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The effects of experimental pain on primary motor cortex neuroplasticity associated with novel orofacial motor learning

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Preface

This PhD thesis study is based on four papers (I-IV). The experimental studies were performed at the Orofacial Pain Laboratory, Centre for Somatosensory Motor Interaction, Department of Health Science and Technology, Aalborg University, Denmark.

Paper I: Boudreau S, Wang K, Svensson P, Sessle BJ, Arendt-Nielsen L (2009) Vascular and psychophysical effects of topical capsaicin application to orofacial tissues. *Journal of Orofacial Pain*. (OROFAC PAIN 2009;23:253–264)

Paper II: Zhang Y, Boudreau S, Wang M, Wang K, Sessle BJ, Arendt-Nielsen L, Peter Svensson (2009) Effects of periodontal afferent inputs on corticomotor excitability in humans. *Journal of Oral Rehabilitation*. (doi: 10.1111/j.1365-2842.2009.02016.x)

Paper III: Boudreau S, Romaniello A, Wang K, Svensson P, Sessle BJ, Arendt-Nielsen L (2007) The effects of intra-oral pain on motor cortex neuroplasticity associated with short-term novel tongue-protrusion training in humans. *Pain* 132:169-178. (doi: 10.1016/j.pain.2007.07.019)

Paper IV: Boudreau S, Hennings K, Svensson P, Sessle BJ, Arendt-Nielsen L (2010) The effects of training time, sensory loss, and pain on human motor learning. *Journal of Oral Rehabilitation*. (doi: 10.1111/j.1365-2842.2010.02103.x)

Abbreviations

• N	Newton
• ml	Millimetre
• cm	Centimetre
• s	Seconds
• min	Minutes
• hrs	Hours
• PET	Positron emission tomography
• fMRI	Functional magnetic resonance imaging
• ICMS	Intra cortical micro stimulation
• TMS	Transcranial magnetic stimulation
• MEP	Motor evoked potential
• CoG	Centre of gravity
• AUC	Area under the curve
• T	Motor threshold
• FDI	First dorsal interosseous
• AD	Anterior diagastric
• GG	Genioglossus
• MI	Primary motor cortex
• SI	Primary somatosensory cortex
• SII	Secondary somatosensory cortex
• LA	Local anaesthetic
• TRPV1	Vanilloid receptor
• TMD	Temporomandibular disorder
• TMJ	Temporomandibular joint
• VAS	Visual analogue scale
• MPQ	McGill Pain Questionnaire

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Summary

Cortical neuroplasticity, as reflected by a cortical reorganization or changes in the excitability of the primary motor cortex (MI) has been shown to occur in association with peripheral nerve lesions, brain injury, chronic pain, and motor learning. However, it remains unclear if experimental pain modulates the cortical neuroplasticity associated with motor learning in humans. This PhD thesis study has provided evidence that the capsaicin pain model is a suitable method to investigate the modulatory effects of acute orofacial pain on the motor performance and cortical neuroplasticity of the face MI associated with short-term novel tongue-task training in humans. This PhD thesis study has shown (I) topical application of capsaicin to the tongue results in burning pain, increases in blood flow and temperature for a minimum of 30 min and that (non-noxious) tactile afferent feedback in the tongue is unaltered during this time (II) application of capsaicin or carbocain to the periodontal ligament is not associated with changes in the cortical excitability of the tongue or jaw MI, as measured by transcranial magnetic stimulation (TMS) in humans (III) topical application of capsaicin to the tongue reduces motor performance and interferes with the changes in cortical excitability of the tongue MI, as measured by TMS, which would otherwise occur in association with 15 min of novel tongue-task training in humans (IV) reduced mucosal sensitivity of the tongue tip and intra oral pain differentially interfere with the incremental gains in motor performance associated with 15 min of novel tongue-task training in humans (V) a sufficient number of within-session task-repetitions may exist for long-term novel motor training regimes such that extended training times do not facilitate additional gains in overall motor performance. These present findings may have implications on the design of motor rehabilitation regimes in which limited training time is available, or when sensory loss or pain is present.

Dansk Sammenfatning

Kortikal neuroplasticitet, reflekteret ved kortikal reorganisering eller ændringer i aktivitet af den primære motor cortex (MI), er blevet påvist ved perifere nerve læsioner, hjerne skade, kronisk smerte og motorisk indlæring. Dog er det stadig usikkert om eksperimentel smerte modulerer kortikal neuroplasticitet associeret med motorisk indlæring hos mennesker. Denne afhandlings undersøgelser giver beviser for, at capsaicin smertemodellen er en passende metode til at undersøge modulatoriske effekter af akut orofacial smerte på motorisk præstationsevne og kortikal neuroplasticitet af ansigtets MI associeret med kortvarig uprøvet tunge-træningsopgave hos mennesker. Denne afhandlings undersøgelser har påvist at (I) topisk applikation af capsaicin på tungen resulterer i brændende smerte, forøger blodgennemstrømningen og temperaturen i minimum 30 minutter og at (ikke smertefuld) taktile afferent feedback i tungen er uændret i dette tidsrum (II) applikation af capsaicin eller carbocain på de periodontale ligamenter er ikke associeret med ændringer i kortikal aktivitet (målt ved hjælp af transkraniel magnetisk stimulering (TMS)) af tungens eller kæbens MI hos mennesker (III) topisk applikation af capsaicin på tungen reducerer motorisk præstationsevne og interfererer med ændringerne i kortikal excitabilitet af tungens MI (målt ved hjælp af TMS) som ellers ville finde sted efter 15 minutters uprøvet tunge-træningsopgave træning hos mennesker (IV) reduceret slimhinde sensitivitet i tungespidsen og intra-oral smerte interfererer differentielt med inkrementelle forøgelse i motorisk præstationsevne associeret med 15 minutters uprøvet tunge-træningsopgave hos mennesker (V) et sufficient antal af opgave-gentagelser i en session i langvarige nye motoriske træningsregimer er muligvis tilstrækkelig og kan dermed indikere at forlængede træningstider ikke faciliterer yderligere forbedringer i samlet motorisk præstationsevne. Disse fund kan muligvis have implikationer for design af

motoriske rehabiliteringsregimer, hvor begrænset træningstid er til rådighed eller når der er tale om tab i sanseapparatet eller smerte er til stede.

Introduction

The purpose of this PhD thesis study was to elucidate the effects of experimental pain on the primary motor cortex (MI) neuroplasticity associated with novel orofacial motor learning. This PhD thesis study specifically focused on noxious stimulation with capsaicin to the orofacial tissues, face MI cortical neuroplasticity as assessed by transcranial magnetic stimulation (TMS) and novel tongue-protrusion training, and correspondingly the background information has been limited to these topics. The main outcomes of this PhD thesis study, are however, discussed in a broader sense and address the implications that pain may have on cortical neuroplasticity and motor learning in motor rehabilitation settings.

Background Information

Orofacial pain

Orofacial pain refers to any pain in the oral, facial, or head area. A wide range of diseases apart from local disorders can cause orofacial pain, including neurological, vascular and psychogenic (unknown aetiology) causes. Cross-sectional studies indicate that, at any time, about one out of every four adults will have experienced orofacial pain (Locker and Grushka, 1987; Locker et al., 1991; Macfarlane et al., 2002) with women being more commonly afflicted than men (Locker et al., 1991; Macfarlane et al., 2002). To date, the factors which predict the persistence of orofacial pain i.e. chronic orofacial pain are unclear; however a four-year follow up study has shown that persons whom develop persistent and disabling orofacial pain often require medication for their pain, have

additional widespread body pain and a maladaptive response to illness (Macfarlane et al., 2004). Burning mouth syndrome, atypical facial pain/atypical odontalgia, phantom tooth pain, phantom bite syndrome, tension-type headache, temporomandibular joint (TMJ) and muscle pain (TMD), as well as musculoskeletal afflictions, consisting of, for example, myositis, muscle spasms, and fibromyalgia are some examples of chronic orofacial pain conditions. Chronic orofacial pain can also result from spinal cord and brain injuries, i.e. post-stroke pain. A review of the literature suggests that the prevalence of orofacial pain is considerable, for example at any one time, adult population based studies have revealed that persistent burning mouth syndrome can range from 0.7 – 5.1% (Locker and Grushka, 1987; Lipton et al., 1993; Tammiala-Salonen et al., 1993; Thorstensson et al., 1996), tension-type headache 1.6 – 22.0% (Queiroz et al., 2009; Grande et al., 2008), TMD 4 – 21% (Gesch et al., 2004; Marklund and Wanman, 2008) and TMJ pain 3 – 8% (Gesch et al., 2004; Marklund and Wanman, 2007).

It is generally accepted that pain is an unpleasant sensory and emotional experience but also serves as an important biological signal for danger. In most cases, pain limits or reduces movement in order to prevent further injury. However, when pain is sustained over a long period of time and no longer has a protective role pain can become the pathology (Usunoff et al., 2006). Neuropathic pain is an example of this chronic condition may arise when peripheral nerves are damaged by trauma or disease. Postherpetic and trigeminal neuralgia are also examples of known neuropathic pain conditions in the orofacial region. Clinical symptoms of chronic or neuropathic pain can include, for example, spontaneous burning pain, lancinating pain, allodynia (pain produced by a stimulus that is normally non-noxious) and hyperalgesia (increased sensitivity to noxious stimuli).

Orofacial Sensorimotor Physiology and Function

Sensory (afferent) input originating in the orofacial tissues are carried by the cranial nerves and relayed from their respective cranial nuclei to the thalamus and through thalamocortical projections are finally processed at higher cortical areas, for example, the primary and secondary somatosensory cortices (SI and SII), where they can result in conscious perception (Bennett et al., 1987). Orofacial tissues such as the teeth, facial skin, tempormandibular joint and associated musculature are mainly supplied by branches of the trigeminal (V) nerve. Afferent input from these orofacial tissues are carried by the trigeminal nerve through the trigeminal ganglion to the brainstem and are transmitted either to the main sensory nucleus of the trigeminal nerve (responsive to discriminate tactile senses, light touch and pressure) or to the descending spinal tract nuclei, including: (i) the nucleus oralis (responsive to cutaneous sensation of oral mucosa); the nucleus interpolaris (responsive to tooth pulp pain); (iii) the nucleus caudalis (responsive to pain, temperature and crude touch) (Kandel et al., 2000). The trigeminal nerve is also the main motor nerve for the masticatory muscles and originates in the trigeminal motor nucleus. The nucleus of the solitary tract receives afferent input from the anterior 2/3rd of tongue, via the facial nerve (VII), and from the posterior 1/3rd of the tongue, via the glossopharyngeal nerve (IX). The hypoglossal nerve (XII) is a pure motor nerve that innervates the muscles of the tongue and originates in the hypoglossal nucleus.

