Analgesic Effect of Vibro-acupuncture

Quantitative Sensory Testing on Healthy Humans and Chronic Pain Patients

Dennis Boye Larsen

Medicine with Industrial Specialization
Translational Medicine
Master's Thesis

AALBORG UNIVERSITY
DENMARK

Title: Analgesic Effect of Vibro-acupuncture – Quantitative Sensory Testing on Healthy Humans and Chronic Pain Patients
Theme: Medicine with Industrial Specialization, Translational Medicine, Master's Thesis

Project period: September 1st 2014 to May 29th 2015.

Dennis Boye Larsen

Supervisor:
Kelun Wang, *DDS, PhD, Head of Orofacial Pain Laboratory, Center for Sensory-Motor Interaction (SMI), Department of Health Science & Technology Aalborg University, Fredrik Bajersvej 7 D-3 DK-9220, Aalborg SE, Denmark*

Pages: 49
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Abstract

Background & Aims: Acupuncture treatment has attained an important role in Western medicine, and its analgesic benefits are rapidly being accepted for pain alleviation in several disorders. Vibration therapy is another treatment modality that has been investigated throughout the last two decades, and its pain relieving effects is possibly mediated by Aβ-fibers, which inhibits nociceptive transmission at a segmental and central level. A combination of both (vibro-acupuncture; VA) has to our knowledge not yet been attempted. Therefore, the current study aimed to test a novel acu-vibrator device, capable of delivering high-frequency vibration into the deep muscle through acupuncture needles. The effects of the novel VA was compared to manual acupuncture (MA) and placebo acupuncture (PA), to elucidate possible differences on pain and sensory responses in human subjects.
Methods: A subjects- and outcome assessor-blinded, randomized, placebo-controlled cross-over study was conducted, including 30 healthy subjects (21 men; 9 women) and 11 chronic elbow pain subjects (six men; five women). The full battery of quantitative sensory testing (QST) was employed for testing sensory responses to VA in comparison with PA and MA on thermal, mechanical, and pain parameters. Moreover, subjective sensation scales McGills Pain Questionnaire (MPQ), the MGH acupuncture sensation scale (for *Deqi* sensations), and the visual analogue scale (VAS) were used to describe the acupuncture sensation, and pain in the affected arm of chronic pain subjects.
Results: The primary findings of the current study were: Significantly elevated vibration detection threshold following treatment with VA compared to PA and MA ($p = 0.004$) in healthy subjects; time-dependent increases in thermal parameters cold and warm detection thresholds ($p < 0.0001$ and 0.029, respectively), and decreases in cold and heat pain thresholds ($p = 0.032$ and < 0.00001, respectively) for healthy subjects and chronic elbow pain subjects. For mechanical parameters, a time-dependent decrease for mechanical pain threshold was found ($p < 0.0001$) together with increased pressure pain thresholds in the left arm ($p = 0.019$) and tibialis ($p = 0.016$) for healthy subjects. In addition, double-blinding was assessed based on indication percentage for each treatment, and was considered unsuccessful. Several descriptors associated with *Deqi* was increasingly reported during treatment with MA and VA compared to PA, together with vibration. MPQ data showed increased pain quality for MA and VA compared to PA ($p < 0.001$ for both comparisons) for healthy subjects. Corroborating data from VAS ratings showed significantly elevated pain associated with MA and VA, compared to PA ($p = 0.003$ and < 0.0001, respectively). Lastly, chronic elbow pain subjects described their pain quality (MPQ) and intensity (VAS) as being significantly lower following treatment for all three treatments.
Conclusions: The current study showed treatment and time-specific changes in local sensory responses for both thermal and mechanical QST parameters, suggesting an impact on all three main primary afferent nerve fibers involved in exteroception. Similar responses for MA and VA with regards to *Deqi* descriptors, pain quality, and pain intensity were found, suggesting an applicability of VA in future acupuncture trials. Moreover, pain was in general rated lower by chronic elbow pain subjects following each of the three treatments, warranting further investigation. Unravelling the analgesic potential of VA may introduce a novel approach to treating chronic pain in several disorders and provide insight into segmental and central effects of the proposed combination.

