. However, minor weaknesses do not interfere with posture and movement, but may be assessed by muscle strength testing.

Evidently, the enormous variation of muscle strength in between individuals precludes the definition of normal values for the function of a particular muscle. Bedside muscle testing is mostly performed manually and may be semi-quantified into six or − for improved differentiation of minor weakness – eight grades (subdivision of grade 4 into 4−, 4, and 4+) [231]. During testing, the limb position should favor the isolated action of the tested muscle. A focal affliction of motor nerves may be located through the identification of patterns of muscle strength with some representative individual muscles being weak and others intact. However, no such patterns can be identified in case of global weakness, which may occur with a generalized disorder or in the absence of sufficient patient-cooperation [241]. To the author’s experience, pain-induced weakness is not a major issue provided sufficient instruction to the patient (I).

Visible or measureable atrophy is a late sign, which develops secondary to serious and long-standing derervation. It should not be expected with minor nerve lesions. If present, however, atrophy may be concealed by upper limb edema consequent to, e.g., venous and/or lymphatic obstruction.

Many clinicians tend to regard assessment of muscle strength as subjective and of little value in upper limb disorder, except where there is a debilitating degree of weakness [242]. Consequently the evaluation of muscle strength is mostly limited in clinical practice, e.g. to an assessment of grip strength (which is an integration of several muscles with different innervation). There is, however, an ongoing debate on the clinical feasibility of manual muscle testing, and it has been demonstrated that its application can often reveal the character of an upper limb disorder and contribute to the understanding of the patients’ complaints [243,244]. To reach this goal would require an evaluation of a representative sample of individual muscles, which, however, appears to be a less regular part of the physical upper limb examination [245,246]. The identification of focal neuropathies by muscle testing has been demonstrated for, e.g. the ulnar [247], median [248,249], axillary and radial [250] nerves, and the examination technique has been reviewed and refined [244].

Contrary to many other physical examinations of the upper limb, manual muscle testing has been found to be reliable [251,252] and is therefore recommended for clinical practice [253]. A review of more than 100 peer-reviewed studies found manual muscle testing to be clinically useful for evaluating the function of the nervous system [245]. A meta-analysis has showed κ-values for strength in the range from 0.29 to 1.00 (mean 0.65) [239]. Excellent interrater reliability of muscle testing has been demonstrated for many conditions, e.g. idiopathic inflammatory myopathies [254], amyotrophic lateral sclerosis [255], spinal cord injuries [256], and with pareses of the intrinsic hand muscles [257] or the radial nerve innervated forearm muscles [258]. A particularly high reliability of muscle testing was also described in patients with unilateral arm and/or neck pain (κ = 0.68) [251]. However, when individual muscles are not addressed, measures of strength may result in only fair κ-values [162]. A reliability study of manual muscle testing by neurologists reached a grouped κ-value of 0.63, but the inter-rater agreement was much more reliable for the lower limb and actually quite poor for the upper limb [239].

Dynamometric assessment of muscle strength provides a more precise assessment than manual muscle testing, but does not, however, contribute further regarding localizing a nerve affliction. Even without the active participation of the examined subject, the individual muscle function can be reliably examined by means of myographic measurements [259]. Combined with computer models of the innervation pattern of the upper limb nerves and the brachial plexus, this approach may eventually develop to be superior to manual muscle testing, which, however, should be the current practical bedside examination because it is simple and rapid to perform. Several authors have described the techniques for the manual testing of the upper limb muscles and the interpretation of the results [236,241,244,260,261]. Although many regard manual muscle testing as an important diagnostic tool, its current use remains limited. Manual muscle testing has been termed a “lost art” [262].

Sensation. The perception of sensation is the result of a complex integration within the central nervous system of peripheral nociceptive input [263]. Reduced cutaneous sensation can be an early sign in nerve compression. Each of the many techniques for the assessment of sensation has strengths and limitations, but generally sensory testing is regarded as reasonably reliable (κ=0.53) [251]. The Semmes-Weinstein monofilament test is reliable for early compression neuropathies [263,264]. Static and dynamic two-point discrimination has a high intra-rater but variable inter-rater reliability [263] but abnormal responses require advanced stages of neuropathy [265,266]. Both are time consuming and rarely used in clinical practice. The “ten test” allows for multiple points of evaluation of the perception of touch as the examiner’s finger is moved over the skin. It is rapid to perform, reliable and sensitive in early neuropathy [263,267]. Pinprick is a simple way of assessing algesia with a high inter-rater reliability [256]. Evaluation of the threshold for perception of vibration is useful for investigating early [104,265,266,268-273] and minor neuropathy [274,275]. Normal threshold values for vibrometry have been published [276] in spite of large intra-individual differences in the perception of vibration [276,277]. This variability should be taken into account when interpreting responses in groups and individuals [277], for which, however, the response at one location may be compared to that at another location. An elevated threshold to
the perception of vibration has been found with many locations of nerve affliction including brachial plexopathy [278,279]. In limbs diagnosed with neuropathic conditions combined with non-neuropathic conditions and in limbs with isolated neuropathic conditions based on diagnostic criteria of Sluiter et al. [26] we found a significantly reduced perception of vibration in all three nerve-territories and in the ulnar and radial nerve-territories, respectively. Suprathreshold stimulation responses were comparable to the vibration thresholds [103].

The perception of vibration can be studied by a 256 Hz tuning fork, which is simple and rapid in use in the clinical setting [280,281]. Vibrometers working with single or several frequencies permit quantitative assessment [61,105]. In a study of healthy volunteers, the outcomes of assessment with a 128 Hz tuning fork correlates well with vibrometry [282]. In contrast to two-point discrimination, the threshold correlates inversely to even minor fiber loss [275] and to symptoms such as tingling and numbness [271,283]. The perception of vibratory stimulation, however, corresponds poorly with electrophysiological assessments [284,285].

The sensory examination is regarded as a key feature of the physical examination and should include negative as well as positive signs. The assessment may be very sophisticated and to some extent indicate pain mechanisms [150]. I have not found demonstrations of the validity of such extensive assessments, and they are rarely applied in a clinical context. This thesis focusses on simple physical approaches that can be easily learned and are feasible in clinical practice.

Nerve trunk mechanosensitivity. Early signs in nerve compression include spontaneous pain [62] and mechanical allodynia of nerve trunks with palpation [286] and with provocative positions [71,116,117]. Nerve trunk soreness is attributed to increased activity and abnormal processing of non-nociceptive input from the nervi nervorum and mediated by unmyelinated fibers [287]. Mechanical allodynia of nerve trunks and increased mechanosensitivity to stretch of C and Aβ fibers may occur secondary to local neurogenic inflammation of the nerve or its environments with release of neuropeptides [121,196,288,289], even in the absence of axonal damage. Mechanical nerve trunk allodynia may extend distant to the lesion [290] with the entire nerve trunk ultimately reacting as a sensitized nociceptor [291]. The assessment of mechanical nerve trunk allodynia by palpation is reliable (κ=0.59) [251].

Upper limb tension testing involves postures defined to achieve a bias towards each of the three upper limb main nerves (median, radial, ulnar). This technique has been suggested for diagnosing and treating work-related upper limb main nerves (median, radial, ulnar). This technique has been found to achieve a bias towards each of the three upper limb nerve-territories and in the ulnar and radial nerve-territories, respectively. Suprathreshold stimulation responses were comparable to the vibration thresholds [103].

The technique of manual nerve mobilization is mainly applied by physiotherapists and rarely by physicians. The novel "scratch collapse" test has proved useful for the diagnoses of carpal and cubital tunnel syndrome (accuracy 82% and 89%, respectively) [296]. This approach has been applied as an adjunct to manual muscle testing and assessment of nerve trunk allodynia for the diagnosis of entrapment of the axillary and radial nerves [250].

The Tinel sign is a reliable part of the physical examination, which, however, reflects re-innervation in a traumatized nerve [297] rather than the nerve-lesion in itself. It should therefore never be regarded as obligate with nerve lesions. It is not limited to the median nerve on its passage through the carpal tunnel but may be elicited at any location where a nerve is located superficially.

Reflexes. Tapping a muscle tendon briskly causes the muscle to immediately contract due to the two-neuron reflex arc involving the spinal segment that innervates the muscle. The afferent neuron whose cell body lies in the dorsal root ganglion innervates the Golgi tendon organ associated with the muscles; the efferent α–motor neuron in the anterior horn of the cord innervates the muscle. The cerebral cortex and brainstem nuclei exert influence over the sensory input of the muscle spindles by means of γ-motor neurons located in the anterior horn. These neurons supply a set of muscle fibers that control the length of the muscle spindle itself. While hyporeflexia indicates a disorder of one or more of the components of the two-neuron reflex arc itself, hyperreflexia indicates an interruption of corticospinal and other descending pathways. Testing of tendon reflexes is regarded as an important part of the physical examination, but a study of the inter-rater reliability among neurologists and trainees in neurology resulted in a rather poor agreement for both with the highest κ-value 0.35 [298]. Tendon reflexes hardly contribute better to the assessment of peripheral nerve affliction than, e.g. manual muscle testing.

Electrophysiological studies. Characteristic electrophysiological findings have been described with progression of peripheral nerve lesions. However, nerve afflictions may not exhibit any electrophysiological abnormalities. Consequently, negative findings do not indicate normality, in particular with chronic minor nerve afflictions that may still be serious in terms of pain and functional limitations.

Conventional nerve conduction studies can assess the integrity of large myelinated motor or sensory fibers (Aα and Aβ fibers). Following compression, changed axonal transport and intraneurial circulation cause symptoms distal to the compression site [189], but the compression is usually insufficient to actually cause axonal injury [299]. Only the fastest conducting intact myelinated fibers influence the impulse propagation [300]. Consequently, the survival of just a few intact myelinated fibers may result in a completely normal conduction velocity. With disorders affecting small myelinated Aδ and unmyelinated C fibers, the recorded latency and conduction velocity will remain normal. Clinical guidelines suggest that indications of primary demyelination require at least 70% decreased nerve conduction velocity and at least 150% increased distal latency [301].

In accordance with demyelination followed by remyelination, the nerve conduction velocity in chronic nerve compression may be decreased, but in contrast to acute nerve injuries, in which the compound muscle action potentials can-
not be elicited, the amplitude of the compound muscle action potential is normal as long as there is axonal integrity, which is the normal situation in the early phases of chronic nerve compression.

Nerve lesions consisting of a mixture of axon loss and conduction loss, which is the normal pattern in more advanced nerve entrapment, provide a special electrodagnostic challenge. The reduction of the amplitude of the compound muscle action potential relative to normal indicates degeneration of a comparable percentage of motor axons. The percentage of axon loss may be sorted out by careful examining amplitudes of the compound motor action potential elicited from stimulation both above and below the lesion and by comparing the amplitude with distal stimulation by that obtained from the other side. Of the remaining axons, one can estimate the involved percentage by comparing amplitudes or areas obtained with stimulation distal and proximal to the lesion. However, if substantial motor re-innervation occurs via collateral sprouting and alters the innervation ratio of the muscle, the amplitude is less trustworthy than electromyographic assessments. Mixed injuries typically have two or more phases of recovery that include both nerve regeneration and hypertrophy of the existing innervated muscle fibers. The neuropraxic component resolves quickly. Muscle fiber hypertrophy can provide additional recovery, but the axonal component is slower because it depends on distal axonal sprouting and regeneration from the site of the lesion. Patients may experience a relatively rapid but incomplete recovery, followed by a slower further improvement. Sensory recovery may proceed for a longer time than motor [302].

