Experimental and clinical neck pain:
Studies on training-induced neuroplasticity

PhD dissertation

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Bjarne Rittig-Rasmussen, October 2013

Content

Preface

This PhD thesis is based on the work performed during my enrolment as a part-time PhD student at the Danish Pain Research Center, Aarhus University Hospital and the Faculty of Health Sciences, Aarhus University, Denmark (2008-2013).

The thesis is based on the following three papers:

Paper I: Rittig-Rasmussen B, Kasch H, Fuglsang-Frederiksen A, Jensen TS, Svensson P. Specific neck training induces sustained corticomotor hyperexcitability as assessed by motor evoked potentials. Spine (Phila Pa 1976) 2013;38:E979-E984.

Paper II: Rittig-Rasmussen B, Helge Kasch, Fuglsang-Frederiksen A, Svensson P, Jensen TS. The role of neuroplasticity in experimental neck pain: A study of potential mechanisms impeding clinical outcomes of training. Manual Therapy. Submitted September 2013.

Paper III: Rittig-Rasmussen B, Helge Kasch, Fuglsang-Frederiksen A, Svensson P, Jensen TS. Effect of training on corticomotor excitability in clinical neck pain. European Journal of Pain. Submitted September 2013.

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List of abbreviations

1-RM	1 repetition maximum
EMG	Electromyography
HS	Hypertonic saline
HST	Hypertonic saline and training
HSNT	Hypertonic saline and no training
IS	Isotonic saline
IST	Isotonic saline and training
MEP	Motor evoked potential
MPQ	McGill Pain Questionnaire
NRS	Numeric rating scale
PCS	Pain Catastrophizing Scale
TMS	Transcranial magnetic stimulation

Introduction

General introduction

The present studies on training-induced neuroplasticity are inspired by the biomedical and biomechanical paradigms that have been employed in the clinical management of musculoskeletal disorders for several decades. A growing body of evidence indicates that injury, inflammation and pain arising from spinal structures affect not only the affected anatomical region, but also have a significant impact on the function and structure of the nervous system [67,107,116]. Thus, peripheral injury, inflammation and pain in the musculoskeletal system may affect all levels of the somato-sensory and motor control systems of the nervous system, rather than just cause failure of particular somatic components [70,116]. The treatment outcomes of previous and contemporary treatment paradigms are not optimal [69,114], and a paradigm shift towards understanding the underlying neurological mechanisms and neuroplastic changes of various musculoskeletal pain disorders thus seems necessary to improve the clinical outcome [4]. Consequently, this thesis focuses on the neuroplastic mechanisms occurring in healthy participants and in experimental and clinical neck pain induced by training.

Neck pain

Neck pain was chosen because it causes personal and societal problems and affects up to two-thirds of people at some point of their life, with the highest prevalence in European and North American countries [26,54]. Neck pain thus remains one of the most common musculoskeletal complaints in primary care [87]. The estimated 1-year incidence of neck pain ranges from 30% to 50% and neck pain-associated disability ranges from 2% to 11% in the general population [49,51]. Typically, neck pain declines within one month after onset; yet thereafter only minor improvement is seen, and only one-third of patients are completely pain-free after 1 year [114]. Consequently, neck pain represents a major health issue due to bodily disabilities, absence from work and restrictions in social participation [50,54,76].

Diagnostics

One of the challenges in reducing the impact of neck pain is the large variety of specific and non-specific diseases and disorders that involve the spinal column and frequently manifest with pain symptoms. The most widely accepted classification [51] includes four clinical categories: 1) spinal disorders with serious or systemic pathology, 2) spinal pain with neurological deficits, 3) spinal pain referred from non-spinal pathology and 4) non-specific spinal pain, which is assumed to account for 90% or more of all people who experience neck pain. At present, there are no evidence-based methods to identify the structure, pathology and source of pain in the majority of patients with

these non-specific axial neck pain symptoms [18,51]. The inadequate methods comprise various imaging techniques, nerve blocks, manual examinations and psychological tests to determine the extent of contributing psychosocial factors, etc. [48]. Consequently, the majority of neck disorders are categorized as "non-specific neck pain" due to no clear and firm evidence-based signs of underlying pathology. The issue of diagnosis is complex due to the lack of a gold standard and consensus regarding the reliability and validity of diagnostic testing [18,46,48]. Clinical diagnoses are dominated by biomedical and biomechanical paradigms, and the integration of more recent knowledge from pain studies is still in progress. For example, differentiation between inflammatory, neuropathic and idiopathic pain mechanisms and to what extent the amplification of pain (peripheral and central sensitization) plays a role for the individual patient needs to be elaborated and emphasized [25,43,67]. Thus, the present lack of validated clinical findings raises the questions to what extent neuroplastic mechanisms play a role in the majority of patients with neck pain and how they respond to treatment and physical training.

Treatment and training

Contemporary treatment of neck pain frequently consists of counseling, analgesics, spinal manipulations and therapeutic training protocols [51,56]. Yet, a mainstay in the treatment is often a course of physical neck training with focus on strengthening, neck mobilization and stretching exercises [22]. However, neck training protocols usually vary with regard to the specificity, load and frequency of the training [61]. Consequently, it is unclear which type of training is the most effective [51]. Studies evaluating the clinical effects of neck training are heterogeneous and generally only show small to moderate clinical effects [10,47,61]. For example, randomized studies of untrained and non-injured individuals with neck pain indicate that progressive and dynamic strength training can relieve a moderate level of neck pain with up to 50% and provide relevant clinical effects [3,117]. In contrast, mobilization exercises in patients with whiplash-associated neck pain have been shown not to be better than the advice "act-as-usual" [66]. Other studies have shown that too much healthcare too early after a whiplash injury may actually delay the recovery of the neck pain [27,89]. Overall, studies indicate that the natural course of an episode of neck pain appears to be comparable to the effect sizes reported in interventional studies [69,74]. This indicates that the external validity of the clinical outcomes of these studies should be questioned. Consequently, the question that needs to be addressed is how to improve the clinical outcome of neck training.

Clinical outcomes of treatment and training are mainly measured subjectively by the use of scales evaluating components of "body functions" and "activity and participation levels" according to the International Classification of Functioning, Disability and Health (ICF) [2]. Similarly, surrogate

measures such as pain intensity, muscle strength, muscle fatigue, motor learning capabilities and neuroplastic responses can be used in experimental studies to evaluate differences before and after an intervention of physical training.

Transcranial magnetic stimulation and neuroplasticity

Transcranial magnetic stimulation (TMS) and motor evoked potentials (MEPs) have been used extensively as a research and diagnostic tool to measure the integrity of the nervous system in patients or as a tool to measure neuroplastic changes of the corticomotor pathways in the context of various medical interventions or physical training of the trunk, jaw or extremity [30,63,100,107,118]. Notably, the formerly described and frequently used single pulse TMS method is different from repetitive transcranial magnetic stimulation (rTMS), which is used as a therapeutic tool [91,93]. TMS techniques are assessed to be safe and reliable methods with extremely rare occurrences of adverse effects [17,90].

Research has shown that neuroplastic changes can be induced by intrinsic or extrinsic stimuli, and TMS can be used to measure parameters of cortical neuroplasticity and excitability of neural tissues [38]. For example, a magnetic coil can induce an electrical current through the scalp, and with adequate stimulation it can evoke excitation of the corticospinal pathways and elicit electro-myographic (EMG) responses, termed motor evoked potentials, in the contralateral target muscles [45]. Several studies have investigated the neurophysiological and neural changes after training by means of TMS and EMG. The neural parameters of neuroplasticity can be measured as changes in: 1) neuronal polarization expressed by the size of the amplitude of the action potential, 2) the time delay expressed as latencies of the MEP, 3) alterations in the size of the topographic area representing the muscles investigated [13,20,39,45,58,101]. For example, training in pain-free healthy subjects has similarly been shown to increase MEPs (enhance the excitability) of the corticomotor pathways and to increase the motor cortex representation of the extremity muscles after training [45,64,111]. Correspondingly, tongue training has been shown to lower MEP thresholds for up to 7 days after training and to increase the area of corticomotor topography for 1 day after the training [100,101]. The previous studies are supported by functional magnetic resonance imaging (fMRI) showing altered motor-related brain activity 1 week after one session of tongue-task training [5].

Although TMS is extensively used, only a few studies have investigated the neck muscles with this technique [9,42,55,83,85,97], and to our knowledge no TMS studies have yet investigated the neuroplastic changes in the neural pathways controlling the neck muscles in combination with training. This raises the question if training-induced neuroplastic responses in pain-free individuals

and different types of pain patients can be measured and can provide valuable information on how to select the optimal training strategies for patients with neck pain.