1. Introduction

1.1. Acupuncture

Acupuncture is an ancient treatment method of Traditional Chinese Medicine (TCM), in which insertion of fine needles into certain acupuncture points of the body elicits responses such as relief of pain in various disorders, primarily mediated by activation of afferent nerve fibres innervating the skin and muscles [Han, 2011]. This approach to human physiology and pathology is in many ways in contrast to Western medicine, in which scientific objectivity and quantification remain the

accepted options in relation to unravelling pathophysiologic mechanisms of disease [Kaptchuk, 2002]. Naturally, this clash of views on how to perceive the body is detrimental to determine the underlying mechanisms of acupuncture in relation to analgesia, which therefore remain poorly understood. The current thesis will describe acupuncture and its analgesic capacities through anatomy and pathways pertaining to the nervous system, in view of supporting its clinical application.

In 1979, the World Health Organization advocated the use of acupuncture in treatment of 43 symptoms [Naik et al., 2014]. Since then, extensive researches have been performed in order to elucidate the possible application of acupuncture in modern medicine and management of pain. Due to lack of consensus on proper control groups, relatively small sample sizes, and severe lack of long-term follow-up effect of acupuncture, several reviews warrant for larger well-designed trials in view of elucidating the analgesic effect of acupuncture [Sun et al., 2008, Cao et al., 2012, Naik et al., 2014]. Nonetheless, the mechanism of descending pain inhibition mediated by the peripheral and central nervous system (PNS and CNS, respectively) may partly explain how acupuncture induces analgesia following stimulation. In this respect, insight into the processing of sensory information of the PNS and CNS is crucial in terms of understanding how acupuncture affects not just locally, but possibly through segmental and central effects.

1.1.1. Sensory processing in the peripheral and central nervous system; relation to acupuncture

The three major functions of the human sensory system comprise exteroception, interoception, and proprioception. Exteroception and interoception describes the perception and response to external and internal stimuli whereas proprioception is the control of balance and body position [Abraira and Ginty, 2013]. Peripheral sensory transmission elicited by external stimuli is mediated by primary afferent nerve fibers constituting largely three distinct groups; (1) Aβ-fibers, (2) Aδ-fibers, and (3) C-fibers [Julius and Basbaum, 2001]. The large myelinated Aβ-fibers are characterized as low-threshold mechanoreceptors and are activated by tactile stimulation including touch, vibration, and skin indentation [Delmas et al., 2011]. In contrast, the smaller high-threshold thinly myelinated Aδ-fibers and small unmyelinated C-fibers function as nociceptive mechanical and polymodal thermo- and chemical receptors, owing to their activation upon stimulation of noxious mechanical, thermal, or chemical stimuli [Delmas et al., 2011]. The primary afferents are distributed throughout the skin, muscles, tendons, and joints, as well as viscera. The cell bodies of these pseudounipolar neurons (known as first-order neurons) are located in the trigeminal ganglion and the dorsal root ganglion, the two major sensory organs of the PNS, and project to second-order neurons in the substantia gelatinosa (SG) of the dorsal horn which convey sensory information to higher brain centers [Patestas and Gartner, 2006]. Ensuing the reception of peripheral input, the CNS respond by initiating a cascade of events involving autonomic and humoral responses which inhibits ascending signal transduction of noxious stimuli at the SG level (descending projections) [Cui et al., 1999]. The revolutionary gate control theory (GCT) by Melzack and Wall [1965] has long been regarded as the best describing (with modifications) theory of pain modulation through innocuous stimulation (Figure 1). Briefly, in the event of noxious stimuli through C- and Aδ-fibers, the inhibitory interneuron of the SG is inhibited. By simultaneous or immediate following activation of Aβ-fibers (and non-nociceptive Aδ-fibers, Aβ/Aδ) by innocuous stimulation, this inhibitory interneuron is activated,