Prolonged F-wave latencies and wave abnormalities may occasionally be demonstrated with proximal nerve injury [303] but the validity of this examination is unknown. In a series of patients with neurogenic thoracic outlet syndrome, no F-wave abnormalities could be elicited even with provocation [304]. The Hoffmann-reflex is a highly sensitive reflex with amplitudes resulting from complex neural mechanisms that act synchronously [305,306]. This reflex may become a valuable tool for the assessment of nerve afflictions, but studies demonstrating its diagnostic value in upper limb patients are needed.

The electromyographic examination should include a quantitative study of motor units from both weak and intact muscles. However, the outcome may appear normal in proximal muscles distal to the lesion, and abnormalities are more likely in distal muscles. Chronic compression neuropathy is often characterized by such heterogeneous affliction of the fascicles with those located peripherally tending to be more involved than fascicles in a protected position in the central part of the nerve [198,300,307]. This selective involvement of fascicles may result in normal electromyography. Fibrillation may reflect muscles supplied by a few afflicted axons with the remaining axons working normally and muscle responses appearing normal. Furthermore, the duration of a static lesion tends to restrict the electromyographic abnormalities to progressively fewer and more distally located muscles. Re-innervation may be so efficient in initially denervated proximal muscles that electromyography cannot determine that they were ever involved [308].

It should be apparent from the above, that a peripheral nerve lesion is not always reflected by electromyography, and that false negatives as well as false positives occur. Although based on simple principles, the electrodagnostic demonstration of nerve lesions remains a challenge. The limitations of electrophysiological assessments are important to know, and pitfalls abound in practice [309-312]. Electrophysiology is clearly better for demonstrating certain peripheral nerve entrapments, e.g. carpal tunnel syndrome, than others. Still, even for carpal tunnel syndrome, the ability of nerve conduction studies to reflect symptoms, function [313] and physical findings [314] has only moderate sensitivity and specificity and a low predictive value when looking at populations [315]. The limitations of electrophysiology are even more serious with other locations of nerve affliction such as posterior interosseous [316,317] or median [249,318-321] neuropathy at elbow level, or with brachial plexopathy [278,321-324]. In a practical context, a standard electrophysiological approach cannot identify or exclude these conditions.

The American Association of Neuromuscular and Electrodiagnostic Medicine has addressed the appropriate performance of electrodagnostic studies and called for the electrophysiologist to plan studies following an appropriate history and a physical examination of sufficient detail for localizing a possible neuropathy. Indicated needle electromyographic studies should then be performed in addition to nerve conduction studies [325]. Inconsistencies may result from temperature change, variations between nerve segments with faster conduction velocity proximally than distally, and the effect of age. Other sources of error include excessive spread of stimulation current that may inadvertently activate neighboring nerves, anomalous innervation, and inaccurate surface measurements, which do not reflect the actual length of the nerve [310]. The traditional method of detecting abnormal nerve conduction by comparison with normal values from a control population lacks sensitivity [322].

A review in 2008 concluded that surface electromyography may be useful for detecting neuromuscular disease, but that there are insufficient data to support its utility for distinguishing between neuropathic and myopathic conditions [326].

Upper limb compressive neuropathies remain a clinical diagnosis [234] and several authors have warned against uncritical use of electrophysiological testing [300,327]. Leffert noted: “The techniques of electrodiagnosis are available to either aid the clinician in confirming the clinical diagnosis or to helplessly becloud the issue and contribute to an unnecessary or inappropriate operative procedure. It therefore behoves the surgeon to have a working knowledge of the tests, their limitations, and particularly the interpretation of reports” [327].

Findings in patients with extensive occupational exposure to pneumatic grinding tools and severe sensorineural symptoms are illustrative for the limitations of electrophysiology. While measures such as hand strength and vibrotactile thresholds discriminate between more and less symptomatic patients, nerve conduction studies did neither correlate with symptoms nor with clinical and quantitative sensory tests [328]. However, a recent study showed group wise reduced sensory conduction velocities for the median and ulnar nerves across the wrist in 21 computer workers compared to 21 controls – especially on the dominant side [329]. In a mixed group of neurological patients with weakness as the dominant symptom, targeted electrophysiological studies were also shown to be accurate [330], but whether this applies in patients with pain as the dominant symptom is not known.

Imaging. Magnetic resonance imaging (MRI) allows visualization of the intrinsic nerve, including the fascicular pattern, and of the surrounding structures such as muscle abnormalities [331-333]. It is, however, usually normal until there is evident axonal degeneration and muscle wasting [334]. MRI has visual-
ized median nerve damage and regeneration in the carpal tunnel [333] and forearm [335], and has also been applied for, e.g. the supraspinal in nerve [336], the ulnar nerve at the elbow [337], and the brachial plexus [338]. MRI has permitted differentiation of median and radial neuropathy at elbow level from medial and lateral epicondylitis, respectively [339], and has demonstrated pathology suggesting median nerve and brachial plexus inflammatory changes in patients with NSAP [50]. High resolution ultrasound imaging has demonstrated swelling proximally to the compression site [340] in the ulnar, radial [341] and median nerves [115,341,342], brachial plexus [343,344], and cervical roots [345]. Ultrasound is reported to be more sensitive than MRI in demonstrating peripheral nerve pathology (93% vs. 67%) that was diagnosed from surgical exploration or clinical and electrophysiological assessment, and also identified multifocal lesions better. The specificity was equivalent (86%) by the two approaches [346]. However, the study of nerve entrapment by MRI and ultrasound is still restricted to a limited number of experts, and little is known about the validity of these techniques in patients with upper limb pain. With future technical improvements and extension of skills these imaging techniques appear promising.

**DIAGNOSTIC GOLD STANDARDS VS. CONSTRUCT VALIDITY**

Diagnostic case definitions constitute a challenge in the absence of satisfactory gold standards for the physical elements involved. In particular, difficulties may arise where the pathology underlying a disorder is unknown or when the disorder cannot be readily diagnosed. In this situation, one can view the diagnosis as useful for classifying people for the purpose of preventing or managing illness rather than as a label for a disease process. With this perspective, the value of a case definition as useful for classifying people for the purpose of preventing or managing illness rather than as a label for a disease process is its practical utility in distinguishing groups of people with the illness process. With this perspective, the value of a case definition as useful for classifying people for the purpose of preventing or managing illness rather than as a label for a disease process is its practical utility in distinguishing groups of people with the illness process.

**Study 1**

This thesis encompasses three clinical studies and eight papers:

**Study 1**

*Scope and aims of the studies*

This thesis encompasses three clinical studies and eight papers:

*Study 1*

Based on four papers (I, II, III, IV) deals with the development, description and validation of a physical diagnostic approach to the upper limb nerves.

*Study 2*

Applied the physical approach in Study 1 (I, II) in patients with computer-related upper limb complaints. Based on the hypothesis that computer-related upper limb disorders are of a neuropathic character and involve nerve affections with particular locations (V), a similar examination (I, II) was applied in symptomatic and non-symptomatic computer operators in work (VI). Finally, the outcome was studied of an intervention addressing symptoms and findings in accordance with peripheral nerve afflictions (VII).

*Study 3*

Focused on work-related risk factors for brachial plexopathy among patients in the primary health sector. A questionnaire on mechanical exposures, psychophysical perceptions and psychosocial factors at work was completed by patients with brachial plexopathy and by matched control subjects from the same clinics without upper limb complaints (VIII).

The three studies had the following aims:

*Study 1*

- To describe and to determine the inter-rater reliability of manual testing of the upper limb muscles (I), and of the assessment of mechanosensitivity of nerve trunks (II), sensibility in homonymous innervated areas as assessed by touch, pinprick and tuning fork (II), and of neurological patterns defined to reflect specific locations of focal neuropathy (II);
- To approach the construct validity of the examination by determining the relation of identified neurological patterns to the presence of symptoms characteristic for focal neuropathies (III);
Study 3
- To analyze the feasibility of a neurological upper limb examination limited to manual muscle testing of six muscles only (IV).

Study 2
- To develop a hypothesis with regard to the character of computer-related upper limb disorder from the outcome of the neurological examination from Study 1 applied in a clinical sample of patients with severe symptoms (V);
- To study the feasibility of this hypothesis by application of the same neurological examination in actively working computer operators with or without symptoms (VI);
- To analyze the influence of stretching/mobilization of nerves on symptoms and physical findings (VII).

Study 3
- To analyze the relation of potential physical and psychosocial work-related risk indicators to brachial plexopathy (VIII).

Patients and methods

Patients
Three study groups were involved (Table 2).

Study methods and applied interventions

Study 1
Blinded to any information relating to patients, two examiners performed identical physical examinations including the variables in Table 3 (I, II). Based on the topography of nerves and their muscular and sensory innervation, 10 neurological patterns (Table 4) were defined. Each pattern was characterized in accordance with a localized nerve affection with a specific location. The two examiners classified all limbs with respect to the presence or absence of pattern(s) (III).

The inter-rater reliability was calculated for each neurological parameter (I, II) and for the identified neurological patterns (II). In order to assess the construct validity of the examination, and to determine the predictive values, the outcome of the physical examination in terms of presence or absence of neurological pattern(s) was compared to the presence of complaints (pain, weakness and/or numbness/tingling). Other examiners collected information about the patients’ complaints (III). As it may be regarded as complicated to examine a high number of neurological items, the feasibility in terms of sensitivity and specificity of an assessment limited to manual testing of six muscles (IV) was assessed with comparison to symptoms and to the outcome of the more comprehensive examination (III).

Study 2
A consecutive series of heavily exposed and severely handicapped computer-aided designers underwent a physical examination of the upper limbs nerves (Table 3). Questionnaire information on precipitating factors before disease onset and status with regard to symptoms and employment was collected at the initial clinical contact and ½ – 1½ year later. Patients were encouraged to freely move and use the symptomatic upper limb within the limits of immediate and subsequent aggravation of pain, and offered physiotherapy based on neurodynamic principles [139,349,350]. The patients tried to resume computer work after optimization of workstation ergonomics and work-organization. Patients unable to do so received advice with regard to vocational rehabilitation with emphasis on maximal variation during future work and use of the upper limbs close to the body. Repetition, static postures, and the use of force was discouraged (V).

Actively working graphical computer operators in two divisions of an engineering consultancy company answered a modified Nordic Questionnaire on perceived pain in the shoulder, elbow, and wrist/hand with scores for each region on a VAS-scale 0 – 9.

In addition, they underwent an upper limb neurological examination by an examiner blinded to the study subjects’ symptoms (Table 3). The relation of pain summarized for all three regions to each neurological finding and to three neurological patterns defined to be in accordance with brachial plexopathy, posterior interosseous neuropathy and median neuropathy at elbow level, respectively, (V) (Table 4) were studied in the dominant limb (VI).

Workers in one division participated in a six-month upper limb stretching course based on neurodynamic principles (350-352). The stretching aimed to promote nerve-mobility at the three implicated locations (Table 4). The first and second modality aimed to stretch the volar forearm flexors and the second additionally to stretch the pronator teres muscle. The third modality aimed to mobilize the brachial plexus and the median nerve, and the fourth the radial nerve.