The tongue is densely innervated by various types of mechanoreceptors (Jacobs et al., 2002); with the tongue tip being particularly rich (Grossman, 1964). The superficial mechanoreceptive afferents of the tongue respond to mechanical distortion arising, for example, from contact between the tongue and teeth whereas, deeper mechanoreceptive afferents encode information about tongue position (Trulsson and Essick, 1997). Tongue

movements result from various combinations of extrinsic and intrinsic tongue muscle activity (Lowe, 1980). The extrinsic tongue muscles are comprised of the genioglossus (GG), hyoglossus and styloglossus muscles, refer to Fig 1. In particular, tongue protrusion is accomplished by contraction of the intrinsic tongue muscles (verticalis and transverses) and the extrinsic genioglossus muscle moves the tongue forward in space. Genioglossus muscle activity, as measured by EMG and single motor-unit activity, during an unimpeded tongue-protrusion task increased with protrusion and decreased with retraction (Pittman and Bailey, 2009). However, during an impeded tongue-protrusion task genioglossus muscle activity remained constant and intrinsic muscle activity increased with increasing force production (Pittman and Bailey, 2009). These findings suggest that genioglossus muscle activity is related to tongue position or stabilization of the tongue in space and intrinsic tongue muscle activity contributes to force development as also suggested by McClung and Goldberg, 2000.

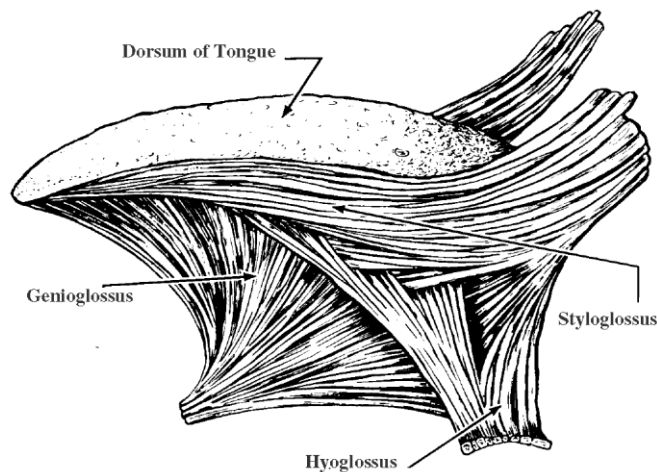


Fig 1: Main muscles of the tongue (Adapted from www.homesteadschools.com)

It is well known that the tongue has a significant role in a number of complex orofacial sensorimotor functions (Lowe, 1980), such as such as speech (Murray et al., 2006; Hiiemae and Palmer, 2003), mastication (Hiiemae and Palmer, 2003; Dellow and Lund,

1971), swallowing and respiration (Lowe and Sessle, 1973; Sawczuk and Mosier, 2001). In a series of sub-human primate studies (Lin et al., 1994; Lin et al., 1993; Martin et al., 1999; Martin et al., 1997; Murray et al., 1991; Murray and Sessle, 1992b; Murray and Sessle, 1992a; Yao et al., 2002a; Yao et al., 2002b), the face MI or primary somatosensory area (SI) of the primate cerebral cortex has been shown to modulate the production and control of mastication, swallowing, and more 'simple' movements such as tongue-protrusion and jaw closure. These cortical areas have been investigated using intracortical microstimulation (ICMS), reversible cooling of the cortex, and single cortical cell recordings. These studies have documented the importance of the face, jaw, and tongue SI and MI areas in the production and control of orofacial movements and of tactile information from the mouth to these areas, and have characterized the activity patterns of the cortical cells accounting for the animal's ability to change and control the force or direction of the movement. These findings have provided new insights into how the cortex is organized to allow primates to produce orofacial movements, and also explain why severe impairment of orofacial function can occur clinically after damage (e.g. stroke or trauma) to these areas of the cortex.

Cortical Neuroplasticity

The reorganization of neuronal connections, and the associated changes in their excitability, is characteristic of "cortical neuroplasticity," and can be defined as a morphological or functional change in the cortical properties such as strength of internal connections, altered representational patterns, or neuronal territories (Hess and Donoghue, 1996; Sanes and Donoghue, 2000; Calford, 2002). Sensorimotor reorganization within the primate cerebral cortex occurs dynamically throughout life, for

example during central nervous system development in early childhood, but has also been reported in association with peripheral nerve lesions associated with the limbs (Cohen et al., 1991; Chen et al., 2002), brain injury (Jenkins and Merzenich, 1987; Dancause et al., 2005), chronic and phantom limb pain (Karl et al., 2001; Krause et al., 2006; Dettmers et al., 2001), novel motor skill acquisition (i.e. motor learning) (Classen et al., 1998; Cohen et al., 1993; Hlustik et al., 2004; Karni et al., 1995; Koeneke et al., 2006; Pascual-Leone et al., 1995; Perez et al., 2004; Svensson et al., 2003b; Svensson et al., 2006) as well as changes in the orofacial somatosensory environment (Sessle et al., 2007).

The Effects of Sensory Loss or Pain

In rats, trimming or extraction of the mandibular incisors have been associated with a decreased representation of the anterior digastric (AD) muscle in the face MI (Sessle et al., 2007), whereas transection of the lingual nerve results in delayed increases of the GG muscle representation in the face MI (Adachi et al., 2007). In humans, local anaesthesia (LA) of the orofacial tissues has been associated with immediate increases in face MI excitability (Yildiz et al., 2004; Halkjaer et al., 2006), and anaesthesia of the hand muscles, but not the neighbouring non-anaesthetized hand muscles, has also been associated with increases in cortical excitability of the hand MI (Rossini et al., 1994). Additionally, ischemia of the forearm has been associated with immediate increases in hand MI excitability (Cohen et al., 1993; Brasil-Neto et al., 1992; Ridding and Rothwell, 1997; Ziemann et al., 1998a; Ziemann et al., 1998b) as well as a simultaneous decrease in MI excitability associated with the muscles distal to the ischemia (Cohen et al., 1993). In contrast, there is little evidence which supports that changes in cortical excitability of the face MI occur in association with acute noxious stimulation to the orofacial tissues. For example, in humans, capsaicin-induced tongue pain, hypertonic saline-induced masseter muscle pain,

or hypertonic saline-induced masseter muscle pain was not associated with changes in cortical excitability of the face MI (Halkjaer et al., 2006; Romaniello et al., 2000), as measured by transcranial magnetic stimulation (TMS). In rats, changes in cortical excitability of the face MI, as measured by ICMS, also did not occur in association with hypertonic saline-induced tongue pain (Murray et al., 2006), however increases in cortical excitability of the face MI did occur in association with glutamate-induced tongue pain (Adachi et al., 2008). Overall, these aforementioned studies support the notion that acute orofacial pain may not be associated with immediate changes in cortical excitability of the face MI in humans, as measured by TMS.

The Effects of Motor Learning

Psychophysical studies have demonstrated that the incremental acquisition of motor skills follows two distinct stages: first, an early, fast learning stage in which considerable improvement in performance can be seen within a single training session and second, later, slower learning stage in which further gains can be observed across several sessions (and even weeks) of practice (Karni et al., 1998). In addition to these two stages, an intermediate phase corresponding to a consolidation period of the newly learned motor routine has been proposed (Karni et al., 1998; Karni and Sagi, 1993; Brashers-Krug et al., 1996). Finally, with extended practice, the newly learned motor routine is thought to become resistant to both interference and the simple passage of time. Once over-learned, a motor skill can be readily retrieved with reasonable performance despite long periods without practice.

Several brain structures, including the striatum, cerebellum, and motor cortical regions of the frontal lobe, are critical for the acquisition or retention of motor skills. Positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) studies in

humans have revealed multiple representations of a motor movement for the limb MI (Sanes and Donoghue, 2000; Grafton et al., 1993; Schieber, 2001), consistent with ICMS findings that limb MI (Kwan et al., 1978; Sessle and Wiesendanger, 1982) and face MI (Murray and Sessle, 1992a; Huang et al., 1988) of awake monkeys show multiple sites (“nests” or “efferent zones”) that represent a particular motor movement. In humans, TMS studies have revealed that motor learning is associated with MI neuroplasticity (Classen et al., 1998; Cohen et al., 1993; Hlustik et al., 2004; Karni et al., 1995; Koeneke et al., 2006; Pascual-Leone et al., 1995; Perez et al., 2004; Svensson et al., 2003b; Svensson et al., 2006), consistent with ICMS findings in sub-human primate studies (Remple et al., 2001; Kleim et al., 2004; Sessle et al., 2005; Kleim et al., 2002). Additionally, in sub-human primate studies it has been shown that increases in task proficiency are correlated with increases in synaptic efficacy of the MI (Monfils and Teskey, 2004) through processes such as strengthening of horizontal cortical connections in layers II/III (Riout-Pedotti et al., 1998) and increases in synapses per neuron in layer V (Kleim et al., 2002) of the MI. It is generally accepted that the MI is specifically engaged during the acquisition phase of novel motor skills (Sanes and Donoghue, 2000; Ioffe, 2004) in both humans and sub-human primates and that the changes in MI excitability that occur in association with motor learning are not the result of increased muscle or nerve excitability (Muellbacher et al., 2001).

Face MI Neuroplasticity and Motor Learning

In the case of the face MI, cortical neuroplasticity as reflected in an increased excitability of the area of MI representing tongue motor activity (i.e. tongue MI) has also been shown to occur in association with one-week of daily one-hour (Svensson et al., 2003b) and indeed with only one-hour (Svensson et al., 2006) of novel tongue – protrusion training in humans,

and is supported by correlated findings in monkeys trained in an analogous tongue-task (Yao et al., 2002a; Sessle et al., 2005). These monkey studies revealed increases in the proportion of discrete tongue M1 efferent zones and neurons associated with tongue-protrusive movements following 1 - 2 months of novel tongue-task training. The human and monkey data thus indicate that face M1 neuroplasticity may play a significant role in orofacial motor learning.

Overview of Key Unifying Methodologies and Technologies

This section provides an overview of the key and unifying methodologies and technologies that are particularly relevant for this PhD thesis study of the effects of pain on M1 neuroplasticity and novel motor learning. This overview does not, however, cover all of the methodologies or technologies used in the PhD thesis papers (I – IV). Additional information regarding these methodologies and technologies can be found in Appendix A.

Transcranial Magnetic Stimulation (TMS) and Cortical Motor Mapping

A current can be induced in the brain by using a magnetic field. The magnetic field crosses the scalp and skull safely and painlessly (Pascual-Leone et al., 1993). TMS works by concentrating induced eddy currents locally near a target by using a pair of opposing pulsed magnetic fields such as those produced by a figure-of-eight coil. This facilitates stimulation of the motor cortex of the human brain within a 4 mm (Noirhomme et al., 2002) to 5 mm resolution (Ueno, 1999), and is reproducible within a 1 mm range. Most TMS studies use a figure-of-eight coil for precision; however other stimulation properties such as duration, intensity, and frequency tend to vary between studies.