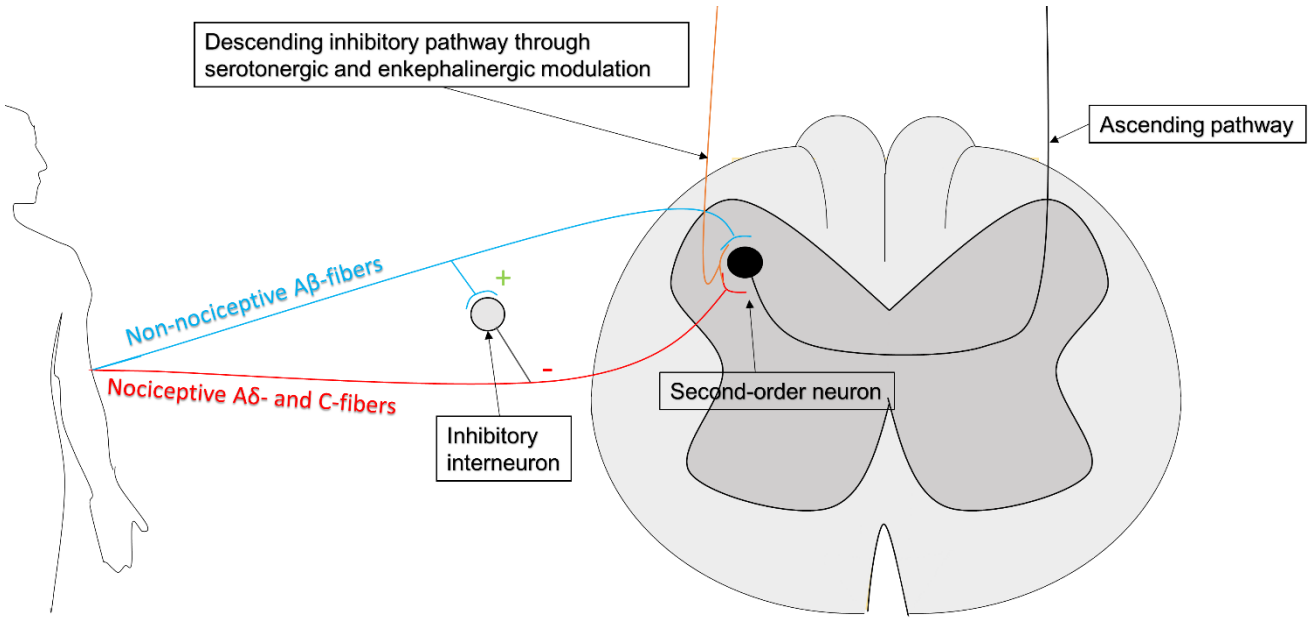

Figure 1. Mechanisms associated with analgesia at a segmental level. The gate control theory describes pain inhibition through Aβ-fiber activation (+) of the inhibitory interneuron, effectively blocking nociceptive transmission through Aδ- and C-fibers (-). Moreover, acupuncture analgesia is mediated, at least partly, through activation of segmental serotonergic and enkephalinergic neurons (descending inhibitory pathway) mediated by central structures, pertaining to pain inhibition. C*reated by the author*.

which in turn presynaptically inhibits the signal transmission from first-order to second-order neurons, effectively reducing the pain perception [Melzack and Wall, 1965, Moayedi and Davis, 2013].