The intervention subjects were instructed in the exercises and encouraged to perform them at least three times daily during workdays and additionally after hours. Subjects from the other division served as controls. At the end of the intervention, the participants underwent a second identical evaluation by questionnaire and blinded physical examination. For both groups, the perceived pain and the individual and patterns of physical findings at baseline and at follow-up were compared. In subjects with no or minimal pain at baseline, the relation of incident pain to the summarized findings for the parameters contained in the definition of nerve affliction at the three locations was additionally studied (Table 4) (VII).

Study 3
Upper limb patients fulfilling defined criteria for brachial plexopathy in a previous study [170] and matched control patients without upper limb complaints from the same general practitioners completed a questionnaire [353] about mechanical exposures, psychophysical perceptions at work and psychosocial work-environmental factors (VIII). The responses for cases and controls were compared.

The definition of brachial plexopathy in Study 3 (VIII) required fulfillment of four criteria:
- Pain in the neck, shoulder, arm or hand or weakness in the shoulder, arm or hand or subjectively changed sensibility in shoulder, arm or hand;
- Reduced strength in posterior deltoid, biceps brachii, radial flexor of wrist muscles and in one or more of the following: Triceps, short extensor of wrist, long extensor of thumb, long flexor of thumb, abductor pollicis brevis, pectoral, flexor digitorum profundus V,
and abductor digiti minimi muscles. With a supraclavicular affliction, the infraspinatus is weak and the radial flexor of wrist intact unless the infraclavicular brachial plexus is also involved.

- Sensory abnormalities in the axillary territory;
- Mechanical allodynia of the brachial plexus (at the scalene triangle or infraclavicularly behind the pectoralis minor muscle).

**Physical examination**
The applied upper limb neurological examination is a modification of the classical neurological examination and intended to represent a feasible and simple clinical approach. The examined items varied in between the studies (Table 3) and consisted of the following qualities:

- The muscle function was assessed and quantified (with subdivision of grade 4 weakness into 4-, 4, and 4+) [354] in selected individual muscles regarded as representative of the upper limb nerves (Table 3). The muscles were manually tested from proximal to distal with consistent comparison right and left. The positioning and stabilization in three different exit postures aimed to optimize the isolated action of each muscle. The strength in a certain muscle was simultaneously assessed bilaterally. This was viewed as advantageous compared to other approaches in the neurological literature [260,261].
- The sensibility to moving touch [267,355], pinprick

<table>
<thead>
<tr>
<th>Table 2. Study groups involved in empirical studies</th>
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<tbody>
<tr>
<td><strong>Subjects</strong></td>
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<td>Study 1</td>
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<td>Study 2</td>
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<tr>
<td>Study 3</td>
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</table>
and the perception of vibration (tuning fork 256 Hz [272]) were assessed in homonymous innervated upper limb territories (Table 3). Deviation of sensibility from normal was quantified as “marked” with an allodynic reaction, or when touch, pain or vibration could either not be perceived at all or was reduced sufficiently to be clearly apparent to the examiner from the patient’s reaction, and as “mild/any” with any other divergence from normal. For the latter assessment, findings were compared with sensibility in territories regarded as with normal sensibility. Sensory abnormalities were defined as any identified deviation from normal regardless of sensory gain or loss in the assessment [99].

- Nerve trunks were palpated at defined locations with a manual pressure of 3 KP from proximal to distal [62,117,286] (Table 3). Mechanosensitivity was quantified as “marked” with an allodynic response when

### Table 3. Neurological variables

<table>
<thead>
<tr>
<th>Item tested</th>
<th>Study 1</th>
<th>Study 2</th>
<th>Study 3</th>
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<tr>
<td><strong>Manual muscle testing</strong></td>
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<tr>
<td>Posterior deltoid</td>
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<tr>
<td>Pectorals</td>
<td>+</td>
<td>+</td>
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<tr>
<td>latissimus dorsi</td>
<td>+</td>
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<tr>
<td>Biceps brachii</td>
<td>+</td>
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<td>Triceps</td>
<td>+</td>
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<tr>
<td>Infraspinatus</td>
<td>+</td>
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<tr>
<td>Extensor carpi radialis brevis</td>
<td>+</td>
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<tr>
<td>Flexor carpi radialis</td>
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<tr>
<td>Flexor pollicis longus</td>
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<tr>
<td>Extensor pollicis longus</td>
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<tr>
<td>Abductor pollicis brevis</td>
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<tr>
<td>Extensor carpi ulnaris</td>
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<tr>
<td>Flexor digitorum profundus V</td>
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<td>+</td>
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<tr>
<td>Adductor digiti minimi</td>
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<tr>
<td>Rhomboid</td>
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<tr>
<td>Brachioradial</td>
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<td>Supinator</td>
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<td><strong>Aesthesia</strong></td>
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<tr>
<td>Axillary nerve</td>
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<td>Medial cutaneous nerve of arm</td>
<td>+</td>
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<tr>
<td>Medial cutaneous nerve of forearm</td>
<td>+</td>
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<td>+</td>
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<tr>
<td>Musculocutaneous nerve</td>
<td>+</td>
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<tr>
<td>Radial nerve</td>
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<td>Median nerve</td>
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<tr>
<td>Ulnar nerve</td>
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<tr>
<td><strong>Assessment of sensibility</strong></td>
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<tr>
<td>Axillary nerve</td>
<td>+</td>
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<td>Medial cutaneous nerve of arm</td>
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<td>Medial cutaneous nerve of forearm</td>
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<td>Musculocutaneous nerve</td>
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<td>Radial nerve</td>
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<tr>
<td>Median nerve</td>
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<tr>
<td>Ulnar nerve</td>
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<tr>
<td><strong>Tuning fork 256Hz</strong></td>
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<tr>
<td>Median nerve (2nd fingertip)</td>
<td>+</td>
<td>+</td>
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<tr>
<td>Ulnar nerve (5th fingertip)</td>
<td>+</td>
<td>+</td>
<td>+</td>
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<tr>
<td>Radial nerve (Dorsal radial triangle)</td>
<td>+</td>
<td>+</td>
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<tr>
<td><strong>Assessment of nerve trunk mechanosensitivity</strong></td>
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<tr>
<td>Supraclavicular brachial plexus (Scalenus triangle)</td>
<td>+</td>
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<td>+</td>
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<tr>
<td>Clavicular brachial plexus (divisions level)</td>
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<td>+</td>
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<tr>
<td>Infraclavicular brachial plexus (cord level)</td>
<td>+</td>
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<td>+</td>
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<tr>
<td>Suprascapular nerve (Scapular notch)</td>
<td>+</td>
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<tr>
<td>Axillary nerve (Quadriangular space)</td>
<td>+</td>
<td>+</td>
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</tr>
<tr>
<td>Musculocutaneous n. (Coracobrachial m.)</td>
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<tr>
<td>Radial nerve (Triceps arcade)</td>
<td>+</td>
<td>+</td>
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<tr>
<td>Posterior interosseous n. (elbow)</td>
<td>+</td>
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<td>+</td>
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<tr>
<td>Median nerve (elbow)</td>
<td>+</td>
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<tr>
<td>Median nerve (Carpal tunnel)</td>
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<tr>
<td>Ulnar nerve (elbow)</td>
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<tr>
<td>Ulnar nerve (Guyon’s canal)</td>
<td>+</td>
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</table>
the patient reacted with an avoidance reaction/jump sign, "medium" when the patient expressed the pressure as seriously uncomfortable, and "mild/any" with any other soreness regarded as exceeding normal.

For this assessment, the level of mechanosensitivity was compared to reactions regarded as normal to pressure elsewhere along nerves.

Statistics
For the Papers I, II, and III, the statistical package of EPI-info (version 2.0) was applied for data entry and SPSS (ver. 11.0) for further statistical analyses. The data in the papers IV and VI-VIII were processed by Stata (ver. 9.2).

Study 1
The reliability of the inter-rater assessment of the individual neurological items and of the overall identification of limbs with/without pattern reflecting focal neuropathy was analyzed by Cohen’s $\kappa$-statistics (I-II). Odds-ratios for the relation to symptoms of strength reduction defined by both examiners were calculated (I).

In order to avoid an arbitrary cut off point in the sub-classification of neuropathy with specific locations, the calculation of the inter-rater reliability of identified neurological patterns was based on a continuous scale defined by the sum score of the ratings from each of the required physical findings (muscle strength, sensibility, and mechanosensitivity). The reproducibility between the two examiners of identifying neurological patterns defined to reflect peripheral nerve afflictions with certain locations (Table 4) was studied by calculating the correlation coefficient (II).

In limbs with agreement between the examiners on presence or absence of any pattern, the diagnostic sensitivity, specificity, and positive and negative predictive values of the combined tests were determined in relation to complaints. Additionally, the pre-test odds = prevalence of complaints, the likelihood ratio for a positive test = sensitivity/(1 – specificity), and the post-test odds = pre-test odds x likelihood ratio were calculated [356]. The post-test probability (the diagnostic confidence of the blinded physical examination in relation to complaints expressed as the post-test odds/(post-test odds + 1) was compared to the pre-test odds. Similar calculations were performed for each examiner (III).

The inter-rater reliability of manual muscle testing of six muscles and the correlation to symptoms of any weakness identified was assessed by Cohen’s $\kappa$-statistics. In addition, the relation of presence or absence of any weakness to symptoms and to the outcome of the comprehensive examination applied in the previous papers (I-III) was assessed by Cohen’s $\kappa$-statistics, and the diagnostic sensitivity, specificity, and the positive and negative predictive values were determined for each examiner. Similar calculations were made for limbs rated unanimously by the two examiners (IV).

Study 2
In the clinical case study (V), the changed level of reported pain from the initial consultation to follow-up was assessed by Friedman’s test. In the workplace study, pain scores summarized for the three upper limb regions (min=0, max=27) in the mouse-operating and contralateral limbs were compared by a Wilcoxon test and the relation to each physical item analyzed by Kendall's rank correlation. The relation of summarized pain to each pattern was studied by a test for trend across ordered groups (patterns) (VI).

Changes from baseline to follow-up of self-reported pain (for subjects who answered both questionnaires) and of individual and patterns of neurological findings were studied in the intervention group and among controls. Incident pain was

<table>
<thead>
<tr>
<th>Location of neuropathy</th>
<th>Pattern</th>
<th>Muscles with reduced function</th>
<th>Nerve territories with sensory abnormalities</th>
<th>Study 1</th>
<th>Study 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brachial plexus (Upper trunk)</td>
<td>Infraspinatus</td>
<td>Axillary</td>
<td>+</td>
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<tr>
<td></td>
<td>Posterior deltoid</td>
<td>Musculocutaneous</td>
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<td></td>
<td>Biceps brachii</td>
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<tr>
<td>Brachial plexus (Cord level)</td>
<td>Posterior deltoid</td>
<td>Axillary</td>
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<td></td>
<td>Biceps brachii</td>
<td>Musculocutaneous</td>
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<td></td>
<td>Flexor carpi radialis</td>
<td>Median nerve</td>
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<tr>
<td>Suprascapular nerve (Suprascapular notch)</td>
<td>Infraspinatus</td>
<td>-</td>
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<td>Axillary nerve (Quadrilateral space)</td>
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<td>Axillary</td>
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<td>Biceps brachii</td>
<td>Musculocutaneous</td>
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<tr>
<td>Radial nerve (Upper arm)</td>
<td>Triceps</td>
<td>Radial</td>
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<td></td>
<td>Extensor carpi radialis brevis</td>
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<td></td>
<td>Extensor pollicis longus</td>
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<tr>
<td>Posterior interosseous nerve (Arcade of Frohse)</td>
<td>Extensor carpi ulnaris</td>
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<tr>
<td>Median nerve (Elbow level)</td>
<td>Flexor carpi radialis</td>
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<td></td>
<td>Flexor pollicis longus</td>
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<tr>
<td>Carpal tunnel</td>
<td>Abductor pollicis brevis</td>
<td>Median</td>
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<tr>
<td>Ulnar nerve (Elbow level)</td>
<td>Flexor digitorum profundus V</td>
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<tr>
<td></td>
<td>Abductor digiti minimi</td>
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<td>Ulnar nerve (Guyon’s canal)</td>
<td>Abductor digiti minimi</td>
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studied in subjects with no or minimal pain (less than 2) at baseline summarized for hand, elbow and shoulder. Paired samples were studied by a Wilcoxon signed rank-sum test and non-paired samples of the same parameters by a Mann-Whitney rank test (VII).