Since the motor cortex has direct projections to the spinal cord and cranial nerve motor nuclei, TMS can produce a visible twitch in a resting muscle. By producing a visible twitch, or using EMG records, motor threshold measures (T) can be quantified and the focal point 'hot spot' can be determined in the motor cortex for that target muscle. Incremental movements away from the hot spot can also generate a motor map of the target muscles. The centre of gravity (CoG) of these motor maps can then be calculated and used to visualize reorganization features and quantify changes in, for example, the face MI area. Motor cortical stimulus – response curves plot the size of the EMG potential or muscle twitch, otherwise known as the motor evoked potential (MEP, Fig 2) evoked by TMS at a fixed site on the scalp at a range of different intensities. One disadvantage of these methods is that current can spread away from the focal point of stimulation, thus the size of the motor map and distribution of excitability within should be considered in regards to these limitations (Toga and Mazziotta, 2002). Currently, TMS cannot distinguish between changes in cortical organization and changes in excitability, as both can occur simultaneously. In this PhD thesis study the term 'reorganization' is used to describe neuroplasticity associated with an expansion/contraction or shift in the CoG of a motor map which represents a peripheral extremity, and 'changes in cortical excitability' as a quantifiable change in an MEP for a given cortical stimulation site.

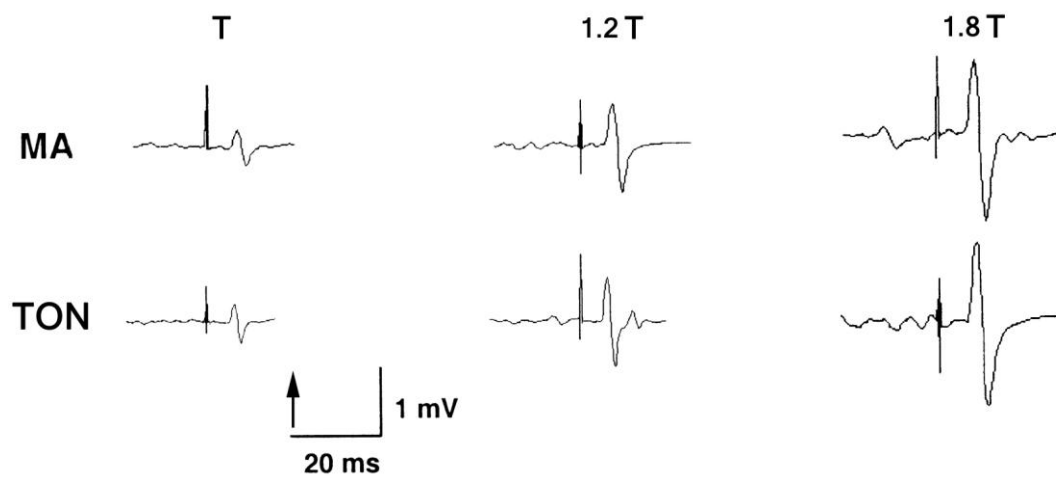


Fig 2: Examples of TMS – MEPs for the masseter (MA) and tongue (TON) muscles at increasing % TMS output intensities based on motor thresholds (T) for the tongue and masseter (Paper II).

Capsaicin Pain Model

Topical application or intradermal injection of capsaicin is a widely used method in humans to induce experimental pain together with peripheral and central sensitization. Capsaicin, is an ingredient of hot peppers, and has been shown to bind to the vanilloid receptor (TRPV1) (Caterina et al., 1997; Caterina and Julius, 2001) on nociceptive afferent endings and may sensitize polymodal A-fibers (Kenins, 1982; LaMotte et al., 1992; Beydoun et al., 1996; Magerl et al., 1987; Rau et al., 2007) or C-fibers (LaMotte et al., 1992; Rau et al., 2007; Baumann et al., 1991). In this PhD thesis study, topical application of capsaicin was administered to the orofacial tissues in humans order to evoke one or all of the following: intense burning pain, spontaneous pain, allodynia, hyperalgesia and neurogenic inflammation (the area of redness extending beyond the site of application). The barrage of nociceptive afferent input, following capsaicin application, can lead to a prolonged functional alteration in the nucleus caudalis, as shown in sub-human primate studies, known as central sensitization of trigeminal second-order neurons in the caudal trigeminal nucleus. This central sensitization, following noxious stimulation to the orofacial tissues, can be reflected by a lowering of the activation threshold, receptive field expansion, increased response to afferent stimulation, or the recruitment of silent nociceptors, (Sessle, 2001; Bartsch and Goadsby, 2003).

Assessment of Experimental Pain and Sensory loss

Pain is described as an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage (Merskey and Bogduk, 1994). In this PhD thesis study, the subjective experience of pain was measured

with a visual analog scale (VAS), which is a reliable and valid method for measuring the intensity of clinical or experimental pain (Price et al., 1994). Unless otherwise stated, the VAS used in this thesis investigation consisted of a 10 cm vertical line labelled with anchor points 0 = no pain and 10 = most pain imaginable. In addition, changes in response to mechanical afferent stimulation, following noxious stimulation or application of a local anaesthetic to the orofacial tissues, were measured by nylon hair von Frey filaments. A large number of studies have successfully used von Frey filaments as a means to assess (non-noxious) touch sensations in the oral mucosa (Jacobs et al., 2002).

Tongue - task Training Regime

Rationale

In this PhD thesis study, there were practical and clinical reasons for choosing a tongue – task training regime. One practical reason for choosing a tongue – task training regime is that the tongue has a large representation in the MI which makes the tongue MI easily accessible for TMS. Additionally, the tongue-task training regime, consists of tracking a moving target box by controlling tongue-protrusion force output, and is considered to be an extremely novel visual-motor task when compared to, for example, finger tapping and hand-arm pointing and reaching motor tasks. Clinical reasons for choosing a tongue – task training regime include the common occurrence of pain in the tongue, such as burning mouth syndrome (glossodynia) (Locker and Grushka, 1987; Lipton et al., 1993; Tammiala-Salonen et al., 1993; Thorstensson et al., 1996), or in the trigeminal region, such as temporomandibular disorders (Gesch et al., 2004; Marklund and Wanman, 2007) and craniofacial neuralgias (Manzoni and Torelli, 2005). Additionally, the tongue has an

essential role in various sensorimotor functions, such as mastication, swallowing and speech, which are commonly affected in neurologically impaired adults or post-stroke patients.

Tongue – task training

In this PhD thesis study, all subjects performed a modified version of a novel tongue-task training regime (Fig 3) that was first described and used in monkeys (Murray et al., 1991) and later implemented in human tongue-task training studies (Svensson et al., 2003b; Svensson et al., 2006; Boudreau et al., 2007). All subjects sat in a dental chair with their forehead and chin placed into a headrest and chinrest, respectively. The headrest and chinrest were affixed to the dental chair which ensured a consistent head position and a tongue protrusion distance to a force lever that was located directly in front of the subject. An easily viewable computer screen was also located directly in front of the subject.

In this PhD thesis study a tongue-task training session consisted of repeating 72 or 144 tongue-task training trials, which resulted in a training time of 15 or 30 min, respectively. Tongue task training was defined as the attempt to accomplish the goal set for each tongue task trial within the tongue-task training regime. The goal of a tongue-task trial was to maintain a cursor (0.25 cm x 0.25 cm) within a moving target box (0.5 x 0.5 cm). At all times the location of the cursor relative to the moving target box, as shown in Fig 3, was displayed on the computer screen such that subjects had a constant visual feedback of their current performance. At the onset of a tongue-task training trial, the target box vertically ascended 4 cm from the baseline position (ascending phase) at a rate of 4 cm/s (target box rise time) to a holding position (holding phase) where it remained for 1.5 s then vertically descended back to the baseline position (descending phase) at a rate of 4 cm/s. In order to maintain the cursor within the moving target box subjects were required to

generate an appropriate amount of tongue-protrusion force onto the surface of the force lever. Changes in the pressure applied to the force lever resulted in a vertical displacement of the cursor position. A 4 cm vertical displacement of the cursor, as displayed on the computer screen, from the baseline position was calibrated to a force of 1 N. Thus, the ascending and descending rates of the target box in the ascending and descending holding phases, respectively, was equivalent to 0.25 N/s. A rest period of 10 s occurred between each tongue task trial.

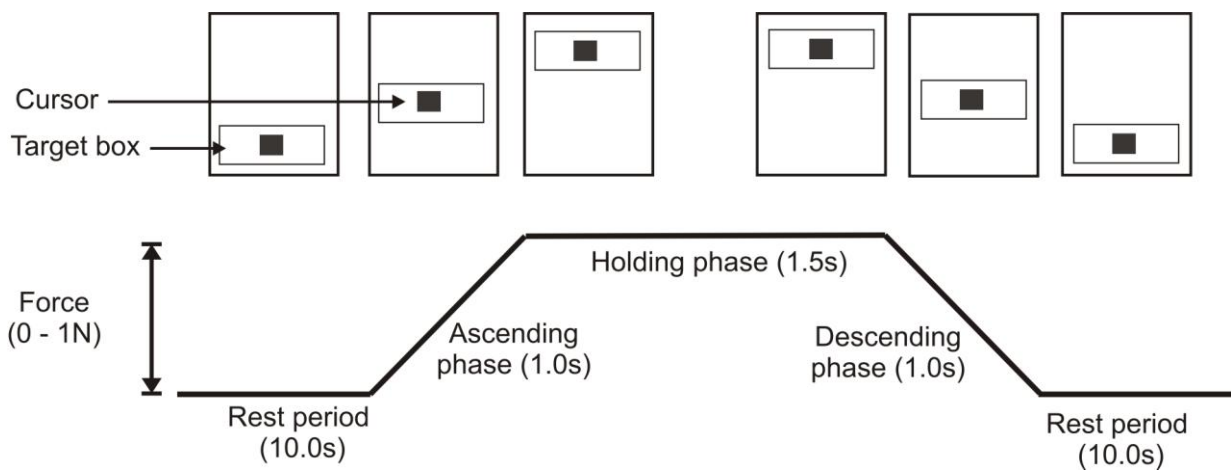


Fig 3: Schematic of the tongue – task training regime which shows the location and motion of the target box and the cursor movement, as controlled by tongue – protrusion force output, for a single tongue-task training trial (upper drawing) and the associated force output curve with respect to time for the cursor (lower drawing; drawing not to scale).