In relation to acupuncture, the needling sensation is thought to mainly activate mechanoreceptors (i.e. Aβ- and Aδ-fibers, *Deqi* sensation) and/or introduce local trauma resulting in activation of C-fibers, thereby initiating a cascade of descending inhibitory events [Leung, 2012, Otti and Noll-Hussong, 2012, Zhu et al., 2013] (Figure 1.). *Deqi* is described as a distinct needling sensation upon insertion, often exacerbated by manipulating the needle (e.g. twisting), and activates distinct brain regions, as witnessed in functional magnetic resonance imaging (fMRI) [Hui et al., 2005, Zhu et al., 2013]. This supports the notion that central effects play a pivotal role in the analgesic effect of acupuncture. Furthermore, the prominent role of enkephalinergic and serotonergic neurons in acupuncture analgesia has been extensively discussed in earlier reviews [Lin and Chen, 2008, Chang, 2013, Han, 2004]. Important to note is, that the above stated possible mechanisms of action of acupuncture in relation to analgesia may be too simplistic [Chang, 2013]. Acupuncture has been demonstrated to initiate other events such as anti-inflammatory actions through release of proinflammatory mediators (e.g. tumor necrosis factor-α, interleukins, and chemokines) at the needling site and modulation of neurotransmitter systems such as glutamate and endorphin release [Leung, 2012]. Therefore, these concurrent events first of all adds to the complexity of describing acupuncture analgesia with one single mechanism, but secondly, supports the notion that acupuncture could be effective in treating a wide variety of disorders. Together, the extensive body of evi-

dence on acupuncture analgesia, and the gradual decoding of underlying mechanisms, supports the analgesic capacity and therefore its clinical use.

1.1.2. Application of acupuncture in clinical pain conditions

In the clinical setting, two distinct types of treatment modalities are currently employed; (1) manual acupuncture (MA); and (2) electro-acupuncture (EA). The main difference between the two is the method by which the therapeutic effect is carried out. During MA, the acupuncture needles are inserted and afterwards twisted in various directions and at different speeds depending on the therapeutic aim [Leung, 2012]. For EA, the needle is inserted but instead of manual stimulation, an electrical impulse is sent through the needle at different frequencies, pulse widths, magnitudes, and pulse intervals according to the treatment goal [Ulett et al., 1998, Napadow et al., 2005]. Earlier lines of evidence suggest that differences between MA and EA exist, pertaining to brain regions activated following application, where EA elicits a more widespread activation of higher brain centers than MA [Napadow et al., 2005, Kong et al., 2002]. This could indicate that the effect of conventional MA can be enhanced, at least on a central level, by combining external stimuli with the acupuncture needles at the acupoints of interest. However, contradictory evidence in humans when comparing MA with EA in relation to pain relief exists [Tsui and Leung, 2002, Plaster et al., 2014]. Nonetheless, both types of acupuncture have proven effective in reducing pain in a wide array of common acute and chronic pain syndromes [Chen et al., 2010]. Chronic low back pain has been of special interest concerning acupuncture, and several lines of evidence have demonstrated significant improvements in psychophysical parameters such as pain intensity and pain disability. For instance, Leibling et al. [2002], showed significant decreases in pain intensity and disability in chronic low-back pain (LBP) sufferers receiving acupuncture complementary to conventional physiotherapy. Of important note is that sham-acupuncture (minimal needling principle) showed similar effects, indicating a placebo effect [Leibing et al., 2002]. In support, another large scale study including 1162 LBP patients showed significant improvements in pain disability, pain intensity, and quality of life following acupuncture and sham-acupuncture compared to conventional therapy, albeit also supporting a possible placebo effect [Haake et al., 2007]. Moreover, acupuncture has been indicated for prophylactic and disability treatment for headaches (notably migraine and tension-type headache). In a randomized controlled multicenter trial including 270 tension-type headache patients, a significant reduction of days with headache was found when treated with acupuncture and sham-acupuncture, compared to no acupuncture (patients waiting for treatment) [Melchart et al., 2005]. In addition, acupuncture has been shown effective in reducing disability pertaining to migraine attacks when compared to mock acupuncture (i.e. no insertion of needles) [Facco et al., 2008]. Musculoskeletal disorders such as lateral epicondylitis have been extensively studied in relation to acupuncture effectiveness. Earlier evidence has shown the acute effect of acupuncture, where a single-session trial with acupuncture and mock acupuncture (pencil-probe device for inducing the feeling of acupuncture) showed a significant effect of acupuncture in pain relief, and pain relief duration [Molsberger and Hille, 1994]. In a follow-up study, Fink et al. [2002] showed a significant increase in strength and decrease in functional impairment in both acupuncture and sham-acupuncture groups two weeks after treatment (but not follow-up two months), with acupuncture showing the best improvement. Important to note is that no control group (i.e. not receiving acupuncture) was included, and the significant reduction in pain