**Study 3**
The exposures for patients classified as brachial plexopathy and control patients without upper limb complaints were compared by a Wilcoxon rank-sum test. Odds-ratios and dose-response relationships were studied by logistic regression (VIII).

**ETHICS**
Signed informed consent was obtained from the participants in all studies, which were approved by the local Ethics Committee.

**RESULTS**

**Study 1 (I, II, III, IV)**
The median relative inter-rater agreement of muscle strength dichotomized as normal or reduced was 81% and the median \( \kappa \)-value 0.54. This was further improved to 0.57 when calculations were restricted to 28 subjects with unilateral complaints (I). Reduced muscle strength was significantly related to pain, weakness and/or numbness/tingling in 38 out of 82 limbs with a median odds ratio of 4.0 (range 2.5 - 7.79) (I).

The inter-rater reliability for sensitivity to touch, pain and vibration, and for mechanosensitivity was reflected by median \( \kappa \)-values of 0.69, 0.48, 0.58, and 0.53, respectively. The reproducibility of identifying the neurological patterns defined to reflect specific locations of peripheral nerve afflictions (Table 4) was fair to excellent with a median correlation coefficient = 0.75. The overall agreement regarding identification of limbs with/without defined pattern(s) in accordance with focal nerve afflictions was good (\( \kappa = 0.75 \)) (II).

The majority of patterns reflected brachial plexopathy at cord level (unanimously identified in 21 instances in 82 limbs). In all but one of these, patterns reflecting distal neuropathy – in particular involving the posterior interosseous and median nerves at elbow level – were additionally identified. In contrast, carpal tunnel syndrome and ulnar neuropathy at elbow level were rare (one and two limbs, respectively) and in none of these instances found in isolation (II). The two examiners agreed on the absence of any pattern in 38 limbs. With concordance between the examiners with regard to the presence or absence of any pattern, the sensitivity, specificity, positive and negative predictive values were 0.73, 0.86, 0.93 and 0.90, respectively. While the pre-test odds for unanimously classifying a limb with regard to presence of symptoms amounted to 0.46, the post-test probability was 0.81. For each examiner, the post-test probability was 0.87 and 0.88, respectively (III).

Limiting the physical assessment to six muscles, the two examiners recognized weaknesses in 48 and 55 limbs, respectively, with moderate agreement (median \( \kappa = 0.58 \)). Out of these, 35 and 32 limbs, respectively, were symptomatic. There was good correlation between findings and symptoms for one examiner (\( \kappa = 0.61 \)) and fair correlation for the other (\( \kappa = 0.33 \)). Both reached high sensitivity (0.92, 0.84) but less satisfactory specificity (0.70, 0.50). Weaknesses agreed upon by the two examiners correlated moderately with symptoms (\( \kappa = 0.57 \)) (IV).

**Study 2 (V-VII)**
The rather uniform physical findings in the clinical case study of patients with severe computer-related upper limb disorders indicated in all patients a pattern in accordance with brachial plexopathy at cord level combined with median and posterior interosseous neuropathy at elbow level. 86% of patients reported aggravating factors (high work intensity, overwork etc.) during the months prior to the onset of symptoms. In spite of significantly reduced symptoms at follow-up, the prognosis was serious in terms of work-status and persisting pain. Only 2 out of 21 patients were able to continue computer work (V).

Symptoms were frequent among computer operators in occupation. The respondents reported pain, paraesthesia or subjective weakness in 67, 23, and 7 limbs, respectively, out of 96 mouse-operating limbs. In spite of minimal summarized pain-scores (exceeding 4 on a scale from 0 to 27 in only 33 limbs), abnormal physical findings were prevalent. Symptoms and findings were much more frequent in the mouse operating limb than contralaterally. The summarized pain correlated significantly to a reduced function in five muscles (deltoid, biceps brachii, radial flexor of the wrist, short radial extensor of wrist, and ulnar extensor of the wrist), to mechanical nerve-trunk allodynia at one location (posterior interosseous nerve) and to elevated threshold to vibration in two cutaneous innervation territories (median and radial nerves). The defined criteria for diagnosing brachial plexopathy were satisfied in 9/2, of median neuropathy in 13/5 and of posterior interosseous neuropathy in 13/8 mouse-operating/contralateral limbs, respectively. For each of the three patterns that reflected these three locations of neuropathy there was a significant trend between the summarized pain and the summation of scores for the items contained in each pattern (VI).

At follow-up after stretching there was a significant reduction of the summarized pain-score among cases, whereas the level of pain was unchanged in the control subjects who did not participate in stretching. Physical findings reflecting upper limb peripheral nerve afflictions were unchanged in both groups. Incident pain correlated to physical findings in accordance with the three locations of nerve affliction (VII).

**Study 3 (VIII)**
According to the defined criteria, 9 and 12 limbs were diagnosed as right and left supraclavicular brachial plexopathy, respectively, with bilateral affliction in five. 52 and 37 limbs were diagnosed as right and left infraclavicular brachial plexopathy, respectively, with bilateral involvement in 12. Nine and eight patients had a combination of supraclavicular and infraclavicular plexopathy on the right and left side, respectively.

A high proportion of cases with brachial plexopathy had additional non-neuropathic diagnoses (based on the criteria in reference [170]) with the major concomitant diagnoses on the right/left side being rotator cuff disorder (12/8), and lateral epicondylitis (19/12), respectively. Simultaneous presence of epicondyliitis and rotator cuff disorder was identified in one right limb. In all limbs except one with brachial plexopathy there was additional peripheral neuropathy according to the diagnostic criteria (170). The peripheral affliction involved primarily the median nerve at elbow level and the radial/posterior interosseous nerves.

Assessed as the extent during the workday or days/week, standing, arms extended > 45°, neck flexion, and
repetitive work were significant risk indicators for brachial plexopathy with clear dose–response relationships. These findings were supported by psychophysical responses that also identified the perceptions of adverse limb postures, high work pace and the use of force as risk indicators. The identified psychosocial relations to brachial plexopathy were limited to measures that also reflect physical exposures (VIII).

DISCUSSION
The three studies in this thesis applied a modification of the classical neurological bedside examination with the intention to identify and locate focal upper limb peripheral neuropathies. The definition of neuropathies was based on the course and innervation patterns of the upper limb nerves. The diagnostic process involved a systematic assessment of nerve trunk allodynia at location(s) indicated by the neurological pattern(s) of weaknesses in selected representative muscles and sensory disturbances in homonymous innervated cutaneous territories.

The applied physical examination has provided new observations: Irrespective of the study sample (patients referred to a specialized secondary center for occupational medicine, computer workers in active work, or upper limb patients seeking care in primary general practice) (170) (Table 2), the physical examination identified neurological patterns consistent with peripheral nerve involvement in a high proportion of study subjects.

The neurological patterns were identified with reasonable inter-rater reliability, and their presence correlated to upper limb complaints. The examination emphasized the identification of minor degrees of paresis and sensory disturbances, which were common in the studied samples. Paralysis, atrophy, analgesia or anesthesia was not seen. The examination is rapid and simple to perform, easy to learn and does not require sophisticated equipment.

Typical symptoms in NSAP include pain [47,61,62], subjective motor [47,61,71] and sensory [47,61,70] disturbances. Physical findings in NSAP include weakness [54,74-77], sensory abnormalities [34,95-98] including allodynia [61,99,100] and altered perception of vibration [61,101-106,153], and nerve trunk mechanosensitivity [50,96,112-115]. These symptoms and findings are remarkably similar to those of the symptomatic study subjects in the three studies.

Three patterns in accordance with defined criteria for focal upper limb nerve afflictions located at the brachial plexus at cord level, the posterior interosseous nerve and the median nerve at elbow level accounted for a major proportion of the morbidity in the studied samples. The frequent combination of brachial plexopathy and distal neuropathies justifies a further discussion about these conditions and the “double crush” phenomenon [221].

The identified patterns would not be recognized by a standard physical assessment but only following a systematic examination of representative neurological items. As described in every neurological textbook, the classical neurological upper limb examination represents a key diagnostic approach to disorders of the nervous system including peripheral nerve afflictions. Clinicians and researchers may refrain from performing a neurological examination, which is sufficiently detailed for the purpose, in particular when neurological abnormalities to be expected are minor. Physical examinations tend to pay little attention to the neurological items that are the key elements in the physical examination on which the three studies of this thesis is based. Systematic manual muscle testing and nerve trunk palpation [150] is rarely applied, while sensory assessment tends to be more practiced. The reluctance to include a sufficient number of representative neurological items in the examination may be due to the lack of consensus regarding standardized clinical tests and the significance of positive tests. The applied neurological examination and its interpretation may be regarded as complicated, and a systematic examination of the upper limb nerves does require a familiarity of the functional anatomy and the course and innervation patterns of nerves. The examiner also needs some experience in applying the tests. Diagnostic controversies regarding in particular the focal nerve afflictions that according to this thesis appear to be most common (brachial plexopathy, posterior interosseous and median neuropathy at elbow level) may understandably result in uncertainty regarding their frequency. Consequently, perceiving these locations of focal neuropathy as rare, or wrongly assuming that electrophysiological standard approaches will identify them when present, may reduce the efforts to look for them.

The importance of including clinical neurological tests to reach a diagnosis in upper quadrant disorders has been emphasized [357] and there is increasing evidence for the relative significance of the assessment of individual muscle strength, sensory deviations from normal and adverse mechanosensitivity of nerve trunks [251,358]. An insufficient examination may result in missing information of potential diagnostic assistance, and may explain the rather limited support in the literature to the role of the peripheral nerves in work-related upper limb disorders such as nerve afflictions at the three locations, which according to this thesis seem to be the most frequent.

The most difficult part in diagnosing a plexopathy and other upper limb nerve afflictions is probably that it requires an adequate amount of clinical suspicion combined with a thorough anatomical knowledge of the peripheral nervous system and a meticulous physical examination. Once a set of symptoms is recognized, e.g. as a potential plexopathy, the patients’ history and course of the disorder will often greatly limit the differential diagnoses [178]. The only published study of diagnostic distribution of upper limb morbidity that includes the outcomes of a systematic neurological examination (strength, sensation, nerve trunk allodynia) on a major series of patients in general practice is the study by Laursen et al. [170] that contributed the cases for Study 3. Based on history and neurological findings, 167 out of 322 upper limbs diagnosed with brachial plexopathy constituted the largest diagnostic group in this sample. Posterior interosseous neuropathy was identified in 39 limbs and median neuropathy at elbow level in 61 limbs [170].