Thesis Hypothesis and Structure

This PhD thesis study is based on four papers (I – IV), as described schematically in Fig 4. The main hypothesis of this PhD thesis study is that orofacial pain modulates the primary motor cortex (MI) neuroplasticity and motor performance associated with novel tongue-task training in humans. However, before addressing the main hypothesis of this PhD thesis study, the sensory and vascular responses produced by topical application of capsaicin cream to the tongue dorsum were first determined (Paper I). In addition, the notion that orofacial pain is not associated with cortical neuroplasticity of the face MI was further addressed by determining if noxious stimulation with capsaicin to the periodontal ligament of lower incisor is associated with cortical neuroplasticity of the face MI (Paper II). The third study (Paper III) specifically addressed the main hypothesis of this present thesis and determined the effects of experimental orofacial pain on the cortical neuroplasticity of the tongue MI associated with novel tongue – task training. The main findings of third study initiated the fourth study (Paper IV), which is a comprehensive and detailed analysis of motor behaviour which investigated the effects of training time, sensory loss, and pain on motor learning associated with novel tongue – task training. All the experimental studies associated with the PhD thesis papers were carried out on healthy male or female volunteers and conducted according to the Declaration of Helinski.

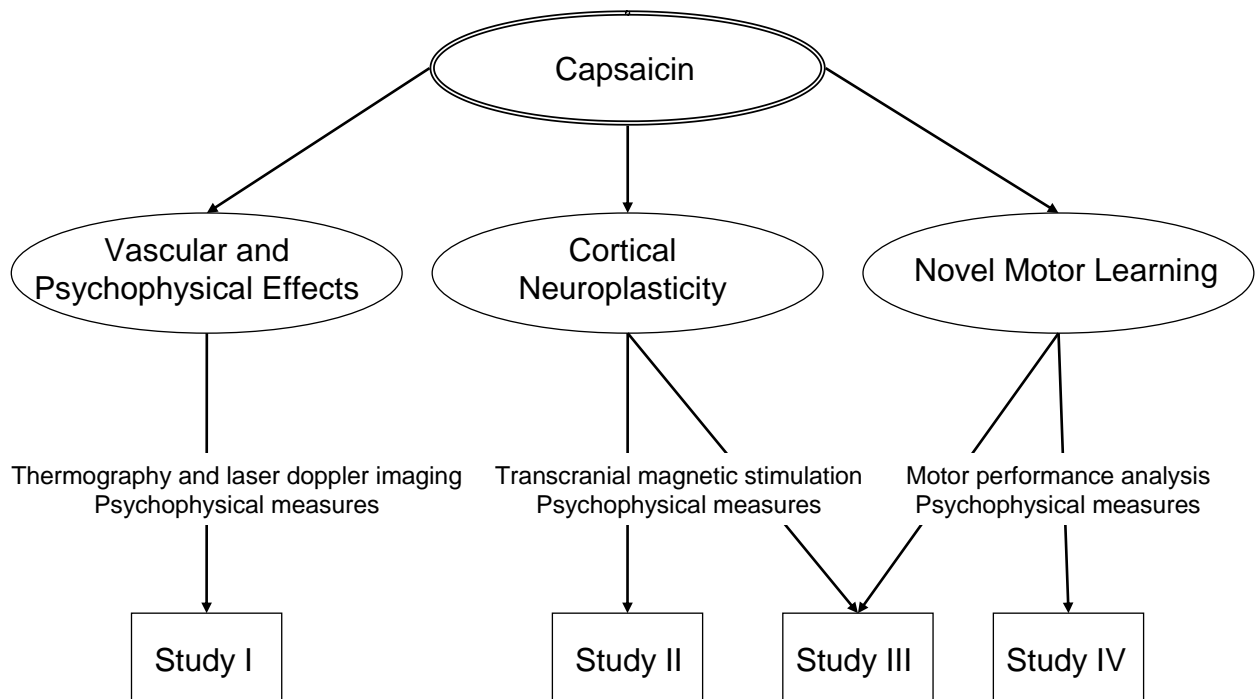


Fig 4: Thesis structure for the four papers (I – IV) which have examined the effects of noxious stimulation with capsaicin to the orofacial tissues on vascular and psychophysical responses (Paper I), cortical neuroplasticity of the face MI as assessed by transcranial magnetic stimulation (Paper II and III), and novel orofacial motor learning as assessed by a comprehensive analysis of motor behaviour (Paper III and IV).

Specific Aims, Methodology and Results for Papers I – IV

This section states the specific aims of the PhD thesis papers I through IV, gives a general overview of the associated methodology and results, and specifically highlights any results that have a fundamental impact on the main hypothesis of this present PhD thesis study. A detailed description of the methodology and technology used in these papers can be found in Appendix A.

Paper I: Vascular and Psychophysical Effects of Topical Capsaicin

Application to Orofacial Tissues

Aim: To characterize and contrast the changes in sensory and vascular responses produced by topical application of capsaicin cream to the glabrous lips and tongue dorsum.

Overview of Methodology

This study consisted of 2 experimental sessions, separated by a minimum of 24 hrs, and each session consisted of a capsaicin and a vehicle trial. Subjects received 1 ml of topical application of 1% capsaicin or vehicle cream to the glabrous skin of the upper and lower lips or to the dorsal surface of the tongue for 5 min. Thus, the 2 sessions included a capsaicin-lip trial, vehicle-lip trial, capsaicin-tongue trial, and a vehicle-tongue trial. Application of capsaicin or vehicle cream to the glabrous lips and tongue was randomized between the first and second sessions. Cross-contamination of capsaicin cream was

eliminated by performing the vehicle trial first and the capsaicin trial second. In each session, a rest interval of 20 min occurred between the capsaicin and vehicle trial.

Subjects rested in a supine position on a comfortable bed for the duration of each trial, with the exception the 20 min rest interval before the onset of the second trial at which time they were able to sit or stand up. Before baseline measures were performed all subjects rested in a supine position in the bed for approximately 3 min. For each trial, vascular changes were objectively measured by laser-Doppler imaging and thermography and are reported as changes in blood flow and changes in temperature, respectively. The area of capsaicin-induced flare was traced by the investigator onto acetate sheets. Mechanical sensitivity tests were determined by using a von Frey filament. Burning pain intensity was recorded on an electronic visual analog scale (VAS) and burning pain area was outlined by the subjects on drawings of the orofacial area that included the lips and tongue. All of the above measures were recorded immediately before and at 5, 15, and 30 min after capsaicin or vehicle cream application. For each capsaicin and vehicle trial, a modified version of the McGill Pain Questionnaire (MPQ) (Melzack, 1975) was completed immediately after the last measurement in order to determine common pain quality descriptors for each trial. The order of measurements were: (1) blood flow, (2) temperature, (3) mechanical sensitivity tests, (4) visual flare, if present, (5) completion of orofacial drawings, and (6) completion of the modified MPQ. For the capsaicin and vehicle trials, recordings of burning pain intensity began immediately before and continued until 30 min post-application.

General Results

Overall, this study has shown that there are some similarities but several differences between the responses evoked by noxious stimulation of the glabrous lips with capsaicin compared to those evoked from the tongue. The main findings were that the burning pain and increases in blood flow and temperature occurred after 5 min of capsaicin application to the glabrous lips and tongue and greater increases in blood flow and temperature accompanied more intense burning pain and larger areas of perceived pain for the lips compared to the tongue. Additionally, the location of distinct areas of increased temperature differed between the capsaicin-lip and capsaicin-tongue trials. Lastly, capsaicin application to the glabrous lips and tongue did not alter the mechanical sensitivity in these tissues. The several differences between these responses to noxious stimulation of the glabrous lips and tongue may have implications for examinations of orofacial somatosensory functions

Highlighted Results

Burning pain was indicated by all subjects after capsaicin, but not vehicle, cream application to the tongue or glabrous lips and was associated with an increase in temperature and blood flow (Fig 5). However, the increases in blood flow and temperature in the capsaicin-tongue trials were lower when compared to the capsaicin-lip trials. Additionally, the burning pain intensity at 30 min was lower compared to the burning pain intensity at 5 min for both the capsaicin-lip and tongue trials. Compared to the vehicle trials, there was no difference in the ratings of mucosal mechanical sensitivity at the tongue site after capsaicin application to the tongue. Overall these present findings show that capsaicin application to the tongue is associated with a moderate, but decreasing,

burning pain intensity for a minimum of 30 min and that capsaicin application to the tongue does not alter the (non-noxious) tactile feedback in the tongue. This finding has a direct implication on the methodological considerations associated with the main hypothesis of Study III which aims to determine the effects of experimental orofacial pain on motor performance and cortical neuroplasticity of the tongue MI associated with novel tongue-task training in humans. Ideally, a moderate constant burning pain should occur during novel tongue-task training, and these findings suggest that, if needed, an additional application of capsaicin cream to the tongue may be required to maintain a moderate burning pain sensation.

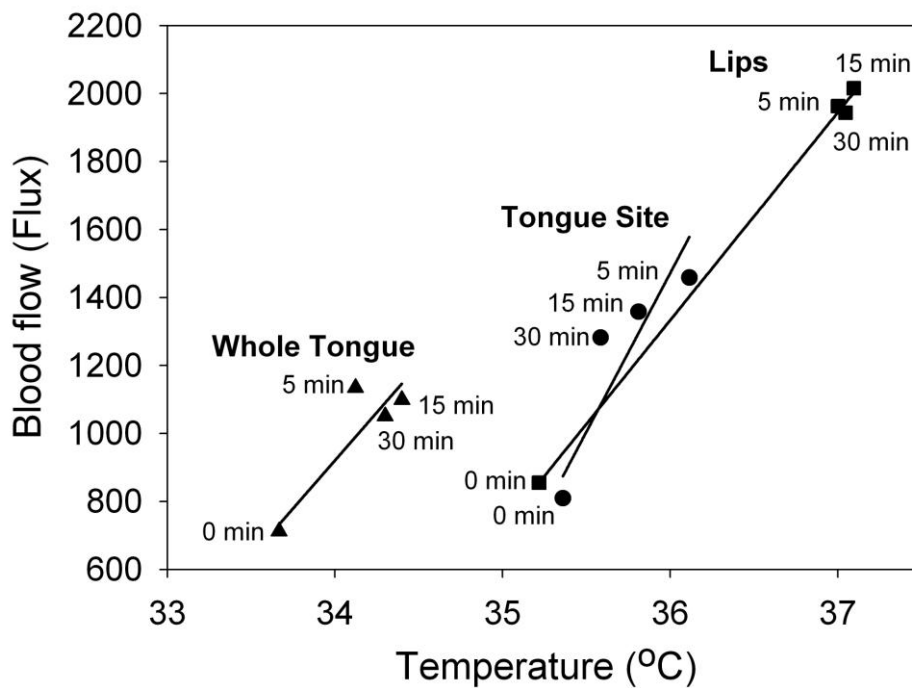


Fig 5: Correlated increases in blood flow and temperature with respect to time for the whole tongue (▲), tongue site (●), and glabrous lips (■) (Paper I).

Paper II: Effects of Periodontal Afferent Input on Corticomotor Excitability in Humans

Aim: To determine if cortical neuroplasticity of the tongue or masseter MI is associated with experimental pain or a transient loss of sensory afferent feedback in the periodontal ligament.