and functional impairment, at least at two months follow-up, could merely be the natural course of lateral epicondylitis [Fink et al., 2002]. Despite a certain heterogeneity in trials relating to acupuncture effect, the overall verdict seems to be that acupuncture elicits, at least short-term, analgesic effects in several different pain syndromes [Trinh et al., 2004, Gadau et al., 2014]. The exact mechanisms of action remain to be defined, and controversial evidence warrants further investigations into the effect of acupuncture analgesia in clinical pain [Green et al., 2002].
Collectively, acupuncture is widely used in the management of several different disorders and remains a mainstay alternative treatment of clinical pain, despite the possible placebo effect. Moreover, application of electrical impulses has proven to improve the efficiency of the various stimulation points used in acupuncture, and favors the use of external stimulation with conventional MA. This opens for exploration into other modalities which, when applied to MA, may prove more efficient in managing pain. Returning to the notion of non-noxious stimuli being able to lower perceived pain (see section 1.1.1.), vibration could potentially be another treatment modality that in combination with acupuncture may improve efficiency, owing to its pain alleviating properties.

1.2. Vibration and alleviation of pain

Vibration has long been considered a therapeutic modality capable of alleviating pain. However, despite the apparent pain reducing effect, the underlying mechanisms remain largely unknown. Earlier evidence in cats suggests that analgesia is achieved through high frequency stimulation of the low-threshold Aβ-fibers, which in turn alters and inhibits nociceptive transduction through dorsal horn neurons [Salter and Henry, 1990]. Moreover, high-frequency vibration was shown to suppress activity in areas relating to pain in the somatosensory cortex in monkeys, further supporting the notion that vibration stimuli induces central changes to the perception of pain [Tommerdahl et al., 1999] (see also the proposed GCT mechanism in section 1.1.1.).
Indeed, the pain alleviating properties of vibration has been demonstrated by several lines of evidence. As early as in 1968, Sullivan et al. [1968] reported an increase in radiant heat pain threshold when vibration was applied simultaneously to the dorsal surface of healthy subjects' forearm. Later, vibration therapy at 100-200 Hz was shown to alleviate pain in patients suffering from chronic myofascial or musculoskeletal pain, including lateral epicondylitis [Lundeberg, 1984]. Kakigi et al. [1992] reported that concurrent application of vibration and movement of the finger when subjected to a laser beam-mediated pain, overall significantly increased pain thresholds in healthy subjects. Furthermore, earlier evidences indicate a possible application of vibration therapy in the orofacial field [Nanitsos et al., 2009, Ottoson et al., 1981], albeit controversial evidence is available [Hutchins et al., 1997]. The many different pain scenarios in which vibration therapy has been applied and found effective, supports the framework idea of the GCT, i.e. in this case innocuous vibration stimulation carried predominantly by Aβ-fibers, may alter nociceptive transmission on a segmental and central level. Therefore, it seems reasonable to hypothesize that vibration alongside acupuncture may provide a beneficial combination for providing efficient pain relief in chronic pain disorders such as lateral epicondylitis, which lack both definite pathophysiology and efficient treatment [Ahmad et al., 2013].