Following application of a comprehensive amount of neurological tests in 485 symptomatic workers Pascarelli & Hsu noted the high frequency of multimorbidity. There was no detailed description of the execution and interpretation of the applied tests, nor for the precise diagnostic criteria, which however, emphasized nerve trunk soreness/Tinel phenomena. Based on diagnostic criteria of others [70,324,359], brachial plexopathy was identified in 70%. Radial tunnel syndrome was described in 7%, lateral epicondyilitis in 34%, and cubital tunnel syndrome and medial epicondyilitis in 64% and 60%, respectively [72]. Where tolerated, isometric muscle testing was performed according to Kendall & McCready [260] but the muscles tested were not described in details. While no patients had biceps or triceps weakness, reduced strength in forearm and hand was described as common. In the absence of systematic testing of all relevant muscles, however, posterior interosseous

DANISH MEDICAL JOURNAL 19
neuropathy could well be interpreted as lateral epicondylitis, and median nerve affliction at the distal humoral supracondylar process (which according to the studies in this thesis is the most important location of proximal median neuropathy) could be understood as cubital tunnel syndrome or medial epicondylitis. Brachial plexopathy in the absence of biceps weakness is a surprising finding, which questions the applied technique for manual muscle testing.

Brachial plexopathy is often termed thoracic outlet syndrome, which has been defined as "upper extremity symptoms due to compression of the neurovascular bundle in the area of the neck just about the first rib" [55], or as a syndrome characterized by upper limb pain, paraesthesia, numbness, and early fatigue due to nerve compression [226]. Weakness, muscular fatigue and elevated vibration perception thresholds correspond fully to focal nerve afflictions such as brachial plexopathy but may also involve central mechanisms [101,153]. Pain represents the main feature of the neurogenic form [360], which is said to comprise 95% of patients [55]. There is no consensus regarding diagnostic criteria for brachial plexopathy [221,361,362], which may be viewed as rare [363] or overlooked [221]. Some authors have distinguished between a "true" neurologic thoracic outlet characterized by neurologic deficits such as atrophy and distinct electrophysiological findings, and the much more frequent painful "disputed" form without neurological abnormalities, e.g. in terms of weakness [363]. The "disputed" thoracic outlet syndrome is controversial for several reasons including reports that it very frequent, and often bilateral, the lack of agreed-upon clinical features, the disagreement about whether it is a neurovascular or solely a neurologic disorder, and that it cannot be demonstrated by electrophysiology [361]. It is described following single-episode trauma or cumulative injury [361] that can cause scarring in and around the brachial plexus or repetitive motion-induced muscle imbalances [157,363]. The distinction between "true" and "disputed" neurogenic thoracic outlet syndrome seems arbitrary as the outcome of surgical treatment was the same in the two groups [364] and may merely be a question of the severity of the condition.

In contrast to other orthopedic disorders, symptoms are worse after than during exercise, and heavy work during the day is likely to result in misery at night, whereas quite days may lead to more comfortable nights [359]. Symptoms may be provoked by neck rotation and head tilting or with upper limb tension tests or arm abduction to 90° in external rotation [365]. The available provocative clinical tests and their accuracy have been reported [221], and include provocative maneuvers such as Roos’ and Elvey’s tests [278,357,362], which, however, have limited diagnostic value [293,366]. Hooper et al. have discussed the diagnostic approach to brachial plexopathy and challenged the fact that symptoms may vary greatly and that “double crush” may be an accompanying feature. A careful history and physical examination based on a systematic and thorough neurological examination are regarded as the most important components in establishing the diagnosis, which relies on distinct neurological findings [221]. The scope of identifying muscular weakness for the diagnosis has been mentioned by several authors [55,221,357,359,367,368] but sensory assessments, e.g. of the threshold for perception of vibratory stimulation, remains more emphasized [278,279,357].

Thoracic outlet syndrome has been proposed to be renamed as a cervicoaxillary syndrome, divisible into thoracic outlet (scalene triangle), costoclavicular, and pectoralis minor syndromes [369]. Most literature tends to mainly assign brachial plexopathy to the scalene triangle with accompanying compromise of the lower trunks rather than the less emphasized infraclavicular location described by Wright in 1945 as the hyperabduction or pectoralis minor syndrome [57,370]. The importance of the latter has been stressed from surgical experiences [371-373] and is supported by this thesis. An infraclavicular brachial plexopathy will tend to primarily compromise the lateral-located cords that supply neurons, which innervate the deltoid, biceps, pronator teres and radial flexor of wrist muscles. With further medial involvement of the brachial plexus, additional cords will be compromised and cause weakness in muscles innervated by the radial and ultimately the ulnar nerve. In contrast to an affliction of the brachial plexus at the scalene triangle, there will be an allodynic reaction on mild pressure at the infraclavicular brachial plexus behind the pectoralis minor muscle.

Posterior intersosseous and median neuropathies at elbow level may also be regarded as rare [374,375] as well as common conditions [170,376]. Both are clinical diagnoses that should be based on neurological findings [249,250,317,318]. There is limited understanding of the relation to work of brachial plexopathy as well as focal nerve afflictions involving the posterior intersosseous or proximal median nerves. Based on clinical case studies rather than actual epidemiological studies, the assumed risk factors in work for brachial plexopathy have been summarized and described by several authors [72,221,226,361,362,377]. A recent review has, however, identified many methodological limitations that challenges conclusions about the issue of work-relatedness [362]. Mosely et al. reported brachial plexopathies in occupations with exposures including outstretched arms and forceful work [378]. Feldman et al. mentioned overhead work, arm abduction and backward extension, and repetitive abduction and adduction movements of the shoulder [379]. Observations of workers (including computer operators) [72,226,357] have supported clinical indications of brachial plexopathy as a frequent cause of upper limb pain, weakness, and/or paraesthesia [161,349,359,380-382] – even when symptoms are distal only [381].

Pascarelli & Hsu found brachial plexopathy in 70% of 485 computer operators and musicians, who underwent a comprehensive physical examination [72]. Based on interviews, outcomes of Roos’ test and presence of tenderness over the brachial plexus in the supraclavicular fossa in 200 workers (heavy industrial work, office work, cash register operators), Sällström et al. described an 18% prevalence of brachial plexopathy, which was regarded as related to awkward work postures and continuous muscle tension in specific occupations rather than to the actual heaviness of the work [226]. These studies, however, are case series and there are no previous epidemiological studies of work-relatedness.

Posterior intersosseous neuropathy (radial tunnel syndrome) has been described as related to repetitive motions incorporating forceful or resisted forearm supination, wrist dorsiflexion or radial deviation [378], and forceful forearm rotation or abrupt extension of the elbow [379]. Hammering is an example of high risk exposures [379]. More recently Roquelaure et al. demonstrated the relation of radial tunnel syndrome to occupational risk factors such as exertion of force (OR 9.1), prolonged static load applied to the hand (OR 5.9), and work posture with the elbow fully extended (OR 4.9) [383].

According to Feldman et al. [379] and Mosely et al. [378] median nerve affliction at elbow level (pronator syndrome) is related to forearm rotation and particularly pronation.
accompanying forceful finger flexion. Examples are writing and manipulating levers [379]. The syndrome has more recently been identified in a series of female milkers [384].

Many occupations have been implicated in posterior or interosseous and median nerve afflictions at elbow level [378,379].

Study 1 (I, II, III, IV)
The study of the reproducibility and construct validity of the neurological upper limb examination was conducted with its intended clinical application in mind. The formal semi-quantitative examination was based on simple methods and equipment. It is logical and practical and can be used in any clinical setting.

The outcome and validation of a systematic neurological examination as in Study 1 of a series of patients with and without arm pain have not been previously reported. Although the identification of defined neurological patterns constitutes the basis for the classical neurological examination, the inter-rater reliability of pattern-recognition appears to be a new observation (I and II). The quantification of findings such as the sub-classification of the upper range of the graduation of muscle strength [354] permitted the identification of minor pareses.

The high frequency of findings suggesting brachial plexopathy is in accordance with studies of workers [72] and patients in general practice [170]. Most brachial plexopathies were located at cord level. It is therefore crucial that the scope is not limited to the scalene triangle but includes the more distal parts of the plexus – in particular the course below the clavicle and behind the pectoralis minor muscle. Median neuropathy at elbow level was regularly associated with soreness on the passage below Struthers’ ligament/supracondylar process on the distal and anteromedial humerus. Therefore palpation should not be limited to the course between the two heads of the pronator teres muscle but include other potential locations of median nerve entrapment [385]. The frequent assignment of neuropathy to several locations along the nerves reflects the defined criteria and may indicate an involvement of extended portions of the peripheral nerves – possibly as double or reverse double crush phenomena [180,212,215,218,220,224,229].

The literature supports the reliability of manual testing of individual muscles [245,251-253] and muscle groups [386] and therefore recommends the clinical application of manual muscle testing [253]. The confirmation by others of the reliability of sensitivity measures [162,251,267] and of the assessment of nerve trunk mechanosensitivity [251] is also in agreement with the results of Study 1.

The lack of an appropriate “gold standard”, with which the identification of neurological patterns can be compared, prevents the assessment of criteria validity of the physical approach. Instead, physical individual findings and anatomical patterns representing ten locations of neuropathy were related to the presence or absence of upper limb pain, weakness, and/or numbness/tingling regardless of the location in the upper limb of these symptoms. The isolated outcomes of muscle testing, sensory assessment, and nerve-palpation for tenderness as well as the ensuing patterns of findings that represent ten defined locations of neuropathy were all significantly related to symptoms. These findings demonstrate the construct validity of the physical approach.

It can, correctly, be argued that non-specific symptoms such as pain, weakness, and/or numbness and tingling may well reflect disorders other than upper limb neuropathy. It is therefore acknowledged that symptoms are not perfect for comparison and do certainly not represent gold standards. The presence of symptoms, however, was the only feasible standard for comparison. Having all patients undergo bilateral electrophysiological (or imaging) studies that target all potential locations of nerve affliction would be too costly, time consuming and uncomfortable. More importantly, they would not catch the majority of nerve afflictions. The shortcomings of electrophysiological studies are particularly crucial for brachial plexopathy [278,321-324], median nerve affliction at elbow level – pronator syndrome [249,318-321] and posterior interosseous neuropathy – radial tunnel syndrome [316,317], which according to the applied diagnostic criteria were the most frequent locations of nerve affliction in the studied sample of patients. The superiority of electrophysiological studies relative to clinical assessments for the identification of minor upper limb focal nerve afflictions has not been demonstrated and certainly not for upper limb disorders studied in an occupational context [236].

The high ability of the physical examination to predict the presence or absence of symptoms, and the large increase from pre-test odds to post-test probability are remarkable (III). Therefore the suggested physical examination (I-III) may constitute a good diagnostic complementary approach in the clinical setting.