Overview of Methodology

In one of two randomized sessions, separated by one week, subjects received an injection of the algescic chemical capsaicin or the local anaesthetic carbocain to the superficial mid-portion of the periodontal ligament of the lower incisor. Transcranial magnetic stimulation (TMS) was applied to the MI in each session and motor evoked potentials (MEP) were recorded from the tongue musculature, masseter, and first dorsal interosseous (FDI, control) muscle. All MEPs were quantified in terms of peak-to-peak amplitude and area under the curve (AUC) and used to construct TMS – MEP stimulus – response curves and corticomotor maps for the tongue musculature, masseter and FDI muscles. TMS – MEP stimulus – response curves followed by corticomotor maps were constructed before, immediately, 30 and 60 min after injection of capsaicin or carbocain to the superficial mid-portion periodontal ligament. For each session, the TMS – MEP stimulus – response curves and corticomotor maps were based on the motor threshold for the tongue, masseter and FDI muscles. For the stimulus – response curves the increments in % TMS output were 10% motor threshold (T). Corticomotor maps were constructed using the MEPs evoked by a % TMS output that was equivalent to a 110% motor threshold (1.1T) at five predefined sites located over the jaw and tongue MI area. The centre of gravity (CoG)

of these corticomotor maps were then calculated in order to give an amplitude weighted map position of cortical excitability for the tongue or jaw muscle. Self – assessed burning-pain intensity was recorded throughout each capsaicin or carbocain session on an electronic version of a visual analogue scale (VAS). Subjects were asked to rate the intensity of the (non-noxious) mechanical sensation produced by application of a von Frey filament (10 g) to the superficial mid-portion (injection site) on a VAS scale prior to the acquisition of each TMS – MEP stimulus response curve.

General Results

The main findings in this present study (Paper II) were that injection of carbocain, a local anaesthetic or capsaicin, an algescic chemical, to the superficial mid-portion of the periodontal ligament of the lower human incisor was not associated with changes in cortical excitability of the tongue and masseter MI, as measured by peak-to-peak and AUC TMS – MEP stimulus response curves and corticomotor maps. These results suggest that (1) changes in periodontal afferent feedback of a single incisor may be insufficient in producing changes in cortical excitability of the face MI (2) that pain or a transient loss of afferent feedback in the periodontal ligament may not be associated with changes in cortical excitability of the face MI, as measured by TMS - MEPs elicited in the tongue or masseter muscles.

Highlighted Results

Compared to baseline, injection of capsaicin to superficial mid-portion of the periodontal ligament of the lower human incisor resulted in burning pain (6.4 ± 1.0 cm) and was associated with an increased mechanical sensation, as produced by application of the von

Frey filament to the superficial mid-portion of the periodontal ligament. However, burning pain in the periodontal ligament had no main effect on the peak-to-peak amplitude of the TMS – MEPs at all % TMS outputs or the centre of gravity (CoG) of the peak-to-peak and AUC TMS – MEP motor maps for the masseter muscle. Similar results were also found for the tongue musculature. The intense burning pain in the periodontal ligament had no effect on the peak-to-peak amplitude or AUC of the TMS – MEPs at all % TMS outputs or the CoG of the corticomotor maps for the tongue musculature. Overall these present findings showed that capsaicin application to the superficial mid-portion of the periodontal ligament of the lower incisor was associated with intense burning pain but not cortical neuroplasticity or reorganization of the face MI. Furthermore these present findings support the notion that acute experimental orofacial pain is not associated with changes in cortical excitability of the face MI in humans, as measured by TMS. Therefore, this present study (Paper II) has shown that capsaicin application to the tongue is a suitable method to investigate of the modulatory effects of acute orofacial (tongue) pain on motor performance and the changes in cortical excitability of the tongue MI, as measured by TMS, associated with short-term novel tongue-task training.

***Paper III: The Effects of Intra-oral Pain on Motor Cortex Neuroplasticity
Associated with Short-term Novel Tongue-task Training***

Aim: To determine if short-term (15 min) novel tongue-task training is associated with rapid changes in the cortical excitability of the tongue MI, and if noxious stimulation with capsaicin to the tongue modulates the motor performance and cortical excitability of the tongue MI associated with short-term novel tongue-task training.

Overview of Methodology

In one of the two experimental sessions 1 ml of vehicle or 1% capsaicin cream (Pharmacy of Aalborg Hospital, Aalborg, DK) was applied to the tongue at the onset of a 15 min tongue-task training regime. The vehicle and capsaicin tongue-task training sessions were randomized, and the subjects were unaware of which cream they were to receive. The first dorsal interosseous (FDI) was chosen as an internal control since this muscle has been commonly used to demonstrate neuroplasticity of the FDI MI associated with novel motor training of the FDI muscle. TMS was applied to the MI in each session and motor evoked potentials (MEPs) were recorded from the tongue musculature and the FDI muscle (as control). TMS – MEP stimulus-response curves were constructed prior to and again immediately after each 15 min tongue-task training session. The subjects rested in a comfortable chair for 5 min before TMS was applied to the MI. The subjects were also instructed to relax and not to concentrate on any particular subject. The FDI MEPs were measured prior to the tongue MEPs for the construction of the pre-training and vice versa for the post-training TMS – MEP stimulus-response curves. Tongue - task training

consisted of repeating 72 tongue-task training trials, which resulted in a training time of 15 min. The goal of a tongue-task trial was to track a moving target box by controlling tongue – protrusion force output and this was considered to be particularly novel when compared to, for example, finger tapping and hand-arm pointing and reaching motor tasks.

Overview of Results

This study showed that 15 min of tongue-task training was associated with increased motor performance and enhanced TMS – MEP stimulus-response curves and reduced MEP thresholds of the tongue MI. Also, this is the first study to show that the presence of intra-oral pain reduces motor performance and interferes with the cortical neuroplasticity of the tongue MI that would otherwise occur in association with 15 min of novel tongue – task training in humans. These present findings suggest that nociceptive input modulates the adaptive neuroplastic changes in the MI that is known to occur association with motor learning and may impair the ability to learn a new motor task.

Highlighted Results

Burning pain (5.1 ± 0.6 cm) was indicated by all subjects during capsaicin but vehicle, tongue-task training. A small but significant decrease in burning pain occurred with time for the capsaicin session and only two of the nine subjects had a burning pain intensity below 4 cm on the VAS at time = 7 min, thus a second application of capsaicin cream was administered at this time. The tongue-task trial performance scores of all subjects significantly increased with time for both the vehicle and capsaicin tongue-task training sessions. However, after the first 15 tongue-task trials (approximate time = 3.2 min), the mean performance score for each successive tongue-task trial with respect to time was

significantly less for the capsaicin when compared to the vehicle tongue-task training sessions, and the overall motor performance was lower for the capsaicin when compared to vehicle tongue-task training (Fig 6).

The TMS – MEP stimulus-response curves of the tongue MI for vehicle tongue-task training revealed a significant enhancement of MEPs at the end of the training (post-training) compared to pre-training MEP values at 1.4T and 1.5T TMS intensity levels. In contrast, TMS – MEP stimulus-response curves of the tongue MI for the capsaicin session revealed no significant difference between the pre and post-training MEPs of the tongue MI at all TMS intensity levels. A decrease in the tongue MI threshold was found post-training for vehicle but not capsaicin tongue-task training (Fig 6). The pre-training TMS – MEP stimulus-response curves of the tongue MI for the first did not differ from the second tongue-task training session. These present findings showed that rapid cortical neuroplasticity of the tongue MI was associated with 15 min of novel tongue-task training and this may reflect the mechanisms that mediate the slowly evolving neuroplastic changes associated with long-term novel motor learning. Additionally, the absence of these neuroplastic changes in the tongue MI associated with 15 min novel tongue-task training for the capsaicin session suggests that pain interferes with motor learning processes.

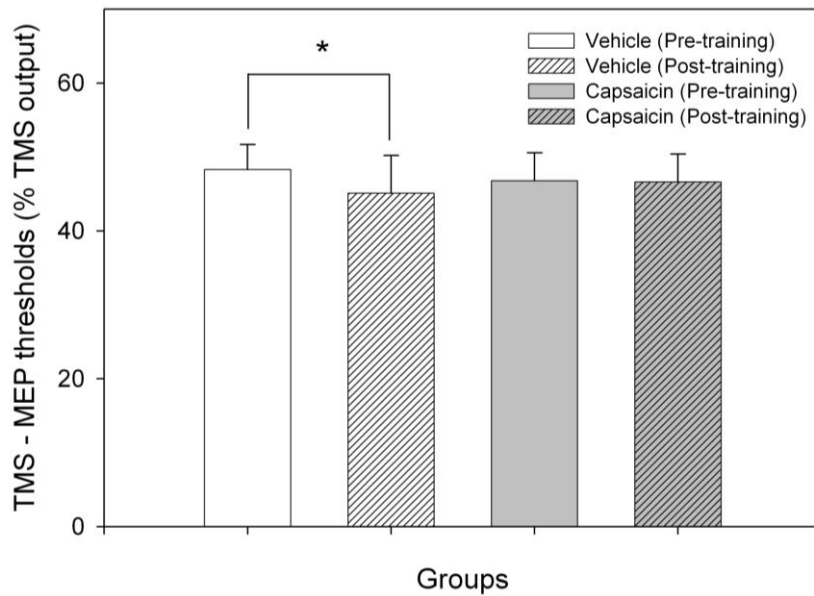
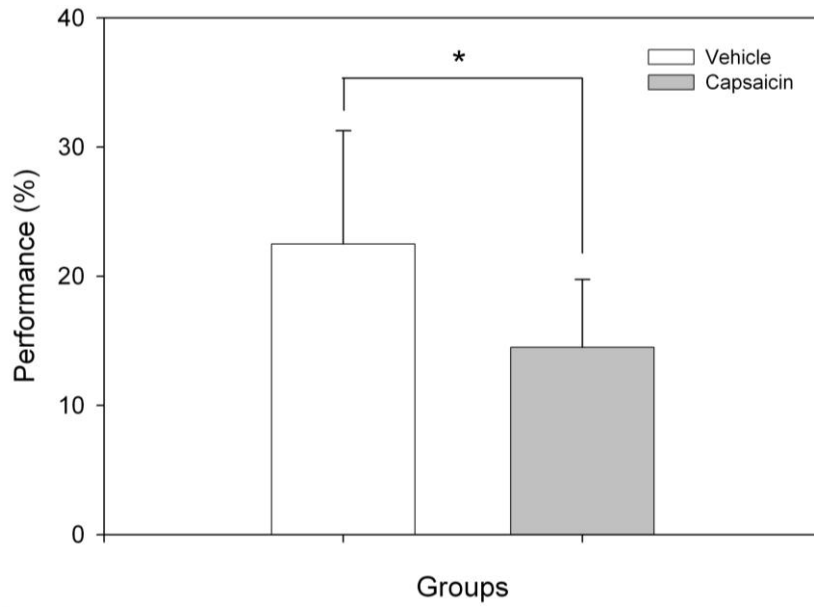


Fig 6: Motor performance (upper) and TMS – MEP thresholds (lower) for the vehicle and capsaicin tongue – task training groups.