1.3. Chronic elbow pain with special emphasis on lateral epicondylitis

1.3.1. Epidemiology and etiology

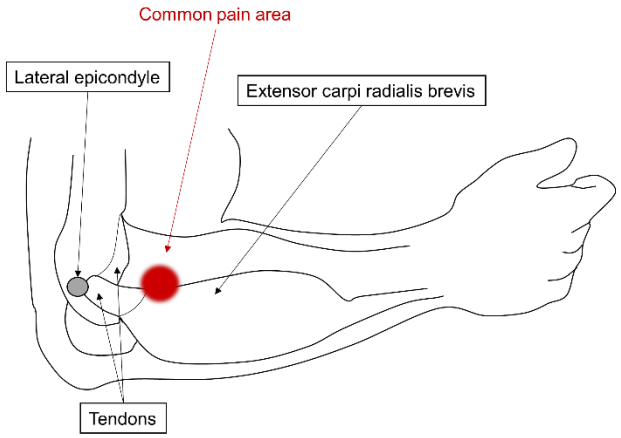

Figure 2. Area of interest in patients suffering from tennis elbow. Degeneration of the musculotendinous structure around the lateral epicondyle underlies the pain associated with tennis elbow. The red dot signifies the area of interest in the current study. *Created by author.*

Lateral epicondylitis (tennis elbow) is a common pain condition in the elbow, with an approximate incidence of 1% to 3% in the general population equally distributed among men (1% to 1.3%) and women (1.1% to 4.0%) [Waseem et al., 2012, Shiri and Viikari-Juntura, 2011]. It is characterized as a tendinosis rather than an inflammatory condition (tendinitis), caused by overuse and results in degeneration of the musculotendinous structure related to the lateral epicondyle [Ahmad et al., 2013, Bass, 2012]. Pathological identification of tennis elbow include the presence of scar tissue in the extensor carpi radialis brevi (ECRB) muscle resulting from microscopic tearing and presence of fibroblasts and vascular granulation in the collagen microstructure (angiofibroblastic hyperplasia) [Nirschl and Pettrone, 1979]. It leaves the affected individual with functional disability, and consequently has a significantly negative impact on the quality of life of the patient and therefore poses a socio-economic burden in form of e.g. loss of productivity and increased health care demand [Walker-Bone et al., 2004, Tosti et al., 2013].

The pathophysiology of tennis elbow is under constant scrutiny, and controversial evidence continuously emerge which effectively impair the understanding of a definite etiology [Hong et al., 2004]. Currently, the consensus regarding the development of tennis elbow is that occupational, environmental, recreational (e.g. sport activities), and preceding pathologies may all attain prominent roles. Contradicting evidence regarding the association of factors such as smoking status and obesity in the development of tennis elbow is available [Shiri et al., 2006, Titchener et al., 2013, Walker-Bone et al., 2012], however, a recurrent association of forceful and repetitive movement and tennis elbow has been reported by several lines of evidence [Walker-Bone et al., 2012, Herquelot et al., 2013, van Rijn et al., 2009]. Additionally, sport activities such as tennis has earlier been associated with the development of tennis elbow, possibly due to the higher activity of the epicondylar region [Gruchow and Pelletier, 1979, Kitai et al., 1986]. Moreover, pathologies pertaining to the upper extremities have been associated with tennis elbow, notably rotator cuff pathology which is a degenerative disorder of the shoulder [Titchener et al., 2013]. The possible predisposing role of rotator cuff disorder may be ascribed to compensating changes in movement of hand and/or forearm [Laban et al., 2005].

Collectively, the wide range of possible predisposing factors combined with a relatively unknown history of this debilitating disorder (span of 10-18 months according to a recent review [Ahmad et al., 2013]) underscore the importance of effective management for affected individuals. Despite the self-limiting nature of tennis elbow [Zeisig, 2012], the multifactorial etiology and inherent potential to transition into chronic pain [Luk et al., 2014], warrants for a more efficient treatment approach in view of yielding a better long-term outcome.

1.3.2. Clinical manifestation and treatment

The clinical manifestation of tennis elbow involves tenderness above the common anterior extensor, anterior and distal to the lateral epicondyle of the humerus, which often extends down the forearm [Brummel et al., 2014, Ahmad et al., 2013] (Figure 2). The diagnosis is based upon physical examination and diagnosis criteria [Sluiter et al., 2001, Harrington et al., 1998], with reproduction of symptoms when applying different diagnostic tests such as the resisted middle finger extension test and the Gardner chair test, as well as diminished grip strength as a secondary symptom to pain. Additionally, imaging techniques such as plain elbow radiographs, magnetic resonance imaging (MRI), and ultrasound imaging are optional methods used in the diagnosis of tennis elbow, albeit rarely [Johnson et al., 2007]. For excellent recent reviews on the current physical examination diagnostic criteria and imaging techniques, see Brummel et al. [2014] and Waseem et al. [2012]. Despite these effective tools in the diagnosis of tennis elbow, no superior mainstay therapy is available for the treatment of tennis elbow.