Construct validity of the physical examination has been further explored in forty limbs in which one or both examiners rated neuropathy as “possibly” or “definitely” present with defined location(s). This study showed a strong correlation in between patterns indicating focal neuropathies at locations along the same nerve or in the same topographical region, and that this correlation cannot be explained by presence of neuropathy located separated from these locations. The findings of each examiner correlated positively (γ > 0.35) in 22/25, respectively, out of 30 limbs with related locations of neuropathy. The patterns of the interrelations identified by the two examiners were similar with no evidence of heterogeneity of location profiles for either examiner [387].

Further support to the construct validity of the examination was provided by a study in which two sets of diagnostic criteria were applied. The criteria applied by Laursen et al. [170] were comparable to those applied in Study 1 while the criteria of Sluiter et al. [26] reflect the current diagnostic practices in clinical occupational medicine. Vibrometric findings were more in accordance with the diagnostic criteria of Laursen et al. [170]. The correlation in Study 2 between physical findings and symptoms (VI), and the effect of an intervention by stretching that specifically aimed to mobilize nerve tissue at the implicated locations (VII) contribute further to the validation of the applied neurological examination.

The examination limited to an assessment of strength in six muscles demonstrated weakness in one or more muscles in almost all symptomatic limbs, but in many non-symptomatic limbs as well. This high sensitivity of the examination indicates the potential for screening. It cannot stand alone, however, because it is highly unspecific (IV). A confirmative diagnosis requires further physical assessment.

The proposed neurological examination appears to represent a feasible supplementary diagnostic approach to upper limb disorders. The biological plausibility and coherence of findings in Study 1 support the diagnostic potential of this approach. It can be applied in different settings with diverse prevalence and severity of upper limb symptoms ranging from
mild to more severe. As with any physical examination, the ultimate aim would be the demonstration of benefit to in-risk persons of its application. Such attempt has been made in Study 2 (VII), but further studies are required.

Potential weaknesses of Study 1 should also be mentioned. It was aimed to minimize the potential source of bias from subjectivity of the examiners’ interpretations of the physical parameters by blinding the examiners to symptoms and to any other information related to the study subjects. The same examiner performed several tests on the same patient. Therefore a certain positive finding may influence the examiner’s interpretation of another test due to expectations. Preventing this potential bias would demand each physical test to be performed by an individual examiner, which was not feasible. Misclassification of the assessment could also result from visible abnormalities and non-verbal communication such as reactions to pain during assessment. However, muscle weakness at or below grade 3 which may be visible was rarely identified and no patient displayed a global pain reaction to the tests. Malingering was not noted as a problem. Most importantly, patients were naïve with regard to the ensuing neurological patterns.

The awareness of the referring physicians of the special interest in upper limb neuropathy in the department may have distorted the composition of the sample and introduced selection bias. This could increase the number of patients with patterns in accordance with focal neuropathy but hardly alter the calculations of reliability and validity.

Mononeuropathy such as carpal tunnel syndrome (and ulnar neuropathy) are generally regarded as the most common upper limb nerve entrapments. Carpal tunnel syndrome is also widely regarded as commonly work-related although this connection has been questioned [388]. Their rarity in the studied sample is therefore remarkable and deserves attention. Ignoring the potential of proximal neuropathy presenting with symptoms mimicking carpal tunnel syndrome (and even electrophysiological findings in accordance with carpal tunnel syndrome) may lead to over diagnosis with consequences for treatment such as unjustified carpal tunnel surgery. 112 patients out of 250 patients with clinical and electrophysiological evidence of carpal tunnel syndrome had pain proximally to the wrist. Thenar muscle strength was significantly larger, the wrist. Thenar muscle strength was significantly larger, the median nerve at the arcade of Frohse, and the median nerve at elbow. All patients displayed characteristic patterns of selective impairments of specific muscles while other muscles were found intact. There were corresponding observations related to altered cutaneous sensibility and nerve trunk allodynia. All patients displayed neurological patterns in accordance with a combined affliction of the brachial plexus at cord level, the posterior interosseous nerve at the arcade of Frohse, and the median nerve at elbow level (V). The identification in patients with computer-related complaints of this combination of neuropathy is a new observation. The severity of the condition demonstrated by the poor prognosis in terms of persistent symptoms and reduced ability to continue computer intensive work (V) is consistent with findings of others [60,394]. It has also been shown that nerve compression, especially with dual compression and brachial plexopathy, has severe effects on the quality of life [395,396].

The hypothesis that these three locations of nerve-afflictions are characteristic for computer-related upper limb pain (V) was subsequently studied on a sample of “healthy” active computer operators (VI) who had less frequent and minor pain than reported elsewhere [68,397-400]. The significant correlations between the perceived pain and the individual neurological findings and patterns that reflect the three hypothesized locations of nerve afflictions, and the significant trend between the summarized pain-scores and the summarized neurological findings indicate a relation between symptoms and findings (VI).

Blinding the examiner to symptoms and to any other information related to the study subjects aimed to minimize a potential bias caused by subjectivity of the examiners’ interpretations of the physical parameters (VI). The same examiner performed several tests on the same patient. Therefore a certain positive finding may influence the examiner’s interpretation of another test due to expectations. Preventing this potential bias would demand each physical test to be performed by an individual examiner, which was not feasible. Misclassification of the assessment could also result from visible abnormalities and non-verbal communication such as reac-
tions to pain during assessment. However, there was no muscle weakness at or below grade 3 and nobody displayed a global pain reaction to the tests in this study population of active workers.

The author has noticed that reduced muscle function in the absence of subjective weakness is common in upper limb patients including computer operators, and at many occasions noticed the surprise of patients when during testing they clearly perceive a weakness of which they were previously unaware. When asked to do their best on both sides, it would be unlikely that the examined subjects would deliberately exert less force than their capability. A detraining effect is also an unlikely explanation for the identified weaknesses. The mostly minor level of perceived pain and the completely normal level of functioning would not cause symptomatic subjects to protect themselves by sparing their upper limb muscles and eventually lose strength. In accordance, examined subjects with an actual identical sensibility in two compared territories would hardly report perception of a difference. The selectivity of neurological findings, e.g. weakness in certain muscles and other muscles with normal strength, and the rarity of patterns reflecting nerve-afflictions elsewhere than at the three locations mentioned support the demonstrated relations to the perceived pain. Most importantly, for the examinees to construct the detected neurological patterns would demand a familiarity with the innervation and topography of nerves that is not plausible. This study dealt with active and generally healthy subjects working in an attractive enterprise. An alleged role of psychosocial factors or somatization is unlikely in this group of computer operators because neurological “abnormalities” were also frequent in non-symptomatic subjects.

The many positive neurological findings in the absence of pain may indicate a latent condition such as a minor pre-clinical dysfunction, which may be related to exposure. Other authors have reported similar findings [61,96,104-106]. This high sensitivity of the physical examination suggests the feasibility for workplace screening of office workers in risk and thereby supports the findings in Study 1. The ability to predict symptoms from the defined patterns of findings (rather than findings in isolation) supports the diagnostic potential of identifying clinical cases of computer-related upper limb disorder. In spite of comparable neurological findings and patterns at the two sides, the clear dominance of symptoms and findings in the mouse-operating limb compared to the contralateral limb contributes to further validation of the physical examination and suggests a relation to work-exposures.

The presence, intensity and consequences of upper limb symptoms (rather than disorders) such as pain in computer operators are well documented. A questionnaire study found significant positive correlations between pain intensity and pain duration in the forearm, elbow, neck, and shoulder in both sexes. Women had more pain, more pain locations and poorer work ability [68]. The relation to exposure is also widely accepted, although the issue of causality has been questioned [401]. An early review concluded that risk factors included computer use with sustained awkward postures, long duration of computer use, and work organizational factors [402]. Incident pain in the neck and forearm is related to certain work-related risk factors such as intensive use of mouse [397,403] and to a lesser degree keyboard [403]. Perceived exertion is also strongly associated with pain in the neck, shoulder, and arm/hand [404].

Studies of the relation of upper limb disorders to computer work have reached conflicting results. A systematic review of research in this area found only limited evidence for such connection and no evidence was considered as moderate or strong. Better documentation was called for [405]. A subsequent meta-analysis of systematic reviews that assessed the evidence for causal relationships between computer work and the occurrence of carpal tunnel syndrome and other upper extremity musculoskeletal disorders among computer users/or office workers concluded that computer use is associated with pain, but that it is not clear if this association is causal. The epidemiological evidence for specific disorders was found to be limited [401].

In a study of 533 visual display terminal workers, 22% had an upper limb diagnosis (tendon and muscle related conditions in 15% and 8%, respectively, and probable nerve entrapment in 4%) [399]. Among 632 newly hired computer operators, the one-year incidence of neck and shoulder symptoms and of hand/arm symptoms was 58% and 39%, respectively. Covering almost all symptomatic cases, the most frequent diagnoses were “somatic shoulder/neck syndrome” and de Quervain’s syndrome [400]. A detailed neurological assessment was not included in the physical examinations. Taking into account the applied criteria, both frequent diagnoses might well represent neuropathic conditions. In a study of keyboard operators, the physical upper limb examination revealed only few neurological abnormalities with the exception of four provocative tests [406]. In a recent cross-sectional study of almost 7000 computer operators in which one out of five had severe or semi-severe pain, the physical examination disclosed only a limited number of clinical upper limb disorders, similar to what one would expect in the general population [397,398]. There was a possible relation of pain to tension neck [397]. Numbness or tingling was noted in 10.9%, located to the median nerve territory in 4.8% and disturbing at night in 1.4%. The latter was interpreted as reflecting carpal tunnel syndrome but unexplained in the remaining subjects [407]. Defined by localized palpation tenderness with withdrawal and by pain with provocative maneuvers, it was possible to diagnose 12 cases of supinator or pronator syndromes, but no incident cases of nerve afflictions appeared during a one-year follow up [403]. There was a 15% elevated vibration perception threshold in subjects with paresthesia compared to subjects without paresthesia in a small sub-sample of the same material consisting of subjects without pain [408]. The examination protocol in these studies did not include a systematic neurological upper limb examination.

A few clinical studies have supported the presence of peripheral nerve dysfunction in computer related upper limb disorders. Based on adverse reactions to brachial plexus stress tests and localized mechanical nerve trunk-alldynia, Pascarelli et al. diagnosed brachial plexopathy in 70% of 485 upper limb patients out of which the majority were computer operators [72]. In another study of computer operators, questionnaire data on symptoms were compared with the outcome of a blinded physical examination (range of motion, reduced muscle function with cut-off level for weakness grade 4, and pain during maneuvers) for which k-values in the range of 0.19 and 0.54 reflected neck-shoulder symptoms and pain during examination [409]. Jensen et al. found normal or only slightly reduced muscular function in symptomatic computer users compared to non-symptomatic computer users and controls [105]. The apparent divergences of the latter to the presented findings (VI) may be a question of statistical power or be due to instrumental testing of the integrated strength of several muscles rather than manual testing of individual muscles.
the manual muscle testing in Study 2 aimed deliberately to fatigue the subjects during testing by allowing up to three reiterations of each muscle test.