Pain and neuroplasticity

Neuroplasticity and functional reorganization are intrinsic, dynamic neurophysiological features of the nervous system that can be induced by an array of intrinsic or extrinsic stimuli. For example, an experience of pain may initiate a cascade of biological and psychological responses [14]. These responses are defined as morphological or functional changes with the following neuronal properties: 1) a change in the strength of synaptic connections, 2) altered representational patterns in the sensory and/or motor cortex of a muscle or limb and 3) reorganization of neuronal territories [39,67]. Similarly, transcriptional modifications of ion channels sensitization, network firing patterns and altered learning and memory function mechanisms are influenced by intrinsic or extrinsic stimuli and can induce adaptive or maladaptive neuroplastic changes in the nervous system [12,15,110].

Neuroplastic changes in terms of altered representation of the somatosensory cortex or primary motor cortex have been shown to correlate with the level of injury and functional recovery following neurological and musculoskeletal conditions [12,37,106]. For example, removing a finger surgically will change the cortical representation of that finger. The cortical area that formerly represented the removed finger will be replaced by an expanded representation of the adjacent fingers. Similarly, after weeks of training of specific fingers, the cortical representation of the trained fingers becomes considerably enlarged compared with their previous areas [14,79].

Experimental pain of low to moderate intensity induced in inactive extremity muscles was shown to exert an inhibitory effect on the neural responsiveness lasting from 30 minutes to a few hours after the pain induction and was related to impaired muscle function [7,34,36,68]. Additionally, motor skill training in patients with recurrent low back pain induced a shift in the cortical representation of the transverse abdominal muscle towards that observed in healthy participants [109]. In another study of acute low back pain, MEP amplitudes of the transverse abdominal muscle were found to exhibit different results depending on ipsilateral or contralateral measurements [108,110]. In patients with fibromyalgia, neurophysiological alterations of the MEP thresholds of the first digital interosseous finger were demonstrated [80]. These changes were significant compared with those of healthy controls and a control group of fibromyalgia patients not receiving psychotropic treatment.

TMS studies generally have small sample sizes (between 1 and 36 subjects), and only approximately half of the studies have included more than 10 subjects. In addition, most studies have lacked appropriate controls and have concentrated on relatively easily accessible aspects of

motor function [7]. For example, muscles in the hand have frequently been used, although the hand was not involved in the condition examined [80,103] .

Summary

Neck pain is frequent, but the majority of patients do not have a clear diagnosis. Accumulating evidence indicates that neuroplastic mechanisms may be a vital factor that hampers the optimal clinical outcomes. Training is a key component in the management of these patients. Neuroplastic responsiveness of the primary motor cortex has been shown to become enhanced, inhibited or modified by training and pain. This responsiveness in terms of increased, inhibited or altered cortical excitability and reorganization can be recorded and monitored by TMS and MEPs.

Studies of training-induced neuroplasticity and of the interaction between pain and motor control have provided us with unique insight into mechanisms that may underlie potential future rehabilitation strategies. Consequently, these neuroplastic mechanisms may be a key element in improving clinical outcomes of training in a range of musculoskeletal impairments and associated pain conditions [53,93]. However, data on the responsiveness of the corticomotor pathways representing the neck muscles induced by training and in the context of pain are still lacking. Thus, the aims of this thesis are to investigate if research from other anatomical regions can be extended and extrapolated to the neck region and consolidated by a study design including controls.

Aim

The overall aim for this thesis was to investigate the neuroplastic effects of neck training on the corticomotor pathways representing the neck muscles in pain-free participants, participants exposed to experimental pain and patients with chronic neck pain; the secondary aim was to investigate the possible effects on motor learning capabilities, muscle strength, muscle fatigue and pain.

Study I:

Aim: Investigation of training-induced effects on the corticomotor pathways of the neck muscles.
Hypothesis: Specific muscle training and coordination training yield significantly increased MEP amplitudes persisting 7 days after training.
Additional experiments: Effects of training on muscle strength, muscle fatigue and motor learning.

Study II:

Aim: Investigation of training-induced effects on the corticomotor pathways of the neck muscles and motor learning in healthy volunteers randomized to either experimental neck pain or no pain.
Hypothesis: Experimental pain would impede training-induced corticomotor excitability and motor learning capabilities.
Additional experiments: Effects of experimental pain and concomitant neck training on pain experience, muscle strength and muscle fatigue.

Study III:

Aim: Investigation of training-induced effects on the corticomotor pathways of the neck muscles in patients with chronic neck or knee pain and in pain-free participants performing no training.
Hypothesis: Neck pain would impede training-induced corticomotor excitability in contrast to no impediment of the corticomotor excitability in knee pain or no pain.
Additional experiments assessed the effect of pain and training on muscle strength, motor learning, muscle fatigue, pain experience and pain catastrophizing.

Methods

General description

Study I included healthy pain-free participants in order to test the hypothesis that training can induce measurable neuroplastic changes; study II included healthy participants randomized to either pain (hypertonic saline) or no pain (isotonic saline) in order to investigate how the findings from the first study were applicable in experimental pain; study III included patients with either non-specific neck pain or knee pain and a third control group of healthy and pain-free participants not performing any training in order to investigate the findings from the first two studies in clinical pain conditions.

Transcranial magnetic stimulation

The same procedures with TMS (Magstim 200; Whitland, UK) [17] and EMG (Viking Select Viasys, Ohio, US) were used in all experiments. The TMS principles are extensively described in the literature [23,29,59,118]. The experiment focused on the right trapezius muscle and the right thumb muscle, abductor pollicis brevis (APB), contralateral to the stimulated side. The APB muscle functioned as a within-subject control in all three studies. After TMS stimulation, the amplitudes and latencies of MEPs were recorded with EMG at baseline and after 30 minutes, 1 hour and 7 days.

All participants were sitting upright on a chair while TMS was delivered with a figure-of-eight coil to the left hemisphere corresponding to the motor representation of the right APB muscle and the trapezius muscle. Stimuli were repeated ≈ 4-6 times with increasing intensity until no further increase in amplitude was obtained, and then 10 stimuli were delivered with interstimulus intervals of 5-10 s and averaged. These stimuli were equivalent to 100-140% of the individual motor thresholds. Recordings from the APB muscle were used as a within-subject control and to determine specific effects at the cortical level and differentiate between altered excitability occurring at the motor representation of the trapezius muscle and the APB muscle.

Training

Specific neck training was performed for 20 minutes in all studies. The participants were asked to elevate and lower their right shoulder with a load of 10% of the maximal lifting capacity in order to move a blue line displayed on the screen of a feedback system in close synchronization with an ascending/descending line (Fig. 1-A). A load cell recorded the load and deviations from the curve. Prior to and after the training, the maximal lifting capacity was found by performing a one-repetition maximum (1-RM) test [115].

Coordination training was only performed in the first study. This training was performed using a special training machine, the NeckTech3000™, and it was also performed for 20 minutes. The subject was asked to follow the outer range of a "four-leaf clover" path on the computer screen with

unloaded head/neck movements (Fig. 1-B), and in the last 10 minutes, the subject should keep two crosses as close as possible on the computer screen against a random load in alternating directions (Fig. 1-C). Deviations were recorded to quantify potential learning effects during the training sessions in terms of improvements from the start to the end of the task.
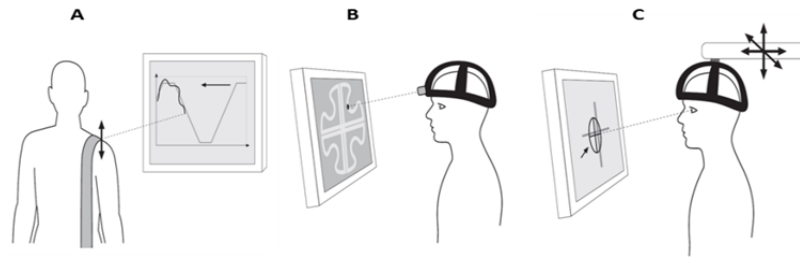
Figure 1. A: Specific neck training: The task was to follow the ascending/descending line on the feedback screen as closely as possible by lifting and lowering the shoulder. B: Coordination training: With the head acting like a joystick, the task was to follow the outer range of a "four-leaf clover" path. C: Coordination training: The task was to keep two crosses as close as possible against a random load in alternating directions.

Experimental pain

In study II, one group received an infusion of hypertonic 5% saline (HS) in the right side of the neck in level with and 2 cm lateral to the spinous process of the third cervical vertebra. A disposable 0.7x19 mm stainless needle was placed in the trapezius muscle at the specified location in a depth of approximately 19 mm, directed in a slightly cranial direction. The needle was connected to an infusion pump via a tube and a 20 ml plastic syringe. A standardized infusion paradigm was chosen with 0.5 ml saline infused over 20 s, followed by a steady infusion rate of 10-15 ml/h for 1200 s [99]. The other group was exposed to the same procedure but received an infusion of isotonic saline (IS). In both groups, pain intensity was rated using a numeric rating scale (NRS) with "no pain" = 0 and "worst pain imaginable" = 10. Pain intensity was recorded 14 times during the 20-minute saline infusion. After the infusion, participants in both the HS and the IS group completed the McGill Pain Questionnaire in order to assess the pain rating index and present pain index [32].