Paper IV: The Effects of Training Time, Sensory Loss, and Pain on Motor Learning in Humans

Aim: To determine the effects of (A) within-session task-repetitions (72 vs. 144) on the time course of motor learning in a long-term novel tongue task training regime and (B) intra oral pain or sensory loss via capsaicin or lidocaine application, respectively, to the tongue on motor learning in a short-term novel tongue-task training regime.

Overview of Methodology

Experiment A consisted of two subjects groups that trained daily on the novel tongue-task for seven consecutive days and again one week post-training. The training sessions consisted of 15 or 30 min of tongue-task training each day, which resulted in 72 or 144 within-session task-repetitions, respectively. Subjective evaluations of training were recorded from each subject on a visual analog scale (VAS) immediately after the conclusion of each tongue-task training day. These evaluations included fatigue, as measured on a 0 – 7 categorical VAS, task complexity, as measured on a 0 – 7 categorical VAS, and overall motor performance, as measured on a 0 – 10 numerical VAS. Experiment B addressed the second aim and consisted of three subject groups that trained once for 15 min (72 within-session task-repetitions) following topical application of lidocaine gel, capsaicin cream, or vehicle cream to the dorsum of the tongue tip. Subjective evaluations of mucosal mechanical sensitivity and burning pain were recorded from each subject on a on a 0 – 10 cm numerical VAS. Mucosal mechanical sensitivity was recorded immediately before and after each lidocaine application prior to tongue-task

training and immediately after training; burning pain was recorded immediately before and every minute during capsaicin or vehicle tongue-task training. All subjects trained in the same novel tongue-task, which required subjects to track a moving target box by protruding their tongue onto a fixed force lever. A detailed analysis of motor behaviour was performed for all subject groups in order to assess motor learning. Motor behaviour was measured in terms of overall and initial motor performance, within-session gains in motor performance, reaction times as well as associated motor performance variables which quantified peak type and error relative to the moving target box (Fig 7).

Overview of Results

A detailed analysis of motor behaviour, revealed (A) that significantly different within-session gains in the initial training session (i.e. 72 vs. 144 task-repetitions) did not differentially affect the time course of the initial (reflective of sleep-dependent improvements) or overall motor performance in subsequent training sessions, as measured for seven consecutive daily training sessions and again one-week post-follow up. (B) Compared to vehicle, lidocaine and capsaicin tongue-task training showed reduced overall motor performance. For the lidocaine group, the detailed analysis of the motor behaviour revealed exaggerated undershoot errors and delayed reaction times and for capsaicin group, exaggerated overshoot and undershoot errors as well as delayed reaction times. It is concluded that, extended within-session task-repetition does not facilitate additional gains in overall motor performance and that sensory loss or pain do not inhibit but hinder motor learning.

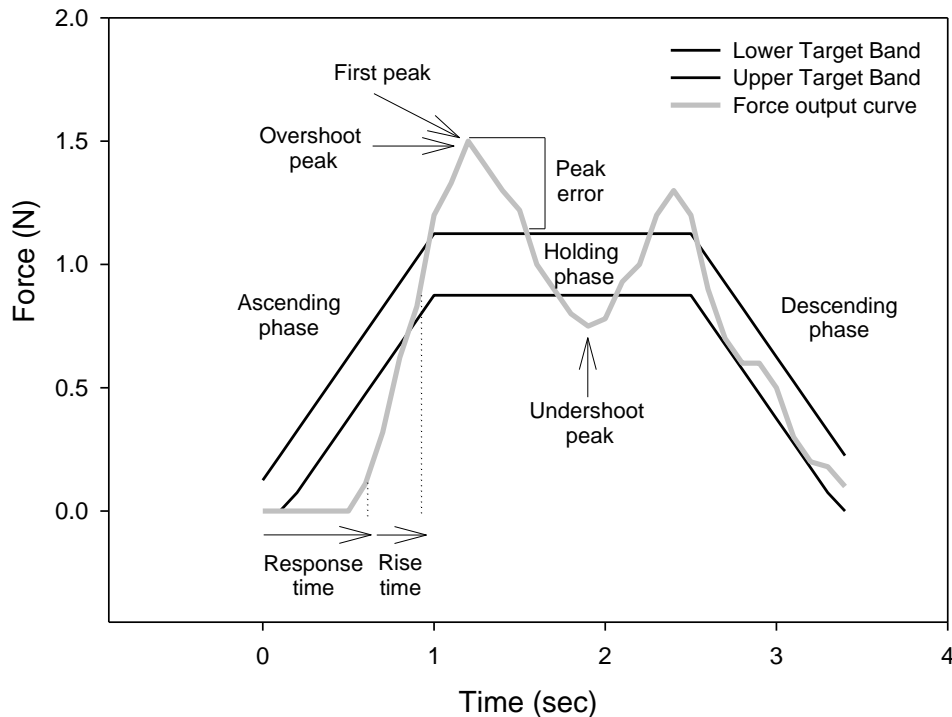


Fig 7: Illustration of a force output curve with respect to time for a tongue-task training trial and the associated motor performance variables that were used for a comprehensive analysis of motor behaviour in Experiments A and B (Paper IV).

Highlighted Results

Experiment A

There was no effect of within-session task-repetitions (72 vs. 144) on the evaluation of overall motor performance, tongue-task complexity, or fatigue, nor was there an interaction with training sessions. There was a main effect of training sessions on the subjective evaluation of overall motor performance and tongue-task complexity, but not fatigue (Fig 8). The comprehensive analysis of motor behaviour revealed that there was no effect or interaction of within-session task-repetitions on the overall or initial motor performance. There was, however, a main effect of training sessions on the initial motor performance. There was no main effect of within-session task-repetitions on the within-session gains in

motor performance, although there was an interaction and a main effect of training sessions. There was no main effect of within-session task-repetitions on the reaction time or main effect of training sessions. The reaction time, an indirect measure of attention, was 633.0 ± 60.0 msec and 599.0 ± 64.0 msec for the 15 and 30 min tongue-task training groups, respectively. These results show that extended with session training (i.e. more than 15 min each day) may not facilitate additional gains in overall motor performance and that the gains in overall motor performance occurred as a result of training and not reduced fatigue or increased attention.

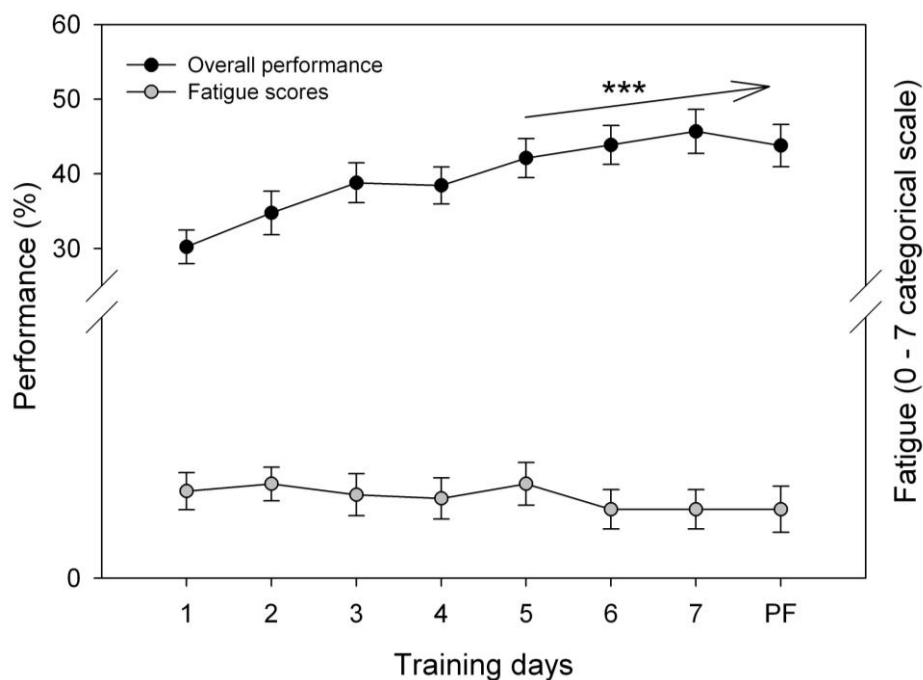


Fig 8: The grouped overall performance and the subjective evaluation of tongue fatigue for the 15 and 30 min tongue – task training groups. The *** → represent a significant increase in performance when compared to training day 1.

The detailed analysis of motor behaviour associated with novel tongue-task training revealed a main effect of training sessions on the error for the overshoot and undershoot

peaks, as well as a decrease in the percentage of undershoot first-peaks. Additionally, it was also found that improvements in motor performance occurred in the holding as well as the ascending phase of the tongue-task, with the former occurring prior to the latter. Lastly, there was no effect of training sessions on the total number of peaks per tongue-task trial and this finding may reflect the inherent biomechanics (tremors or oscillations) of the tongue.

Experiment B

Burning pain was indicated by all subjects during capsaicin but not vehicle tongue-task training and decreased with time however, the burning pain intensity did not drop below 4 on the VAS. A decrease in mucosal mechanical sensitivity of the tongue tip for all subjects in the lidocaine group occurred prior to the onset of tongue-task training and was maintained throughout tongue-task training. The overall performance was lower for the capsaicin and lidocaine when compared to the vehicle tongue-task training group. The initial performance (first 5 tongue-task trials) for the capsaicin but not the lidocaine was lower when compared to the vehicle tongue-task training group. Additional analyses revealed that the mean of the first 10 tongue-task trials for the lidocaine was lower when compared to the vehicle tongue-task training group. Their reaction time for the capsaicin and lidocaine were longer when compared to the vehicle tongue-task training group, which suggests that attention may have been a contributing factor to the reduced overall motor performance in the lidocaine and capsaicin tongue-task training groups. However, all tongue-task training groups had a within-session gain significantly greater than zero. These present results suggest that pain or sensory loss reduces motor performance and interferes with motor learning but small gains in motor performance can still be achieved.

The detailed analysis of the motor behaviour associated with novel tongue-task training revealed that the error of the all undershoot peaks (including first-peaks) was greater for the lidocaine and capsaicin when compared to vehicle tongue-task training group. However, exaggerated errors in all overshoot peaks (excluding first-peaks) were found for the capsaicin when compared to the vehicle tongue-task training group. A distinct pattern of peak type (Fig 9) and error for each tongue – task training group was also found and this finding suggests that sensory loss and pain may differentially affect the motor performance associated with novel tongue-task training.