Many clinical and laboratory studies have demonstrated abnormal findings in computer operators [61,72,105,137,160,329,409-413], which indicate actual disease rather than symptoms only. Sub-clinical median nerve impairment across the carpal tunnel has been demonstrated in computer operators who had more complaints than the controls. However, the amount of complaints did not correlate to electrophysiological measurements [410]. Another research group found that nerve conduction velocity and vibrotactile perception was the same in computer users (secretaries) as in non-exposed controls (nurses), but this study dealt with healthy subjects [153]. The existence of a neuropathic component with computer related upper limb complaints has been demonstrated on a group basis with median and ulnar sensory nerve conduction velocity differing significantly in between 21 symptomatic computer operators and 21 controls, and in between the dominant and non-dominant limb [329]. Several researchers have also found an elevated threshold for perception of vibration [61,105], which persists along with symptoms [411]. Greening found reduced vibrotactile detection in 82% of symptomatic computer users [61]. Incident nerve affictions were reported in 10 monthly follow-ups of call center operators [412]. In symptomatic computer operators who had longer experience of computer use, finger tapping caused reduced strength and median EMG frequency at 25% and 100% maximal voluntary contraction in the flexor digitorum superficialis muscle compared to findings in non-symptomatic computer operators [413]. Perceived muscular tension in office workers has been shown to predict upper limb symptoms in a dose-response manner [414], suggesting that taking action on early symptoms may have a preventive effect.

Reduced descending pain modulation can occur with pain on a lower level than is normally associated with dysfunctional central pain modulation and hyperalgesia [415]. In a study of pressure pain thresholds in the elbow region, dynamic pressure algometry in the forearm, and conditioned pain modulation in computer users with or without mostly minor chronic musculoskeletal pain a normal excitability of the central pain system was demonstrated with low pain intensity while the pressure pain threshold was lower with higher pain intensity. The widespread hyperalgesia indicated central involvement and impaired descending pain modulation in accordance with chronification of pain. Reducing the peripheral input would tend to decrease descending pain modulation and generalized sensitization among computer users with chronic pain. There are yet no such studies of computer operators with high chronic pain intensity [137].

Study 2 supports the role in computer-related upper limb disorders of the peripheral nerves [72,160] and that reactions to lesions or loading of the peripheral nerves are involved [71,157,159,416-418].

Any intervention should preferably rely on an understanding of the phenomena underlying the disorder in question or at least be based on a theory founded on evidence with regard to this issue. In the absence of such understanding, the intervention may target irrelevant issues and would most likely be ineffective. The reduction of symptoms following a six-month course of stretching may contribute to the understanding of the character of computer-related upper limb disorder because this intervention was based on indications of the relation of symptoms to the three locations of upper limb nerve afflictions that were hypothesized (V) as characteristic to computer-related upper limb disorders (VII). The effect of nerve mobilization is sparsely documented by other authors but reduction of lateral arm pain in computer users following radial nerve mobilization has been demonstrated [350]. The positive outcome of the intervention by stretching contributes to a further validation of the applied physical examination in Study 1. The inability of the intervention to reduce the physical findings is in accordance with my clinical observations. At control visits a few months after management (advise to spare the limb in order not to provoke symptoms and physiotherapy based on nerve trunk mobilization [139]) most patients with diagnosed neuropathic upper limb conditions report fewer symptoms while their pareses and sensory dysfunctions persist. A reduction of physical findings may therefore require a follow-up of longer duration.

Complete blinding of the physical examination would require randomization, which was not feasible. However, in order to avoid mutual contacts between the intervention and control subjects and to prevent the controls to engage in stretching, the intervention was offered to staff in one division while the controls were located in a geographically separated division of the same engineering company. More familiarity with the physical examination at the second examination could influence the outcome of muscle testing over time or cause nerve trunk soreness to be perceived as less uncomfortable than previously. This would tend to reduce the number and severity of findings in both groups, which, however, were unchanged. The compositions of the intervention group and the control group were relatively comparable with regard to gender, age, and educational and social background. The exposure in the two groups is likely to be similar due to the identical content and organization of work, workstation ergonomics and psychosocial work environment. No analyses for covariates such as prior disorders and psychosocial factors were performed but the two groups were comparable with respect to these factors (VII).

The demonstration of an effect of the intervention in Study 2 was possible in spite of complicating circumstances. The physical work environment of this small sample of computer operators was already optimized prior to the study, and the studied computer operators had fewer symptoms than reported elsewhere [397-400]. In addition, a proportion of computer workers were non-responding and/or non-participating in the physical examination at both occasions. In fact, only 62 subjects in the intervention group and 16 controls participated in all parts of the study. This small number, especially of controls, is a clear weakness, which together with the high number of limbs without symptoms and findings reduces the statistical power of the study (VII).

Few high quality studies of office workers have examined the effect of work-place interventions on musculoskeletal symptoms of computer operators. A meta-analysis found moderate evidence for no effect of rest breaks and exercise [419], and a summary of systematic reviews on intervention studies among computer users or office workers found limited evidence for the effects of interventions [401]. Rempel has, however, demonstrated the preventive effect of forearm support and ergonomic training of computer workers [420]. In another study, training and workstation adjustments could also reduce the intensity, duration and frequency of symptoms, and improve the functional status and health-related quality of life [421]. The application of a participatory approach to ergonom-
ics has also reduced symptom scores in computer operators [422].

Relief of symptoms in computer workers by stretching was demonstrated by Kietrys et al. [423], and an occupational therapy program, which included nerve glide exercises, was able to reduce pain and improve typing endurance and speed [424]. A recent meta-analysis concluded that there was moderate evidence for a preventive effect of stretching programs [425]. These studies support the outcome of the intervention in Study 2 (VII).

Study 2 has not addressed the issue of causality in terms of work-exposures being responsible for the symptoms, and the identified neurological patterns and the upper limb conditions that the patterns were defined to reflect. Still such relation is plausible. By looking into symptoms and physical findings in order to define upper limb diseases characteristic for computer operators, Study 2 has rather aimed to contribute to the understanding of computer-related upper limb pain. Such an understanding is required for analytical studies of the relation between computer work and upper limb disorders and is also a prerequisite for evidence based treatment and prevention. It is recognized that this issue is complex, and that many mechanisms may be involved.

Study 3 (VIII)
The high frequency of brachial plexopathies in the original sample of patients from which the cases for Study 3 was drawn [170] is in accordance with findings in Study 1. Study 3 has clearly indicated a number of mechanical risk indicators at work for brachial plexopathy with the applied diagnostic definition [170]. Whether based on assessments of physical exposures or of psychophysical perceptions, highly significant relations were demonstrated for adverse upper limb postures, repetitive work, work pace and the use of strength. No previous epidemiological studies have yet demonstrated the relation to brachial plexopathy of these exposures. Similar risk exposures quoted in the literature, however, include outstretched arms and forceful work [378], overhead work, arm abduction, arm backward extension, repetitive shoulder abduction and adduction [379], awkward work postures, and continuous muscle tension in specific occupations [226]. Many trades such as office work and computer operators [72,226,357], musicians [72], and heavy industrial work have been implicated.

Pathophysiological mechanisms can hardly explain two of the identified risk indicators, walking and exposure of the fingers to cold, which may rather be related to the character of work such as a combination of these exposures with other identified risk indicators.

Two exposures were more prevalent among controls than among cases: sitting and computer work. The effect of sitting may be explained by the fact that most sitting work does not involve adverse positions and repetitive work, although undertaking sitting tasks that do involve these exposures may in fact contribute to adverse upper limb postures, e.g. by requiring further arm elevation than work in the standing position. The apparently protective effect of computer work stands in contrast to the findings in Study 2, in which neurological patterns in accordance with brachial plexopathy were present in all patients with intensive computer work (V) and similar neurological findings were frequent in symptomatic computer operators in active occupation (VI). The current findings of more computer work among controls than among cases with brachial plexopathy may be explained by an exposure to computer work of a low intensity, which does not constitute a risk for brachial plexopathy or cause symptoms of sufficient intensity for seeking medical attention. Only few active computer operators in Study 2 (VI) met the rather strict requirements for enrolment as a case in Study 3 (pain or subjectively changed sensibility with defined locations, and reduced strength in defined muscles, and sensory deviation from normal in the axillary territory, and mechanical allodynia at the brachial plexus).

The relation between local vibration and upper limb nerve afflictions is well documented [426], but the relation to brachial plexopathy in the current study was limited. The minor impact of vibration may relate to the distance between the hand and the brachial plexus. A more likely explanation, however, is the few subjects in the sample that were exposed to local vibration.

The identified relations of psychosocial factors to brachial plexopathy were limited to measures that also reflect physical exposures. Workers that are highly exposed to both physical and psychosocial workplace risk factors may be more likely to report musculoskeletal symptoms than workers highly exposed to one or the other. The results of Devereux et al. suggest that interaction between physical and psychosocial risk factors at work increases the reporting of upper limbs symptoms [427].

The analyses assessed the association between the exposures and brachial plexopathy with a supraclavicular as well as the more frequent infraclavicular location. Due to the relative distribution of afflictions at the two locations, the conclusions of Study 3 relate in particular to an infraclavicular rather than to a supraclavicular brachial plexopathy, and again emphasizes the importance of studying afflictions of the full course of the brachial plexus, and not only at the scalene triangle.

The questionnaire for assessment of exposure in Study 3 was a compilation of questions on physical, psychophysical, and psychosocial issues that were developed and validated by others. A questionnaire approach to exposure assessment is generally regarded as inferior to direct observations. However, a French study found that questionnaire information was actually superior to direct observations in identifying workers at high risk of upper limb work-related musculoskeletal disorders [428]. In any advent, due to advantages in terms of costs and practical execution this way of assessing the exposure was the only option in this study. The inclusion of the psychophysical questions has contributed to further qualification of the questions addressing mechanical exposures [429]. The ability of the physical and psychophysical ratings to identify comparable risk indicators supports the consistency of the presented findings.

Based on interviews and examinations performed by the same examiner, the cases were selected in a previous study, which aimed to compare the diagnostic outcomes and the responses to vibrometry of two different diagnostic approaches [170]. It is the normal situation in clinical practice that the same clinician collects anamnestic information on the medical history and performs the physical examination. In the clinical context this is regarded as acceptable although there is a risk that such assessment may be biased, and it is acknowledged that many physical qualities, including those contained in the neurological examination, are of a subjective character. In Study 3 blinded management of information on symptoms and the physical examination was not feasible. Attempts were made, however, to minimize information bias by the strictly structured execution of the symptom interview and the physi-
cal examination [170]. The chosen approach seems appropriate for diagnosing brachial plexopathy according to the defined criteria although it cannot be excluded that knowledge of the patients’ history could influence the prevalence of physical findings [162] and consequently the number of identified cases. Non-experimental research such as in Study 3 has a number of innate methodological constraints. The respondents were informed that this was a study of work exposures and upper limb disorders. The collection on a cross-sectional basis of questionnaire information on exposure may therefore result in information bias. Such bias will be differential and lead to spuriously increased risk estimates if, compared to controls, cases exaggerate their exposures. The absence of differential misclassification has been demonstrated for some of the posed questions [430] while the risk for differential misclassification cannot be excluded in the remaining questions on mechanical exposure [430,431]. It has, however, been shown that questions addressing physical risk exposures cause less misclassification with upper limb disorders than with low back disorders [432]. In this context, the absence of a relation between symptoms and exposures, which the responders would be likely to view as related to upper limb symptoms (e.g. computer work) is noteworthy. Information bias cannot therefore be excluded but is regarded as less likely to seriously distort the results.