Statistical analysis

MEP amplitudes and latencies were analyzed with repeated measures one-way ANOVA and post hoc Tukey tests. Relationships between MEP amplitudes and motor learning were analyzed with parametric correlation analysis. Differences in the 1-RM test and muscle fatigue before and after training were compared with the paired *t*-test, and Grubb's test was used to detect potential outliers. In study I, the sample size required to detect a difference in MEP amplitude equivalent to a 50% increase was estimated from a pilot study and studies investigating the effects after tongue and

biceps training [58,101]. In study II and study III, the sample size was estimated to 15 participants per group in order to detect a difference in MEP amplitude equivalent to 67% or an increase from 1.5 millivolt (mV) to 2.5 mV (SD = 0.8 mV, 90% power, alpha 0.05) [88]. Data are presented as mean values, standard errors of mean (SEM), standard deviations (SD) and 95% confidence intervals (95% CI) as indicated. Statistical analysis was performed with Stata/SE Statistical Software, version 12, and Prism version 6, GraphPad Software. *P*-values ≤ 0.05 were considered statistically significant.

Ethics

All studies were done in accordance with the Helsinki Declaration and were approved by the local ethics committee (ID: M-20070213).

Study l

Participants
Sixty healthy volunteers aged 20-35 years (mean ± SD: 24.2 ± 3.5) were recruited among university students. Inclusion criteria were absence of any medical, physical and psychological problems.

Design
This study comprised three different experiments with 20 subjects in each group. Each subject took part in only one experiment to avoid carry-over effects. In the first group we tested the effect of specific training, in the second the effect of coordination training and in the third the effect of no training.

Primary outcome measures
MEPs from the right trapezius muscle and the right APB muscle contralateral to the stimulated side were monitored and recorded in participants performing either specific, coordination or no training. Amplitudes and latencies of MEPs were recorded at baseline and after 30 minutes, 1 hour and 7 days.

Additional experiments
The 20 participants performing specific neck training tested their muscle strength in the 1-RM test before and after training. Subjective muscle fatigue was recorded after training. Six subjects in the specific neck training group were tested with interference pattern analysis (IPA) in order to measure and record possible objective muscle fatigue after the training [40]. Learning effects of specific and coordination training were measured as the correlation between the relative increase in MEPs and the participants' ability to improve motor control by repeating the training. The participants performing specific training rated their subjective muscle fatigue immediately and 1 hour after training on a 0-10 point NRS. Due to random and minor loads in the coordination training, IPA recordings and fatigue were not evaluated in this group.

Study ll

Participants

Fifty-two healthy subjects (31 women and 21 men) aged 20-32 years (mean ± SD: 23 ± 2) were recruited among university students. Inclusion criteria were absence of any medical, physical and psychological problems and pregnancy.

Design

Participants were randomized to either HS injection and trapezius training (HST) (n = 20) or to IS injection and specific trapezius training (IST) (n = 20). A control group (n = 12) received HS injections and performed no training (HSNT).

Primary outcome measures

The first outcome measure was MEPs from the right trapezius muscle and the APB muscle that were monitored and recorded in participants performing either training or no training. MEP amplitudes and latencies were recorded at baseline and after 30 minutes, 1 hour and 7 days. The second outcome measures were improvements in motor learning during training and the correlation between improvements and changes in MEP amplitudes.

Additional experiments

Two additional experiments were undertaken: 1) Recording of the subjects' muscle strength performance at the 1-RM test before and after the infusion of HS or IS and the training session; 2) recording of pain using the McGill Pain Questionnaire in order to assess the pain rating index and the present pain index; 3) recording of the subjects' muscle fatigue rated immediately and 1 hour after training on a 0-10 NRS.

Study lll

Pain patients and participants

Twenty patients with neck pain, 15 patients with knee pain and 15 pain-free participants (34 women and 16 men) aged 19-39 years (mean ± SD: 27 ± 5) participated. Patients with neck or knee pain were recruited from physiotherapy clinics, and pain-free participants were recruited among university students. Inclusion criteria for patients with neck pain were non-specific neck pain persisting for more than 3 months and absence of any systemic or neurological disease, radiculopathy, radicular pain, history of spinal surgery or pregnancy. Inclusion criteria for patients with knee pain were the same; however, knee arthroscopy cases were included. Inclusion criteria for pain-free participants were absence of any medical, physical and psychological problems.

Design

Experimental study with 1-week follow-up, comparing neck training-induced excitability of cortico-motor pathways in participants with neck pain, knee pain and no pain.

Primary outcome measures

MEPs from the right trapezius muscle and the right APB muscle. MEP amplitudes and latencies were recorded at baseline and after 30 minutes, 1 hour and 7 days.

Additional experiments

Assessment of effect of pain and training on muscle strength, motor learning, muscle fatigue, pain experience and catastrophizing.

Presentation of results

Study l

Amplitudes and latencies

In participants performing 20 minutes of specific neck training, MEP amplitudes recorded from the trapezius muscle increased significantly compared with baseline measurements. The increase from 1.5 to 2.5 millivolts (mV) from baseline to day 7 was equivalent to 67%. Repeated measures one-way ANOVA and post hoc Tukey tests: between baseline and 30 minutes (Tukey $P < 0.05$), 1 hour ($F = 62.04$, $P < 0.001$; Tukey $P < 0.001$) and 7 days after training ($F = 11.28$, $P < 0.001$; Tukey $P < 0.01$)(Fig. 2). In contrast, no significant changes were seen in MEP amplitudes from the APB muscle between baseline, 1 hour and 7 days (Fig. 2) or in MEP latencies from both the trapezius muscle and the APB muscle between baseline, 1 hour and 7 days (Fig. 3).

In participants performing coordination training, no significant changes were seen in MEP amplitudes or latencies from the either the trapezius muscle or the APB muscle (Figs. 2 and 3). In the inactive control group, MEP amplitudes and latencies did not change significantly for either the trapezius muscle or the APB muscle (Figs. 2 and 3). Figure 4 shows the trapezius MEP amplitudes from one representative participant from the groups performing specific, coordination or no training.
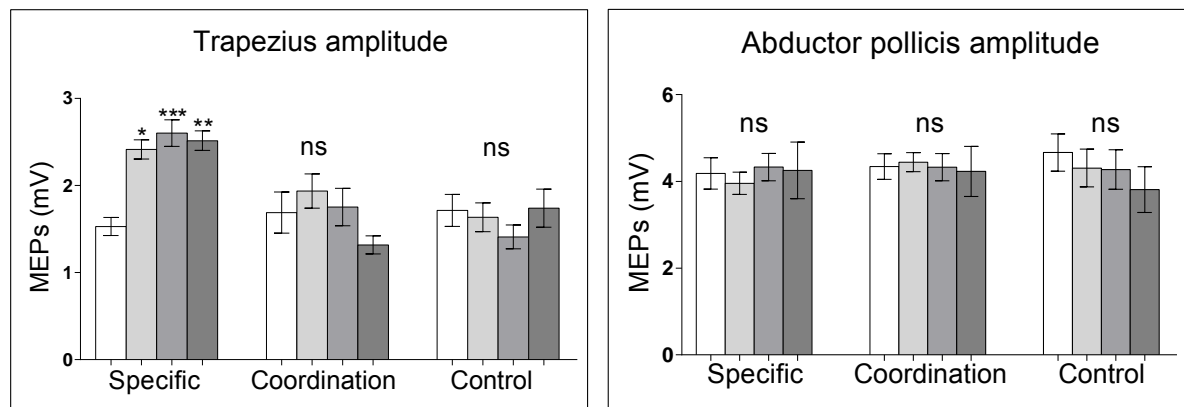
Figure 2. MEP amplitudes from the trapezius and APB muscles in the 3 groups of participants measured at baseline, after 30 min, 1 hour and 7 days. Error bars indicate SEM. * indicates $P < 0.05$; ** indicates $P < 0.01$; *** indicates $P < 0.001$.
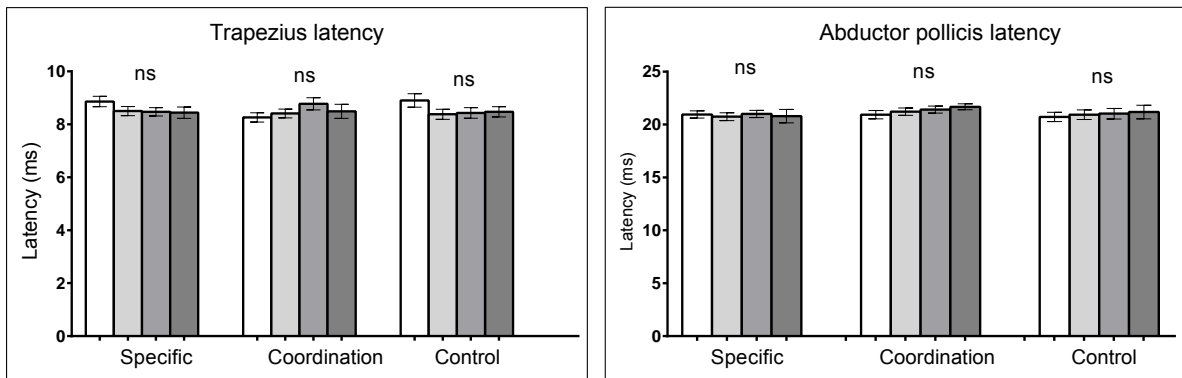
Figure 3. MEP latencies from the trapezius and APB muscles measured at baseline, after 30 min, 1 hour and 7 days. Error bars indicate SEM.
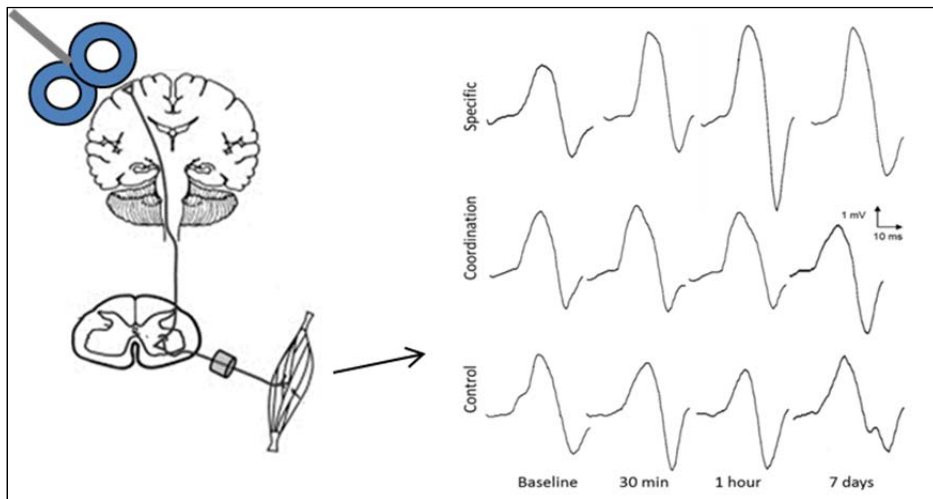
Figure 4. TMS applied to the cortical representation of the trapezius muscle (left) and MEP amplitudes (right) from a representative participant from each group.