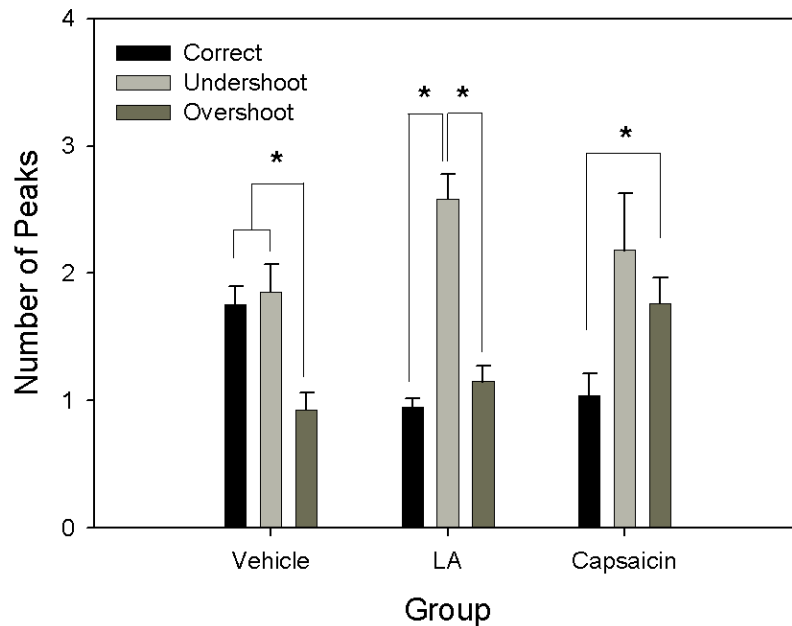


Fig 9: The proportions of correct, overshoot, and undershoot peaks per tongue – task trial for the vehicle, lidocaine (LA), and capsaicin tongue – task training groups. * indicates significant difference between the peak types.

Discussion, Summary of Main Findings, and Future Directions

Capsaicin (Tongue) Pain

Topical application of capsaicin to the tongue dorsum can result in moderate burning pain and associated increases in temperature and blood flow in the tongue (Paper I). Additionally, this burning pain can be sustained for a minimum of 30 min and during this time (non-noxious) tactile feedback, as measured by von Frey hair, on the tongue dorsum is unaltered (Paper I). These findings are consistent with (Baad-Hansen et al., 2003) which showed that moderate burning pain in the alveolar mucosa was not associated with mechanical allodynia (static or dynamic) or hyperalgesia in the alveolar mucosa following topical application of capsaicin to the gingiva. It is well known that capsaicin, is an algescic substance that can be isolated in 'hot' chili peppers and topical application or intramuscular injection of capsaicin is associated with burning pain, visual flare, mechanical or heat hyperalgesia, and vasodilatation (Simone et al., 1989; Simone and Ochoa, 1991; Serra et al., 1998; Takahashi et al., 1999; Wasner et al., 1999; Baron et al., 1999; Andrews et al., 1999; Fuchs et al., 2000; Mohammadian et al., 1998; Sumikura et al., 2003b; Sumikura et al., 2003a; Gazerani et al., 2005). More specifically, capsaicin has been shown to bind to the vanilloid receptor (TRPV1) (Caterina et al., 1997; Caterina and Julius, 2001) in nociceptive afferent endings and may sensitize these nociceptors (Kenins, 1982; Baumann et al., 1991; LaMotte et al., 1992; Beydoun et al., 1996; Magerl et al., 1987; Rau et al., 2007). Indeed, nociceptors which express TRPV1 have been identified in the circumvallate, foliate, and fungiform papillae of the tongue (Ishida et al., 2002) and the TRPV1 receptors found in the fungiform papillae may also be co-localized with

neurogenic inflammatory mediators (Ishida et al., 2002). Additionally, injection of capsaicin into the rat tongue has been associated with the expression of extracellular signal-regulated kinase phosphorylation in nociceptive brainstem relay regions of the trigeminal somatosensory system (Honda et al., 2008). However, despite the evidence that capsaicin induces burning pain in addition to neurogenic responses, such as increased blood flow and temperature, as was found in study I, capsaicin application to the tongue in healthy humans is not associated with peripheral or central changes, as measured by transcranial magnetic stimulation (TMS) in the tongue corticomotor pathways (Halkjaer et al., 2006). However, there is evidence that acute experimental pain is associated with cortical neuroplasticity of the primary motor cortex (MI) in humans, as measured by TMS.

Cortical Neuroplasticity and Pain

There appears to be a growing trend which indicates that the site of an acute noxious stimulus can differentially modulate the cortical excitability of the MI. In spinal systems, for example, decreased cortical excitability of the MI, as measured by TMS, occurs in association with topical application of capsaicin to the hand (Cheong et al., 2003; Farina et al., 2001))} and injection of hypertonic saline into the abductor digiti minimi and/or FDI (Le Pera et al., 2001; Svensson et al., 2003a). However, increased cortical excitability of the MI for the hand muscles and a simultaneous decrease, as measured by TMS, for the proximal (upper arm) muscles has been shown to occur in association with noxious electrical stimulation of the finger (Kofler et al., 1998). The findings of Kofler et al., (1998) are in agreement with the Pain Adaptation Model (Murray and Peck, 2007; Lund et al., 1991) and suggest that the changes in cortical excitability of the MI may contribute to

protective motor control strategies (e.g. reduced range of motion) that can occur in association with a painful limb or muscle. In the case of the trigeminal system, however, there is little evidence which supports that acute noxious stimulation to the orofacial tissues modulates the cortical excitability of the face MI. For example, in humans, topical application of capsaicin to the tongue or cheek, as well as injection of hypertonic saline into the masseter muscle was not associated with changes in cortical excitability of the face MI, as measured by TMS (Halkjaer et al., 2006; Romaniello et al., 2000). Furthermore, injection of capsaicin into the superficial mid-portion of the periodontal ligament of the lower human incisor was not associated with changes in cortical excitability of the tongue or masseter MI, as measured by TMS (Paper II). In rats, changes in cortical excitability of the face (tongue) MI, as measured by ICMS thresholds, also did not occur in association with injection of hypertonic saline-into the tongue (Murray et al., 2006) however, decreases in cortical excitability of the tongue MI did occur in association with glutamate injection (Adachi et al., 2008). These conflicting findings, mainly between the spinal and trigeminal motor systems, indicate that the effects of acute noxious stimulation on the cortical excitability of the MI may be dependent upon, in addition to methodological considerations, within MI cortico-cortico motor connections. In the spinal system, for example, one could argue that acute muscle pain may differentially modulate the excitability of the cortical areas associated with the antagonist or agonist muscle groups, as can be interpreted by the results of Kofler et al., (1998). Furthermore, the magnitude of the change in cortical excitability of these cortical areas may largely depend on the size of the cortical representation of the involved muscles as well as the strength of the within MI cortico-cortico connections between the muscle groups. In the case of the trigeminal system, for example, the cortical excitability of the masseter MI following noxious

stimulation to the tongue, or vice versa, has not been investigated. It is well known that the tongue and masseter muscles have a dually significant role in a number of complex orofacial sensorimotor functions (Lowe, 1980), such as such as speech (Murray et al., 2006; Hiitemae and Palmer, 2003), mastication (Hiitemae and Palmer, 2003; Dellow and Lund, 1971), and swallowing (Lowe and Sessle, 1973; Sawczuk and Mosier, 2001), thus it is conceivable that noxious stimulation to the tongue, for example, may differentially modulate the cortical excitability of masseter MI. Future studies are required to further clarify the effects of noxious stimulation to the orofacial tissues on the excitability of the face MI in humans, with a particular focus on adjacent or proximal cortical representations of the non-stimulated orofacial muscles. Such studies may provide additional insight into the maintenance of pain in chronic pain conditions as well as the associated alterations in orofacial motor control strategies. Nonetheless, the results from this PhD thesis study provide additional evidence that noxious stimulation with capsaicin to the intra oral tissues does not modulate the cortical excitability of the tongue or masseter MI, as measured by TMS in humans. Interestingly, changes in cortical excitability of the tongue MI, have however, been shown to occur in association with motor learning.

Cortical Neuroplasticity and Motor Learning

Increases in motor performance and cortical excitability of the tongue MI, as measured by TMS, have been shown to occur in association with one-week of daily one-hour (Svensson et al., 2003b) and with one-hour (Svensson et al., 2006) of novel tongue-task training in humans, and these changes in face MI cortical excitability are supported by correlated findings of cortical reorganization in the tongue MI of monkeys trained in an analogous tongue – task (Yao et al., 2002a; Sessle et al., 2005). In addition to these findings, short-

term (15 min) novel tongue-task training in humans has also been associated with increases in motor performance and rapid changes in cortical excitability of the tongue MI, as measured by TMS (Paper III; Boudreau et al., 2007). Rapid cortical neuroplasticity of the MI has also been demonstrated, in humans, following 15 to 30 min of goal-directed thumb movement training (Classen et al., 1998). In the study by Classen et al., (1998) TMS over the hand MI was shown to evoke a consistent directional thumb movement and training in the opposite direction resulted in a TMS evoked directional thumb movement in the trained direction. In rats, changes in the firing rate of MI and striatum neurons have been shown to occur following a single 30 min motor training session (Costa et al., 2004) and furthermore increases in motor performance have been correlated with increases in the synaptic efficacy of the MI (Monfils and Teskey, 2004) through processes such as strengthening of horizontal cortical connections in layers II/III of the MI (Rioult-Pedotti et al., 1998) and increases in synapses per neuron in layer V of the MI (Kleim et al., 2002). In contrast to short-term novel motor training, long-term novel motor training (two – four weeks) in humans has been associated with successive increases in motor performance and cortical excitability of the hand MI, as measured by TMS (Koeneke et al., 2006). These findings are consistent with fMRI studies which have shown that motor performance and the cortical areas representing the muscles most critical to a newly learned motor task can slowly and continually evolve over several months (Karni et al., 1995; Karni et al., 1998). Overall, these studies underscore a general principle of cortical neuroplasticity in relation to motor learning and furthermore show that cortical neuroplasticity can occur rapidly and can continually evolve with extended training.

The incremental gains in motor performance associated with extended training may follow two distinct stages: first, an early, fast learning stage in which considerable improvement in performance can be seen within a single motor training session and second, later, slower learning stage in which further gains can be observed across several sessions (and even weeks) of practice (Karni et al., 1998). In addition to these two stages, an intermediate phase corresponding to a consolidation period of the motor routine has been proposed (Karni et al., 1998; Karni and Sagi, 1993; Brashers-Krug et al., 1996). For short-term motor training studies it has been shown that when sufficient initial motor training has occurred, delayed gains in motor performance may be dependent upon periods of sleep rather than the number of within-session task-repetitions (Korman et al., 2003; Korman et al., 2007; Walker et al., 2003).