The selection of the studied samples of patients and controls is another potential source of bias. One acknowledged potential for bias is confounding that may occur when the frequency of risk indicators other than those studied differs in between cases and controls. In spite of instructions, all eligible patients may not necessarily have been selected and the participants may therefore not be representative for all upper limb patients visiting general practice. For example, although the general practitioners were asked to enroll as cases all patients with non-traumatic upper limb symptoms, there could be a reluctance to enroll patients with milder or easily interpretable symptoms rather than patients for which they may have been more inclined to request a second opinion from the research team [170]. Patients may also have delayed consultation until the disorder was sufficiently serious to influence their functional level. Though participants had not previously presented with upper limb complaints during the last year they may not necessarily have been non-symptomatic during that period. One would expect a gradual transition from healthy to ill and upper limb complaints may be recurrent as well as prolonged [433]. 161 out of 279 registered patients were enrolled with 46.7% of men and 36.9% of women refusing participation [170]. The reason for refusal is not known. The high proportion of brachial plexopathies in the original sample (as defined by the applied criteria) may therefore not represent the true distribution among upper limb patients in general practice.

Bias from the selection of controls can also not be excluded. While the general practitioner was asked to select as a matched control subject the first eligible patient who was willing to complete the questionnaire, one cannot be sure if this really happened. Whether the occupations differed in between cases and controls is not known. A higher share of manual workers in the case group could induce a bias of selection. Consequently, although the response rate and the distribution on age and sex were comparable in cases and controls, a potential differential selection may have influenced the composition of the final sample of controls. To exclude bias from selection would require a longitudinal design.

The specificity in terms of causation may also be questioned. The identified risk indicators have previously been linked to upper limb symptoms as well as to diagnosed upper limb disorders other than brachial plexopathy [19-23], thereby suggesting that certain exposures can lead to comparable symptoms but also to different diseases. Comorbidity, in particular rotator cuff disorders, epicondylitis, and nerve afflictions located distally to the brachial plexus (in particular median or radial/posterior intersosseous neurotropathies) was present in a significant proportion of the cases in this study [170]. It is known that comorbidity is associated with worse health outcomes, more complex clinical management and increased health care costs. Mechanisms underlying the coexistence of two or more conditions in a patient include direct causation, associated risk factors, heterogeneity, and independence [434], but their relative role cannot be determined.

While Study 3 has demonstrated associations of brachial plexopathy to work exposures no conclusions can be drawn regarding causality, which needs to be examined in prospective studies of patients with brachial plexopathy without other concomitant disease. In addition, the aggregated effects of the various mechanical exposures, and the interaction in between them should be studied. Most importantly, the demonstration of a reduced occurrence of disease following elimination or reduction of the identified risk exposures would represent an important step towards prevention of brachial plexopathy in an occupational context.

PERSPECTIVES
According to the three studies in this thesis, peripheral neuropathy appears to play a major role in upper limb disorders, including disorders seen in a work-related context. The presented systematic neurological examination can reliably identify abnormal neurological patterns in accordance with the anatomical course and motor and sensory innervation of the upper limb nerves. The presence of these patterns was shown to reflect symptom status and to be in accordance with focal upper limb neuropathy with defined locations in patient samples in clinical occupational medicine and among computer operators. In addition it was demonstrated, that patients in general practice with upper limb complaints fulfilling the diagnostic criteria for brachial plexopathy had more mechanical risk exposures in their work than control patients without upper limb complaints.

Findings in accordance with the definition of brachial plexopathy, in particular at cord level, were common in all studied samples (Table 2). Brachial plexopathy was frequently accompanied by median and posterior intersosseous neuropathy at elbow level (Table 4). This combination of nerve afflictions cannot be demonstrated in the absence of a physical examination containing the relevant neurological items (Table 3). Consequently, the studied neurological examination seems to be able to contribute significantly to the diagnosis in a major proportion of upper limb patients including patients that cannot otherwise be diagnostically classified (NSAP).

This thesis has demonstrated that manual muscle testing, the examination of sensory qualities and assessment of nerve trunk soreness should be perceived as objective assessments with clinical value when performed in a systematic way. The neurologic evaluation should include a sufficient number of individual items to be assessed and quantified systematically [236,241,435]. By incorporating additional upper limb nerve afflictions, the presented examination may improve and extend
the currently prevailing classifications of work-related upper limb disorders.

An interest in upper limb disorders and in particular nerve afflictions is justified for two main reasons. One is the prevailing diagnostic constraints. In spite of attempts to reach consensus about diagnostic criteria, diagnostic practices remain a challenge, and commonly used criteria such as those defined by Slutter et al. [26] that represent the standard diagnostic approach in current occupational medicine are clearly not adequate. The diagnostic shortcomings have led to constructs, e.g. NSAP, which, however, shares many of the characteristics of upper limb nerve afflictions. Acknowledging this diagnostic challenge, the next step would be a curiosity and eventually the introduction of more ambitious diagnostic practices than those currently prevailing classifications of work-related upper limb disorders.

The severe consequences of upper limb nerve compression may be related to the diagnostic challenges, misinterpretations and consequent suboptimal management. Coarse assessments such as of handgrip power and of sensibility at a few locations such as the fingertips may result in overlooking a neurological disorder. Encountered weaknesses should not uncritically be regarded as “pain-induced”, and deviations of sensation that are not limited to a specific dermatome or a single nerve as “diffuse” unless there is evidence for such interpretations. The clinician should also avoid diagnostic misinterpretations inferred by laboratory studies such as electrophysiology or imaging that in a practical context may be less sensitive than the physical examination [236].

Searching for pathology, the clinician should physically examine the patient with a spectrum of valid tests, sufficient for catching the majority of disorders. These tests should be able to identify and locate neuropathic and non-neuropathic conditions and to separate them from each other. A diagnosis that can specify the involved tissue and its location, and that can contribute to the understanding of the underlying pathological mechanisms and pathology opens for optimized management and prevention of these prevalent upper limb conditions.

However, clinical feasibility of the proposed neurological examination demands further studies. It would be particularly important to demonstrate that its application can eventually provide benefit in terms of improved health for individuals in risk.

CONCLUSIONS

Study 1
- The interrater reliability of manual muscle testing was moderate to good in most muscles. Muscle weakness were all significantly related to upper limb symptoms that are characteristic for a neuropathic condition. Manual individual muscle testing appears to be a rewarding diagnostic procedure with upper limb disorders (I).
- Most assessments of sensibility (touch, pinprick and tuning fork) and mechanosensitivity of nerve trunks had a moderate to good inter-rater reliability. Patterns of muscle weakness, sensory deviations from normal, and nerve trunk mechanical allodynia reflecting neuropathy at ten locations were identified with moderate to good reliability. The recognition of neurological patterns appears to be a rewarding diagnostic procedure in patients with upper limb disorders (II).
- The identified patterns reflect the presence of symptoms with a high positive and negative predictive value and high post-test probability (III). The identification of neurological patterns is a key feature of the neurological examination with diagnostic potential.
- An examination limited to the assessment of strength in six muscles is sensitive but unspecific compared to the outcome of the extensive examination (IV).

Study 2
- Rather uniform physical findings in accordance with an infraclavicular brachial plexopathy in combination with median and posterior intersosseus neuropathy at elbow level characterized a sample of computer-operators with severe upper limb complaints. In spite of reduced symptoms at follow-up, they suffered a serious prognosis in terms of work-status and persisting pain (V).
- The cross-sectional study of computer operators in current work showed that individual and patterns of neurological findings in symptomatic subjects reflect the three locations of neuropathy hypothesized (V) as characteristic for computer related upper limb disorder. Pain was common in the studied sample, but of low intensity. Neurological abnormalities were frequent and related to summarized pain. Brachial plexopathy, median neuropathy (elbow), and posterior intersosseus neuropathy were diagnosed in a minor proportion of limbs, in particular the mouse-operating limb (VI).
- A stretching course designed to improve the mobility and available space for the nerves at the three locations reduced the computer operators’ pain level but did not influence physical findings at follow-up. The relation of symptoms to the identified neurological patterns and the effect of stretching provide additional support to the construct validity of the applied neurological examination (VII).

Study 3
- Symptoms and physical findings in accordance with brachial plexopathy are common in the primary health sector (VIII).
- Whether assessed as the extent during the workday or days per week, most physical exposures, in particular adverse upper limb postures, repetitive work, work pace, and the use of force were significant risk indicators for brachial plexopathy with clear dose-response relationships. The identified psychosocial relations to brachial plexopathy were limited to measures that also reflect physical exposures (VIII).

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SUMMARY
Diagnostic consensus criteria cannot be applied in a major proportion of patients with upper limb complaints, many of which are regarded as "non-specific". The three empirical studies in this thesis aimed to address this diagnostic challenge by incorporating representative neurological qualities in the physical examination.

Patterns of muscle weakness, sensory abnormalities and nerve trunk alldynia based on the nerves’ topography and their motor and cutaneous innervation were defined to reflect peripheral nerve afflictions and their locations. The physical examination was first validated on patients in clinical occupational medicine. Next, the neurological patterns were studied among computer operators in order to contribute to the characterization of their disorder. Finally, self-reported work exposures for patients in general practice presenting with symptoms and findings consistent with brachial plexopathy were compared with the exposures of matched control patients without upper limb symptoms.

The inter-rater reliability of manual individual muscle testing, and of assessments of sensibility (touch, pinprick and vibration) and mechanosensitivity of nerve trunks was generally moderate to good. Patterns of findings in accordance with neuropathy at ten locations were identified with moderate to good reliability. The identified patterns reflected the presence of symptoms with high positive and negative predictive values. An examination limited to the assessment of strength in six muscles was shown to be sensitive but non-specific.

Computer operators with severe upper limb complaints are characterized by rather uniform physical findings in accordance with an infraclavicular brachial plexopathy in combination with median and posterior interosseous neuropathy at elbow level. In spite of reduced symptoms at follow-up, the prognosis in terms of work-status and persisting pain is serious. A cross-sectional study of computer operators in current work showed that individual and patterns of neurological findings in symptomatic subjects reflected these three locations of focal neuropathy. Pain was common in the studied sample, but of low intensity. Physical abnormalities were frequent and related to summarized pain. Patterns in accordance with brachial plexopathy, and median (elbow) and posterior interosseous neuropathies were identified in a minor proportion of limbs, in particular in the mouse-operating limb. A stretching course designed to improve the mobility and available space for the nerves at the three locations reduced the pain level but did not influence physical findings at follow-up. The relation of symptoms to the identified neurological patterns and the effect of stretching provide additional support to the construct validity of the applied neurological examination. This study indicates the role of nerve afflictions in computer-related upper limb disorders.

The most frequent pattern in the first two studies was in accordance with brachial plexopathy. Therefore additional analyses addressed the relation of this condition to mechanical exposures at work. Whether assessed as the extent during the workday or days per week, many exposures, in particular adverse upper limb postures, repetitive work, work pace, and the use of force, were significant risk indicators for brachial plexopathy with clear dose-response relationships.

The identification of patterns of physical findings that reflect the function of the peripheral nerves appears to be a rewarding diagnostic procedure in subjects with upper limb symptoms. The relation of patterns to symptoms indicates the diagnostic feasibility of the examination and can contribute to explain symptoms in workers such as computer operators. Patterns in accordance with brachial plexopathy are frequent and related to mechanical work-exposures.

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