Motor learning

Participants performing specific training improved significantly from baseline to the end of the 20-minute specific training (mean ±SD: 7.9 % ± 3.4, $P < 0.05$). The improvement in motor learning was defined as a reduced deviation by repeated training runs. The increased MEP amplitudes and improvements in learning were not correlated (Fig. 5 left).

Participants performing coordination training also improved significantly from baseline to the end of the 20-minute coordination training (mean ±SD: 7.9% ± 6.4, $P < 0.05$). Yet, there was no correlation between these improvements and changes in MEP amplitudes (Fig. 5 right).
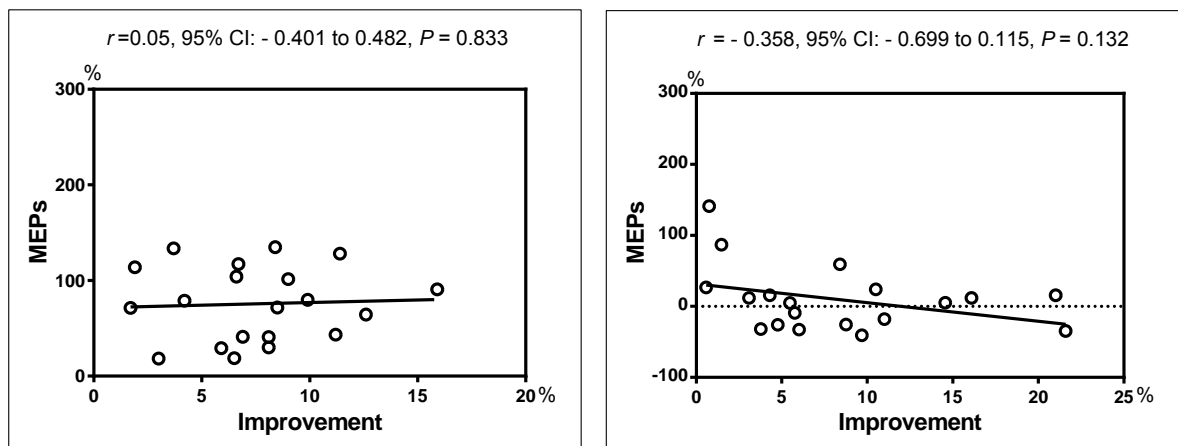
Figure 5. Left: MEP amplitudes by specific neck training did not correlate with learning effects, expressed as the relative improvement in percentage by repeated training. Right: MEP amplitudes measured by coordination training did not correlate with learning effects.

Additional experiments

Muscle strength as measured by the 1-RM test increased significantly from before to immediately after specific neck training from 56.6 kg (SD: 15) to 61 kg (SD: 16) or ≈ 8 % (paired t-test: $P < 0.001$). Out of 20 participants, 16 improved their 1-RM test. Muscle fatigue was only experienced immediately after the training, NRS 2.8 (SD: 1.0), and completely disappeared within 1 hour. Interference pattern analysis did not reveal any differences in objective muscle fatigue after specific neck training in the 6 participants tested ($P > 0.568$).

Study ll

Experimental pain

The infusion of saline induced a steady pain experience in the participants during the 20 minutes of training. The mean NRS intensity for the three groups were HST 4.9 ± 0.4, IST 1.1 ± 0.2 and HSNT 4.8 ± 0.5 (Fig. 6). The NRS difference between HST and IST was 3.8 ± 0.3 (Table 1) and thus significantly different ($P < 0.01$). Data for pain intensities and the McGill Pain Questionnaire scores are seen in Table 1.
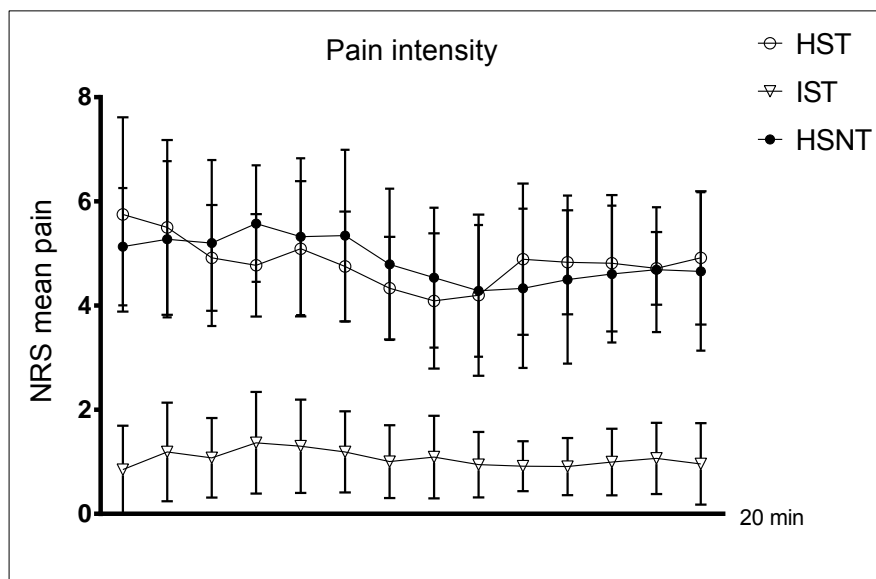
Figure 6. Mean pain intensity measured during 20 minutes of training on NRS in the 3 groups. Error bars indicate SD. NRS, numeric rating scale.

Table 1.
Pain ratings and data from additional experiments

	HST	IST	HSNT	P-values
Pain intensity (NRS)	4.9 ±0.4	1.1 ±0.2	4.8±0.5	0.01 [†] vs [‡]
Pain rating Index	23.4 ±2.8	11.1 ±2.0	30.1±3.7	0.01 -
Present pain Index	1.7 ±0.2	1.2 ±0.01	1.4±0.2	0.01 -
TMS intensity	77.8 ±9.8	77.3 ±7.5	75.4±5.4	0.857 -
Motor learning % (95%:CI)	4.5 (3.1-5.8)	6.2 (4.5-8.0)	-	0.105 -
Fatigue after training	3.7 ±1.3	2.8 ±1.6	-	0.049 -
Fatigue after 1 hour	0	0	-	-
1-RM (kg) before/after	54.5±11/53.8 ±13	57.3±11/62 ±15	59.2±15/55.6±15.6	0.422[†] 0.098[§] 0.010[‡]

[†] = HST, hypertonic saline and training. [‡] = IST, isotonic saline and training. [§] = HSNT, hypertonic saline and no training. Values are means ±SD unless otherwise stated.