A detailed analysis of the motor behaviour associated with novel tongue-task training, revealed that significantly different within-session gains in the initial training session (i.e. 72 vs. 144 task-repetitions) did not differentially affect the time course of the initial (reflective of sleep-dependent improvements) or overall motor performance in subsequent training sessions, as measured for seven consecutive daily tongue-task training sessions and again one-week post-follow up (Paper IV). Furthermore, the time course of these gains in overall motor performance are consistent with a previous tongue-task training study in which subjects trained daily for 60 min (216 within-session task-repetitions) (Svensson et al., 2003b). Together, these two tongue-task training studies suggest that extended within-session training times may not facilitate additional gains in overall motor performance for a novel motor training regime. Such findings may be useful for the design of motor rehabilitation training regimes in which limited training time is available, due to for example, easily fatigable muscles or pain. However, the results of

Paper III, suggest that pain may hinder motor learning, and the impacts that these findings may have for chronic pain patients undergoing motor rehabilitation has yet to be considered.

Cortical Neuroplasticity, Pain and Motor Learning

Motor rehabilitation has been advocated for treatment of chronic low back pain (Jull and Richardson, 2000; Hayden et al., 2005a; Hayden et al., 2005b; Cohen and Rainville, 2002), myofascial pain (Nicolakis et al., 2002a), temporomandibular joint pain (Nicolakis et al., 2002b) as well as swallowing dysfunctions in stroke patients (Robbins et al., 2007) (Robbins et al., 2007) and older adults (Robbins et al., 2005). A main goal of many rehabilitation training regimes is to promote adaptive neuroplasticity at the spinal and supra spinal levels such that long-lasting and beneficial alterations in motor control strategies can be achieved (Gabriel et al., 2006; Kays and Robbins, 2006). However, to date the clinical outcomes (e.g. pain reduction) of these rehabilitation training regimes are inconsistent in chronic pain patients (Hayden et al., 2005a; Zeviani, 2008; van Tulder et al., 2007) and this may be related to the findings that have emerged from this PhD thesis study.

The results of Paper III showed that intra oral pain interfered with the gains in motor performance and the cortical neuroplasticity of the tongue MI that would otherwise occur in association with short-term novel tongue-task training. This finding is also supported by experimental studies on laboratory animals. For example, motor learning deficits at the spinal cord level have been demonstrated in association with experimental pain in rats (Hook et al., 2008; Ferguson et al., 2006) and furthermore, nociceptive (maladaptive) neuroplasticity, as that which can be present in chronic pain patients (Flor, 2003;

Schweinhardt et al., 2006), hindered motor learning for up to 48 hrs (Ferguson et al., 2006). The notion that pain may hinder motor learning is not, frankly, unreasonable. Conceivably, increased stress responses during a cognitive task (Thieme and Turk, 2006), reduced cognitive performance (Apkarian et al., 2004; Dick and Rashiq, 2007; Moseley, 2004a; Weiner et al., 2006; Moseley, 2004b), reduced quality of sleep (Roehrs and Roth, 2005), and attention deficits (Eccleston et al., 1997; Grisart and Plaghki, 1999), all of which have been documented in chronic pain patients, can affect motor learning. To date, the future impact of these findings on motor rehabilitation success, as measured by pain reduction and the ability to promote adaptive neuroplasticity, in patients with chronic pain is uncertain and the mechanisms by which pain may hinder motor learning are even less clear.

Topical application of capsaicin to the tongue has been shown to reduce the gains in overall motor performance (Paper III and IV) and this was mainly characterised by exaggerated overshoot and undershoot errors relative to the target force and delayed reaction times (Paper IV). Conceivably, these exaggerated overshoot and undershoot errors may have resulted from a decrease in the coordination of the intrinsic or extrinsic tongue muscles. Several studies have indicated that experimental muscle pain can modulate neuromuscular control (Madeleine et al., 2008; Arendt-Nielsen et al., 1996; Graven-Nielsen et al., 1997; Zedka et al., 1999; Madeleine and Farina, 2008; Madeleine and Farina, 2008; Madeleine et al., 2006; Ervilha et al., 2004b; Ervilha et al., 2004a; Falla et al., 2007a; Falla et al., 2007b; Falla and Farina, 2008; Sae-Lee et al., 2008a; Sae-Lee et al., 2008b). For example, decreases in the coordination of muscle groups, as indicated by a reorganization in muscle activity, has been shown following experimentally induced muscle pain in a shoulder flexion (Madeleine et al., 2006; Falla et al., 2007b), dynamic

upper limb (Madeleine et al., 1999) or goal-directed jaw (Sae-Lee et al., 2008a; Sae-Lee et al., 2008b) motor tasks. Arguably, the sensitivity of the superficial mechanoreceptors, which respond to mechanical distortion, may have been altered by topical application of capsaicin to the tongue dorsum and this could have contributed to the reduction in overall motor performance. However, the (non-noxious) tactile feedback, as assessed by the mechanical sensations produced by the application of a von Frey filament to the tongue, following topical application of capsaicin to the tongue was unaltered (Paper I). This present finding suggests that topical application of capsaicin to the tongue may not have altered the sensitivity of superficial mechanoreceptors but likely produced a barrage of nociceptive afferent input. The perceived pain, produced by the barrage of nociceptive afferent input, during novel tongue – task training may have been a distraction, and could, possibly account for the delay in the reaction times found capsaicin tongue-task training (Paper IV). However, it has been shown that pain related cortical activity, as measured by fMRI, is attenuated during cognitive load and conversely cognitive-related activity was not modulated by pain in healthy humans (Seminowicz and Davis, 2007).

Topical application of the anaesthetic lidocaine to the tongue tip has also been associated with reduced gains in overall motor performance during a novel tongue-task training regime (Paper IV). These reduced gains in overall motor performance were mainly characterised by exaggerated undershoot errors relative to the target force as well as delayed reaction times (Paper IV). Additionally, topical application of the anaesthetic lidocaine was associated with a reduction in the mechanical sensations produced by the application of a von Frey filament to the tongue (Paper IV), which suggests that a loss in afferent feedback from the superficial mechanoreceptors may have occurred during novel tongue-task training. In hand-arm motor tasks, cutaneous afferent feedback from the hand

is a known requirement for optimal motor control and performance (Nowak et al., 2001; Nowak et al., 2004; Witney et al., 2004). For example, digital anaesthesia of the fingers in healthy humans produces exaggerated predictive grip forces (Nowak et al., 2001), and in the case of complete loss of touch, vibration, pressure, and kinaesthesia in the neck, trunk, and upper and lower limbs exaggerated and inefficient predictive grip forces result (Nowak et al., 2004). To date, the effects of reduced sensory feedback, resulting from age, disease, or trauma, for example, on motor performance of previously learned motor tasks such as gait and balance (Wolfson, 2001; Sturnieks et al., 2008) or hand manipulation (Nowak, 2008) has received considerable attention yet, little is known about the effects of sensory loss on motor performance associated with novel motor learning per se. There is, however, evidence that intelligible speech production and speech motor learning are highly dependent on the acuity of orofacial somatosensory feedback, and can occur in the absence of auditory stimuli (Nasir and Ostry, 2006; Nasir and Ostry, 2008). Nonetheless, this PhD thesis study has shown that reduced mucosal mechanical sensitivity of the tongue tip produces exaggerated undershoot errors relative to the target force during a novel tongue-task training regime and provides evidence that the development of tongue protrusion force is dependent on mechanical afferent feedback from the tongue-tip (Paper IV). Overall, the findings from Paper IV also suggest that a loss of sensory afferent feedback or experimental pain can modulate motor performance associated with motor learning and these sensory manipulations may differentially affect motor learning processes.

Summary of Main Findings

This PhD thesis study has provided evidence that the experimental capsaicin pain model is a suitable method to investigate the modulatory effects of acute orofacial pain on the motor performance and cortical neuroplasticity of the face MI associated with short-term novel tongue-task training in humans (Papers I and II). This PhD thesis study has shown that topical application of capsaicin to the tongue dorsum results in burning pain, increases in blood flow and temperature for a minimum of 30 min and that (non-noxious) tactile afferent feedback in the tongue is unaltered during this time. Additionally, this thesis investigation has provided evidence that acute orofacial pain is not associated with changes in the cortical excitability of the face MI, as measured by transcranial magnetic stimulation (TMS) in humans (Paper II). The main outcome of this PhD thesis study was that topical application of capsaicin to the tongue dorsum reduces motor performance and interferes with the changes in cortical excitability of the tongue MI, as measured by TMS, which would otherwise occur in association with 15 min of novel tongue-task training in humans (Paper III). Furthermore, this thesis investigation has shown that reduced mucosal sensitivity (sensory loss) of the tongue tip and intra oral pain interfere with the incremental gains in motor performance associated with short-term novel tongue task training and also provides evidence that sensory loss and pain may differentially affect the ability to perform and learn a new motor task (Paper IV). Lastly, this PhD thesis study has shown that a sufficient number of within-session task-repetitions may exist for long-term novel motor training regimes such that extended training times do not facilitate additional gains in overall motor performance (Paper IV). The findings from this PhD thesis study

may have implications on the design of motor rehabilitation regimes in which limited training time is available, or when sensory loss or pain is present.

Future Directions

The main outcome of this PhD thesis study suggests that pain may hinder motor learning in short – term novel motor training regimes however, these findings need to be confirmed for long-term novel motor training regimes in both healthy humans and chronic pain patients. There are several studies indicating that chronic pain is associated with nociceptive cortical neuroplasticity in the SI, MI or both (Karl et al., 2001; Dettmers et al., 2001; Flor, 2003; Krause et al., 2006; Strutton et al., 2005; Tsao et al., 2008). To date, the effects of nociceptive neuroplasticity in chronic pain patients on motor learning are unknown. Indeed, the ability to learn a new motor task may be crucial to effectively perform a motor rehabilitation training regime. Previously, it has been shown that nociceptive neuroplasticity, induced by as little as 6 min of uncontrollable shock to the rat leg or tail, results in a motor learning deficit that is maintained for 48 hrs (Ferguson et al., 2006). One could speculate that these findings imply that chronic or persistent pain, as opposed to acute pain may be associated with a motor learning deficit as well. Additionally, there is evidence which suggests that the extent of nociceptive cortical neuroplasticity in the MI of chronic pain patients is associated with motor control deficits (Tsao et al., 2008). It is also unclear if nociceptive cortical neuroplasticity is maintained by peripheral noxious inputs to the brain or vice versa and clarification of this may have a significant clinical impact on the treatment strategies for chronic pain patients. Future studies which aim to clarify the time course and effects of chronic pain on the interaction

between motor control, motor learning, and cortical neuroplasticity of the MI, may lead to the development of improved treatment strategies for chronic pain patients.

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