Amplitudes and latencies

In participants who performed training and were exposed to experimental pain (HST), the amplitudes recorded from the trapezius muscle decreased significantly between baseline and 1 week. Repeated measures one-way ANOVA and post hoc Tukey tests between baseline and 30 minutes (*Tukey P* < 0.001), 1 hour (*Tukey P* < 0.001) and 1 week after training (F = 22.61, P < 0.001; *Tukey P* < 0.01) (Fig. 7). Latencies from the trapezius muscle (F =2.43, P = 0.075) and MEP amplitudes from the APB muscle (F = 2.47, P = 0.071) did not differ significantly from baseline to follow-up (Figs. 7 and 8). Yet, APB latencies differed significantly ($F = 9$ .59, P < 0.01; *Tukey P* < 0.05) between baseline and 1 hour (Fig. 8).

In participants performing training and exposed to IST MEP amplitudes recorded from the trapezius muscle increased significantly between baseline and 7 days. Repeated measures one-way ANOVA and post hoc Tukey tests between baseline and 30 minutes (*Tukey P* < 0.001), 1 hour (*Tukey P* < 0.001), and 1 week (F = 16.66, P < 0.001;*Tukey P* < 0.001) (Fig. 7). Latencies from the trapezius, MEP amplitudes from the APB muscle, and APB latencies did not differ significantly between baseline and 1 week (Figs. 7 and 8).

In participants not performing training but exposed to HSNT, the MEP amplitudes recorded from the trapezius muscle decreased significantly between baseline and 1 hour (*Tukey P* < 0.001) (Fig. 7). Latencies from the trapezius and MEP amplitudes from the APB muscle did not differ significantly (Figs. 7 and 8). Notably, the mean training load and TMS intensity did not differ between subjects randomized to either HST or IST (Table 1).
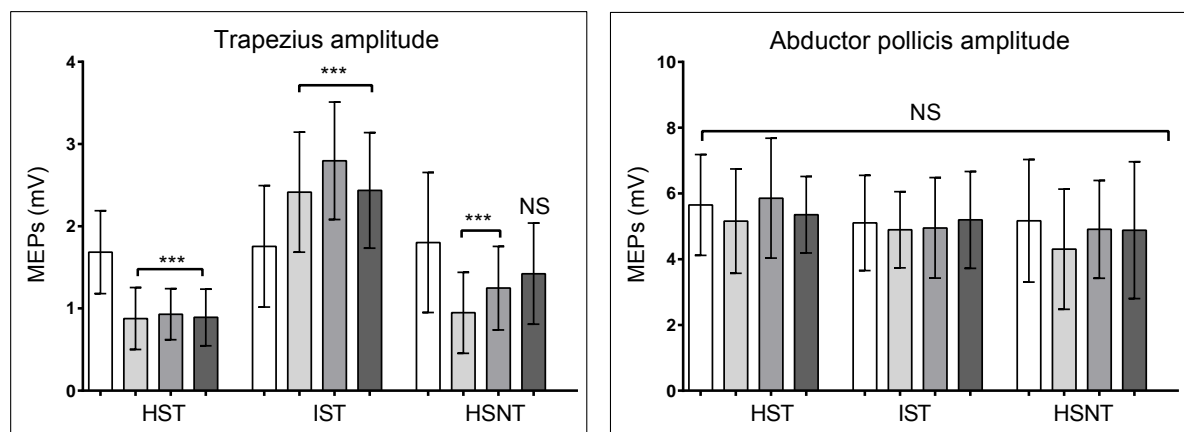
Figure 7. MEP amplitudes in mV from the trapezius and the APB muscles in the 3 groups measured at baseline and after 30 minutes, 1 hour and 7 days. Error bars indicate SD and *** indicates P < 0.001.
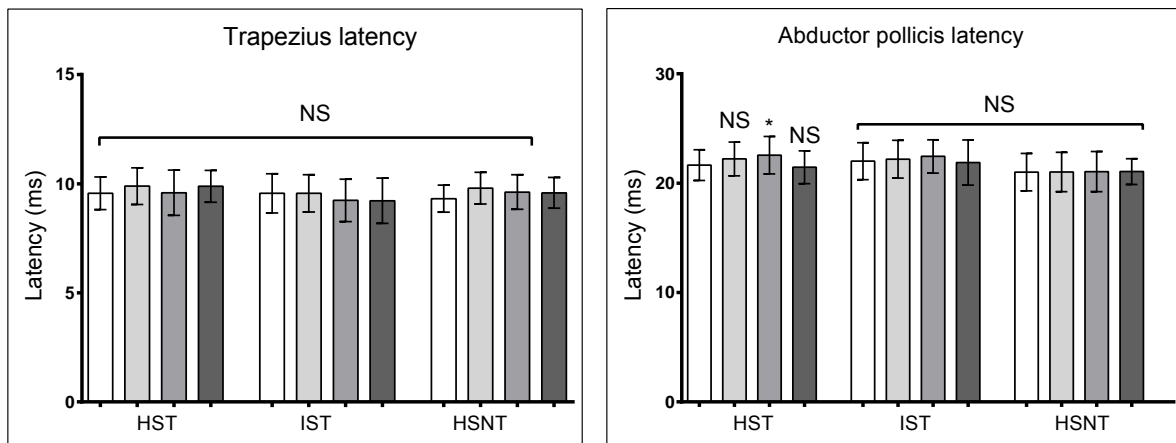
Figure 8. MEP latencies from the trapezius and the APB muscles in the 3 groups measured at baseline and after 30 minutes, 1 hour, and 7 days. Error bars indicate SD.

Motor learning

Motor learning improved significantly in participants exposed to HST and IST, however, no significant differences were observed between the groups (Table 1). In the HST group, the reduced MEPs were positively and significant correlated with the degree of learning (Table 1) (Fig. 9 left). In contrast, the increased MEPs in the IST group were not correlated with the degree of motor learning (Fig. 9 right).
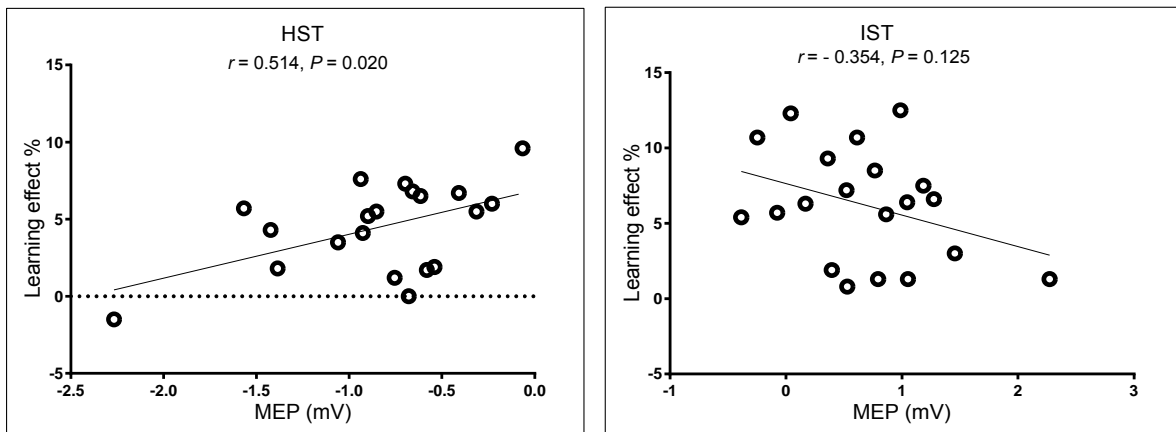
Figure 9. Correlation between motor learning and change in MEP amplitudes from the trapezius muscle in participants exposed to pain (left) and no pain (right).

Additional Experiments

The performance of the 1-RM test did not differ significantly before and after training between those exposed to pain or no pain. Yet, only the IST group increased their performance significantly and muscle fatigue was significantly higher in the HST group (Table 1).

Study lll

Characteristics of participants

There were no significant age and sex differences between groups. Analgesics (NSAID/-acetaminophen) were used by 65% of the patients with neck pain compared with 20% of the patients with chronic knee pain (Table 2).

Table 2.
Characteristics of participants and data from secondary outcomes.

	Neck Pain	Knee pain	No pain	*P*-values
Male/female	14/6	10/5	12/3	0.487
Age	29 (±7)	27 (±6)	25 (±3.5)	0.175
TMS intensity %	77 (±9)	75 (±12)	78 (±13)	0.716
Use of analgesics	65 %	20 %	n/a	0.001
Mean training load (kg)	4.8 (±1.6)	5.2 (±1.4)	-	0.534
1-RM before training (kg)	47.5 (±14)	51.7 (±13.5)	-	0.894
1-RM after training	47.7 (±18)	54.7 (±14.5)	-	0.049
1-RM difference	0.3 (±8.2)	3.0 (±5.5)	-	0.272
Motor learning (95%CI)	8.5 % (7.1-9.9)	6.2 % (4.9-7.5)	-	0.021
Muscle fatigue (NRS)*	5.1 (±0.5)	4.1 (±.5)	-	0.195
Pain rating index	27 (±12)	21 (±8)	-	0.164
Present pain index	1.7 (±0.6)	1.5 (±0.6	-	0.331
Number of words chosen	12 (±5.1)	9.1 (±3.2)	-	0.060
Pain Catastrophizing Scale	16 (±10)	16 (±6)	-	0.878

Values are means ±SD unless otherwise stated. *immediately after training. n/a = not applicable

Amplitudes and latencies

In the group with neck pain, MEP amplitudes recorded from the trapezius muscle yielded a significant variation. Repeated measures one-way ANOVA and post hoc Tukey tests between baseline and 30 minutes were significantly decreased (*Tukey P* ≤ 0.05), but there was no significant difference between baseline, 1 hour (Tukey $P = 0.178$) and 1 week ($F = 3.769$, $P = 0.015$; Tukey $P = 0.067$) (Fig. 10). Latencies from the trapezius muscle and latencies from the APB muscle (Fig. 11) yielded no difference between baseline and 1 week.

In the group with knee pain, the MEP amplitudes recorded from the trapezius muscle yielded a significant variation between baseline and 1 week ($F = 5.174$, $P < 0.001$). Tukey post hoc comparisons showed significantly increased amplitudes between baseline and 30 minutes ($P < 0.01$) and 1 hour ($P < 0.001$), but not after1 week ($P = 0.524$) compared with baseline (Fig. 10). MEP amplitudes and

latencies from the APB muscle and latencies from the trapezius yielded no difference between baseline and 1 week (Figs. 10 and 11).
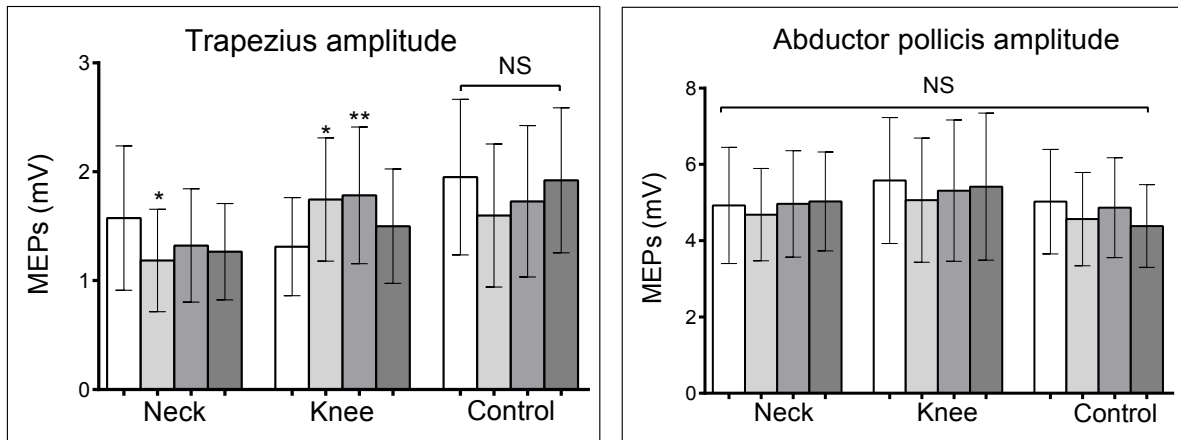

Figure 10. MEP amplitudes in millivolt (mV) from the trapezius and APB muscles in the 3 groups, measured at baseline, after 30 minutes, 1 hour and 7 days. Error bars indicate SD; ns indicates $P > 0.05$; * indicates $P < 0.05$; ** indicates $P < 0.01$.
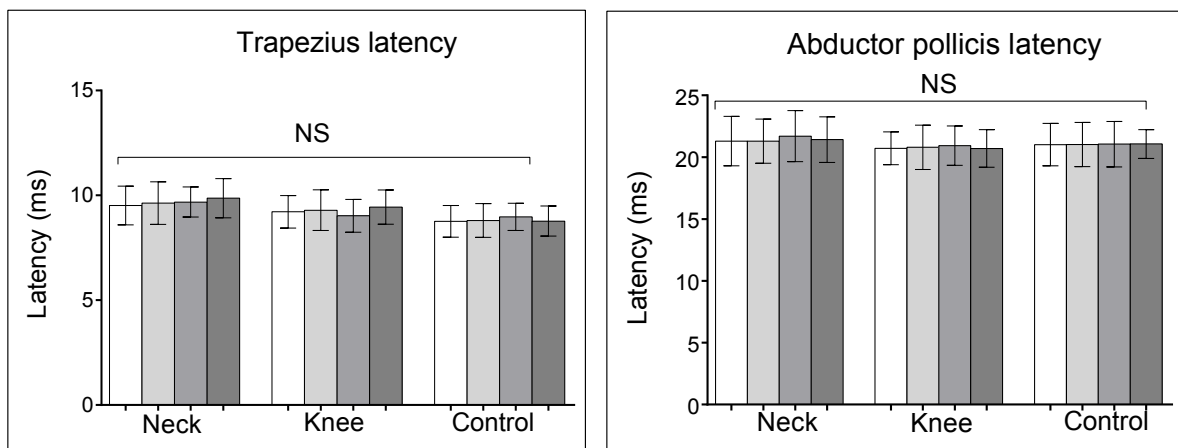
Figure 11. A: MEP latencies in ms from the trapezius muscle and B: the APB muscle in the 3 groups, measured at baseline and after 30 minutes, 1 hour and 7 days. Error bars indicate SD.

In the group with pain-free participants not performing training, measured at the same time intervals, MEP amplitudes and latencies yielded no significant variation between baseline and 1 week for either the trapezius or APB muscle (Figs. 10-A+B and 11-A+B).

The mean ±SD training load was 4.8 kg ± 1.6 kg in the neck pain group and 5.2 kg ± 1.4 kg in the knee pain group and thus did not differ significantly between groups ($P = 0.534$). TMS intensity did not differ between the three groups ($P = 0.716$) (Table 2).

Baseline MEP amplitudes and latencies were tested for differences among groups. MEP amplitudes recorded from the trapezius muscle varied significantly between the three groups ($F = 3.973$, $P = 0.026$). Tukey post hoc comparisons showed significantly higher mean amplitudes in pain-

free participants (mean 1.95 mV, 95% CI: 1.56 to 2.35) versus patients with knee pain (mean 1.31 mV, 95% CI: 1.06 to 1.56) $P < 0.05$. Patients with neck pain (1.57 mV ± 0.66) did not differ significantly compared with the other two groups (not shown). Trapezius muscle latencies also differed significantly ($F = 3.56$, $P = 0.036$). This difference was seen between patients with neck pain (mean 9.5 ms, 95% CI:9.1 to 1.0) and pain-free participants (mean 8.8 ms, 95% CI: 8.3 to 9.2) $P < 0.05$ (not shown). Baseline APB muscle amplitudes ($F = 0.871$, $P > 0.425$) and latencies ($F = 0.471$, $P > 0.627$) did not yield any variation between the three groups.

Motor learning and additional experiments

Motor learning improved significantly during training in both patients with neck pain and knee pain (Table 2). Patients with neck pain improved significantly compared with patients with knee pain (Table 2). No correlation was seen between trapezius muscle amplitudes and motor learning improvements in participants with neck pain and patients with knee pain (Fig. 12). Results from the 1-RM test, muscle fatigue, the McGill Pain Questionnaire and the Pain Catastrophizing Scale are shown in Table 2.
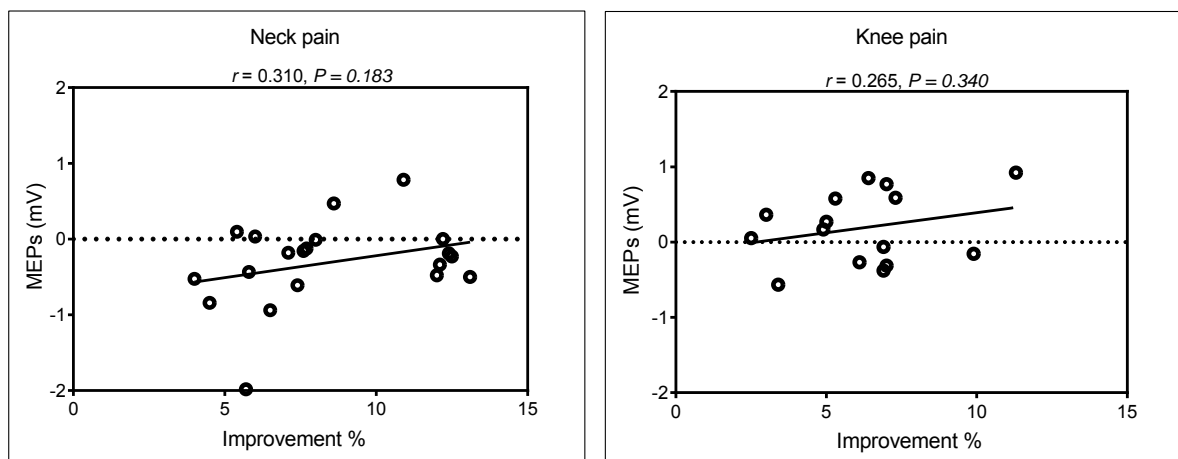
Figure 12. Correlation between motor learning and change in MEP amplitudes in neck pain and knee pain.

Discussion

Main findings

In study l, the hypothesis was confirmed that specific neck training significantly increased and sustained MEPs for up to 7 days after training. In study ll, the hypothesis was confirmed that experimental neck pain and concomitant neck training can significantly inhibit and reduce the excitability of MEPs for up to 7 days. In study lll, the investigation showed that MEPs were significantly but only transiently reduced in patients with neck pain in contrast to the transiently increased MEPs in patients with knee pain.

Interpretation of basic theories

The mechanisms underlying the increased MEP amplitudes after specific and load-dependent training in pain-free participants may be alterations and improvement of the efficiency of neural transmission of the neural pathway projecting to the neck muscles due to the physical training [15,30,64]. Long-term potentiation of motor neurons in the representative part of the motor cortex, decrease of GABA-related cortical inhibitory mechanisms and short-term memory functions occurring in acquisition of movement skills may possibly account for the increased MEP amplitudes [24,72] .

Neuroplasticity may be considered adaptive when associated with gain in function or as maladaptive when associated with negative clinical consequences [28,67]. The surrogate outcome measures in terms of MEPs revealed that maladaptive inhibitory mechanisms may play a role in the presence of pain, in line with previous findings of reduced excitability of the motor cortex in clinical conditions [104,109]. The mechanisms behind the functional neuroplasticity of the maladaptive responses seen in participants exposed to experimental pain and in patients with neck pain are not fully known. However, transcriptional modifications of ion channel sensitization, alteration in synaptic strength, central amplification and expansion of receptive fields, altered network firing patterns [67] and memory functions [15] are some of the possibilities. In perspective, it is important to bear in mind that several neural circuits work interactively, and that the representation on the motor cortex represents movements and not solely activation of a specific muscle. Thus, numerous physiological and psychological factors may influence the balance between adaptive and maladaptive mechanisms. Still, the results from the present studies indicate that localized moderate pain exerts a specific modulating effect on the motor neurons representing the involved muscles without clear indications of the specific underlying mechanisms.

The combination of neck training and localized neck pain versus neck training and knee pain may hypothetically have induced nocebo and pain behavioral responses that negatively affected the

motor performance. However, the reduced or inhibited MEPs in the patients with neck pain were not reflected in their ability to improve motor learning. The neurophysiological cause of these contradictory findings is unknown. These mechanisms have been investigated in conditioning and nocebo studies of Parkinsonian patients [8] and in an fMRI investigation of how fear can affect the motor neurocircuitry and result in decreased activity in the primary motor cortex in healthy participants [16]. Yet, parallel investigations of motor learning and changes in the excitability of the motor cortex are ambiguous [11,57]. Even though these findings are contradictory, the differential effects in MEPs between neck pain and knee pain may be explained by the extensive afferent convergence from neck and orofacial structures to the subnucleus caudalis, which acts like a brainstem relay site for nociceptive information [95,96]. Such convergence mechanisms may hypothetically explain why patients with whiplash-associated neck pain injury are less likely to recover compared with patients with ankle injuries [60].

Comparison with previous studies

Our studies on training-induced neuroplasticity have confirmed that specific neck training can induce changes by means of increased MEPs in line with studies of the tongue, extremity and trunk muscles [12,94,109]. The corticomotor effects induced by training from other areas of the body can be extrapolated to the neck muscles. Caveats have to be borne in mind due to equivocal findings in various studies with findings of either reduced [58] or unchanged corticospinal excitability [62,73] following training. This ambiguity may also explain why the low load in coordination training in this study did not yield any changes in MEPs. Thus, training-induced changes in MEPs seem to vary among cranial, extremity and trunk muscles. Furthermore, the training protocols vary widely among the studies, which makes it quite difficult to compare them [7,52,57,65]. The ambiguousness is shown by, for example, increased MEP amplitudes in low back pain [110] and no interference in local pain in the first dorsal interosseous thumb muscle [57]. Still, MEP amplitudes have commonly been shown to respond with reduced MEPs in response to pain [11,21,33,77,112]. In line with other studies, the results of our present study demonstrate that experimental pain in combination with training enhances the inhibition of MEP amplitudes and, interestingly, extends the time of inhibition from a few hours to several days [36,68,105]. Similarly, no studies have focused on the combination of training and induction of experimental pain, which makes comparison between studies difficult.

In perspective, the reduced and inhibited MEPs in patients with the combination of chronic neck pain and training were only sustained for 30 minutes, resembling the transient inhibition seen in non-training healthy participants exposed to experimental extremity pain [36,68]. Notably, MEPs did not increase as seen in pain-free participant performing the same kind of neck training in study I [88].

In patients with knee pain, increased MEPs sustained for 1 hour and did not demonstrate similar long-term effects to those in pain-free participants in our first study. Yet, the short-lasting increase in MEP amplitudes in knee pain indicates that even pain experienced in a distal body part may limit, at least to some degree, the neuroplastic responsiveness induced by neck training. Yet, the participants exposed to experimental pain had a mean pain intensity of 5 (NRS, 0-10) compared with 3.4 in patients with chronic neck pain. This difference in pain may account for differences in reduced or impeded MEP amplitudes over time.

Motor learning capabilities improved in pain-free participants, participants exposed to experimental pain and patients with neck and knee pain. However, only exposure to experimental pain indicated a correlation between reduced corticomotor excitability and a reduced degree of improvement in motor learning. These results are not consistent with studies of tongue training, indicating that modulation of primary motor cortex neuroplasticity may impair motor skill learning [11,12]. Motor learning improved in all patients, but the patients with neck pain improved significantly compared with the patients with knee pain despite the opposite and reduced MEP responses. This is in contrast to previous studies suggesting that pain may impair motor learning capabilities in tongue training [11,13]. Also, a study of training-induced plasticity of the first dorsal interosseous muscle indicated that remote pain in the infrapatellar fad pad may compromise learning due to distraction or other central processes [57]. The lack of correlation between improved learning performance and increased MEPs in the IS group did not correlate as expected in the light of studies showing that early phase skill acquisition may induce rapid cortical neuroplastic changes [41,81]. Again, the results are not easily comparable due to different study designs with different training protocols, different muscles and various diagnoses investigated [31,113].

In study ll, subjects exposed to experimental pain induced by HS reduced their performance on the 1-RM test in contrast to subjects exposed to IS who significantly increased their performance. The combination of exercise, pain and reduced MEP amplitudes may theoretically explain the long-lasting inhibition of MEPs and the transient muscle fatigue in these participants. The findings resemble studies investigating both experimental and chronic pain showing reduced activity of the corresponding muscles as a result of pain [6,44,71,82].

Muscle fatigue in relation to experimental pain seems uninvestigated, but in the present studies no pain, experimental pain and clinical pain induced transient fatigue. Muscle fatigue in chronic pain conditions has been investigated [78,98], and it is demonstrated that both non-painful fatiguing and non-fatiguing exercises, with no clear knowledge of the underlying mechanisms, are followed by a period of reduced corticomotor excitability [92,100].

Methodological considerations

These studies on training-induced neuroplasticity have focused on neck muscles not earlier investigated. Only a few studies have investigated neck muscles, and these studies have primarily been performed in no-pain and no-training contexts [55,84,86,97]. Thus, the strength of the studies is the examination of the neck region in the context of training and different pain conditions and the use of control groups and a within-subject control muscle; the latter was included to differentiate between altered corticomotor excitability of the trapezius muscle and the APB muscle, respectively, at the cortical level. In addition, follow-up measurements provided the opportunity to measure effects over several days.

The following limitations should be considered when interpreting the results. Study l did not randomize the participants, and follow-up measurements at day 7 were only performed on 10 participants in each group. In study ll, the randomization to either HS or IS was single-blinded. Yet, in order to monitor the pre-set level of pain equivalent to NRS 5, the single-blinded design was considered necessary. In study lll, the pain patients had a mean age of 27 years and they were thus more representative of a younger group of patients with a better prognostic factor than an older group (> 40 years), that are more likely to have more persistent pain and less reducible neck pain [19]. In this perspective, subclassification into age and gender groups could be relevant in future studies.

Over the last three decades, TMS and EMG have been used to investigate the corticospinal tracts and are considered valid and reproducible methods [23,118]. Yet, the neck muscles are not frequently studied with these methods, probably due to difficulties with specific and selective magnetic stimulation of the neck muscles. In this study, this was overcome by stimulating the area representing the motor neurons for the trapezius and APB muscles simultaneously with TMS. In this process, pre-activation of the neck muscles was necessary. Cortical motor thresholds are determined with the target muscles relaxed; however, determining motor thresholds for the neck muscles was done with a slight tonic contraction of the trapezius muscle called active motor threshold [45]. The estimation of motor thresholds of the trapezius is generally very difficult due to natural fluctuations in the excitability of the pyramidal cells and spinal motor neurons and the position of the subjects investigated [1,45], and even more problematic when measuring active motor thresholds. Thus, due to the aforementioned fluctuations, the data on motor thresholds are not included as outcome measures in the present studies.

The NeckTech3000[TM] has been shown to be reliable in healthy subjects with no significant variation between measurements and with an acceptable coefficient of variation [102]. However, the NeckTech3000[TM] is a prototype and therefore not commonly available. The specific trapezius training

device comprising a laboratory electronic load cell and recording software was calibrated before every training session to ensure optimal measurements. Again, the recording software and training protocol was likewise a prototype manufactured for the purpose. Moreover, the training protocols consisting of one training session only simulated the aspects of clinical neck training and the results are limited to this experimental set-up and needs to be further investigated before it can eventually be implemented in the process of optimizing clinical neck training programs.

Clinical relevance and future perspectives

Clinical and experimental findings suggest that training should be well adjusted and performed with greater emphasis on quality, sufficient load and minimal pain in order to optimize the outcome of training, and further to avoid unfavorable neuroplastic changes that are known to occur in association with pain [12,35,39,106,117]. Accordingly, the mechanisms of neuroplastic adaptation and maladaptation have to be taken into account in the planning of combinatorial therapies in order to handle their potentially interactive effects [75]. If training-induced changes can be driven in specific directions by training or combinatorial therapies, these modulations may present an opening to improve the clinical management of not only neck pain, but a variety of musculoskeletal impairments and associated pain conditions [53,93]. For example, improvements in both neuroplastic responsiveness and clinical outcomes may be achieved by either analgesics, pain treatment by sensory-stimulation or TMS given in combination with physical training [53,82,91,93]. Finally, the method used in these studies has the potential to become an assessment tool in the effort to monitor neuroplastic responsiveness and improve clinical outcomes.

Conclusion

This study provides new knowledge about how neck training can influence the excitability of the corticomotor pathways in no pain, experimental pain and clinical pain. The results showed that specific and load-dependent specific neck training significantly increased and sustained the responsiveness of the corticomotor pathways for up to 7 days in pain-free participants. In experimental pain, the results were opposite and exposed an inhibition which lasted 7 days after one session of training. In patients with clinical neck pain, the responsiveness was transiently reduced, and they did not exhibit the same ability to increase the neuroplastic responsiveness as pain-free healthy participants. Training-induced neuroplasticity of the corticomotor pathways seems to manifest differently in no pain, experimental and clinical pain. Increased attention to adaptive and maladaptive neuroplastic responses induced by physical training may prove valuable in process of optimizing clinical outcomes of future neck training protocols.

Summary

Training is a mainstay in the clinical management of neck pain; however, effects of various training protocols are small and improvements are required. Implicitly, the interaction between neck pain and training needs further exploration. A growing body of evidence indicates that injury, inflammation and pain arising from spinal structures not only affect the involved musculoskeletal structures, but also have a significant impact on the nervous system. Such impacts have been shown to correlate with the level of injury and functional recovery following neurological and musculoskeletal conditions. Yet, knowledge about training-induced neuroplasticity in neck pain is still lacking. This thesis investigates the neuroplastic effects of training in pain-free participants, participants exposed to experimental pain and patients with chronic neck pain.

The investigation comprises three experimental studies using transcranial magnetic stimulation and electromyography to elicit and monitor amplitudes and latencies of motor evoked potentials (MEPs) from the trapezius and thumb muscles. One study included 60 pain-free participants performing specific neck training, coordination training or no training; a second study included 52 participants randomized to either experimental pain or no pain; and the third included 35 patients with either chronic neck or knee pain and a group of 15 pain-free participants.

Pain-free participants performing specific neck training yielded significantly increased responsiveness of MEPs from the trapezius muscle lasting 7 days after training. No significant changes were seen following coordination training, no training or in the within-subject control muscle. In participants exposed to experimental neck pain in combination with training, MEPs from the trapezius were also reduced 7 days after training. In patients with chronic neck pain, MEPs were briefly but significantly reduced for 30 minutes after the training.

One training session induced a sustained neuroplastic effect measured by MEP amplitudes and lasted for 7 days after training in pain-free participants. Experimental pain inversely induced a sustained inhibition lasting for 7 days. In patients with neck pain, a brief inhibition of the corticomotor excitability was induced and, notably, the training-induced neuroplasticity did not increase as in participants with no pain. These results have contributed with novel information about neuroplastic responses induced by neck training in no pain, experimental pain and clinical neck pain. The results may prove valuable in the ongoing process of developing more effective training protocols and combinatorial therapies for patients with chronic neck pain.

Dansk resumé

Træning er et vigtigt element i den kliniske behandling af nakkesmerter. Den kliniske effekt af forskellige træningstilgange er dog fortsat utilstrækkelig. Der er derfor brug for yderligere viden om samspillet mellem nakkesmerter og træning. Ny forskning peger på, at vævsskade, inflammation og smerter ikke kun påvirker de involverede muskuloskeletale strukturer, men også har en betydelig effekt på nervesystemet. Denne effekt viser sig som neuroplastiske ændringer og korrelerer med graden af vævsskade og evnen til at genvinde normal funktion ved neurologiske og muskuloskeletale lidelser. Afhandlingen undersøger de neuroplastiske effekter ved henholdsvis træning uden smerter, eksperimentelle smerter samt ved kroniske nakkesmerter.

Afhandlingen omfatter tre eksperimentelle undersøgelser, der anvender transkranial magnetisk stimulation og elektromyografi til stimulation og monitorering af aktiveringsfølsomheden i de motoriske nervebaner. Dette ved at måle amplitudeudslag og latenstider af de motorisk evokerede potentialer fra trapeziusmusklen og tommelfingerens muskel, som kontrolmuskel. Første undersøgelse inkluderede 60 raske forsøgsdeltagere, som udførte enten specifik nakketræning, koordinationstræning eller ingen træning. Den anden undersøgelse inkluderede 52 forsøgspersoner, som blev randomiseret til enten eksperimentelle smerter eller ingen smerter. Den tredje undersøgelse inkluderede 35 patienter med kroniske nakkesmerter eller knæsmerter og en kontrolgruppe på 15 raske deltagere uden smerter.

Forsøgsdeltagerne uden smerter, som udførte specifik træning, fik en signifikant forøget aktiveringsfølsomhed af trapeziusmusklens motoriske nervebaner, som var målbar 7 dage efter træningen. Der var ingen signifikante ændringer i aktiveringsfølsomheden ved koordinationstræning, ingen træning eller ved kontrolmusklen. Eksperimentelle nakkesmerter kombineret med træning viste den modsatte effekt med en signifikant hæmning af aktiveringsfølsomheden, som også var målbar i 7 dage efter træningen. Hos patienter med nakkesmerter var aktiveringsfølsomheden signifikant og kortvarigt reduceret i 30 minutter efter træningen.

Nakketræning uden smerter medførte en signifikant og øget aktiveringsfølsomhed af de motoriske nervebaner, hvorimod eksperimentelle smerter viste en signifikant reduktion. Ved kroniske nakkesmerter var der en signifikant kortvarig reduktion af aktiveringsfølsomheden, som ikke blev forøget sammenlignet med deltagere uden smerter. Undersøgelserne har bidraget med ny viden om neuroplastiske ændringer induceret ved nakketræning udført med og uden smerter. Resultaterne og den anvendte monitoreringsmetode kan potentielt bidrage til udviklingen af mere effektive træningsprogrammer og kombinationsterapier for patienter med kroniske nakkesmerter.

Thesis at a glance

Title of paper	Primary aim	Method	Main findings
Study I: Specific neck training induces sustained corticomotor hyperexcitability as assessed by motor evoked potentials.	Investigation of effects of training on the corticomotor control of the neck muscles in 60 pain-free participants.	Eliciting and monitoring of motor evoked potentials (MEPs) with transcranial magnetic stimulation and (TMS), electromyography (EMG). Intervention: specific neck training, coordination training or no training.	Specific training significantly increased and sustained MEP amplitudes for up to 7 days.
Study II: The role of neuroplasticity in experimental neck pain: A study of potential mechanisms impeding clinical outcomes of training.	Investigation of the effects of training on corticomotor control of neck muscles in 52 healthy volunteers randomized to either experimental neck pain or no pain.	TMS/EMG/MEP Intervention: specific neck training and randomization of groups to either induction of experimental pain or no pain.	Experimental pain and neck training significantly inhibited the excitability of the corticomotor pathways with an effect of up to 7 days.
Study III: Effect of training on corticomotor excitability in clinical neck pain.	Investigation of the neuroplastic changes of corticomotor pathways induced by neck training in 35 patients with chronic neck or knee pain and in 15 pain-free participants.	TMS/EMG/MEP Intervention: specific neck training performed by patients with either neck pain or knee pain.	MEP amplitudes were significantly inhibited immediately after neck training in patients with neck pain compared with patients with knee pain.

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