At present, a broad range of surgical and non-surgical approaches has been initiated in the management of tennis elbow. The surgical treatments include open surgery [Kumar et al., 2004], arthroscopic surgery [Wada et al., 2009, Kniesel et al., 2014], and percutaneous release surgery [Baumgard and Schwartz, 1982] which are offered to approximately 4-11% of patients who do not respond to conventional treatment [Brummel et al., 2014]. These surgical interventions serve to excise abnormal tissue within the ECRB origin, and/or release the tendon, yielding an overall good outcome for the included patients [Johnson et al., 2007]. Moreover, non-surgical treatment includes non-steroidal anti-inflammatory drugs (NSAIDs), bracing, physical therapy, injections of corticosteroids, autologous blood, or platelet-rich plasma, extracorporeal shock wave therapy, laser therapy, and acupuncture (for excellent review on current non-surgical treatments for tennis elbow, see Ahmad et al. [2013]). However, several systematic reviews have pointed out a lack of strong evidence regarding the effects of these treatment modalities [Sims et al., 2014, Smidt et al., 2003, Sayegh and Strauch, 2014]. Together, the large body evidence for treatment of tennis elbow remains somewhat elusive with contradicting results and lack of definite conclusions. In addition, the wide array of options leaves the impression that a superior treatment is yet to be identified [Ahmad et al., 2013], further supporting the notion that management of tennis elbow remains suboptimal at best, in treating the nociceptive aspect of tennis elbow.

In recent years, research into underlying mechanisms of pain has taken a major leap forward through the introduction of standardized Quantitative Sensory Testing (QST) protocols, which holds great promise in producing reliable and reproducible data in relation to pain.

1.4. Quantitative Sensory Testing

Quantitative Sensory Testing denotes psychophysical testing of the different submodalities of the sensory system. In 2006, the German Research Network on Neuropathic Pain (DFNS) published a standardized QST protocol in order to obtain comparability across different research groups. It encompasses seven standardized tests capable of measuring 13 parameters, and provides a full sensory profile of a local point [Rolke et al., 2006a]. The whole battery of tests includes thermal detection thresholds for cold, warm, and paradoxical heat sensations; thermal cold and heat pain thresholds; mechanical detection thresholds for touch and vibration; mechanical pain sensitivity including pinprick and blunt pressure thresholds, stimulus/response-functions for pinprick, dynamic mechanical allodynia, and

temporal summation of repetitive pinprick stimuli [Rolke et al., 2006a]. In this respect, QST offers a full profiling of the immediate status of the entire sensory axis (from the peripheral receptors to the brain) and offers information regarding Aβ-fibers, Aδ-fibers, and C-fibers function and their respective central pathways in several neurological and physiological disorders [Cruz-Almeida and Fillingim, 2014, Backonja et al., 2009]. Furthermore, using thresholds as an outcome, QST can indicate whether 'positive' or 'negative' signs of sensory dysfunction are present. Positive signs include cold-, heat-, and mechanical hyperalgesia (i.e. exaggerated pain to any of these stimulation modalities), and dynamical mechanical allodynia (pain perception following application of normally innocuous stimuli), whereas negative phenomenas pertain to cold-, heat-, and mechanical hypoesthesia (decreased sensitivity stimuli) or hypoalgesia (decreased sensitivity to painful stimuli) [Pfau et al., 2012]. As such, QST offers a mechanism-based approach to define differences in gain-and-loss of sensory function between different pain populations and healthy control populations, bringing us closer to a better insight into pain mechanisms and efficient treatment approaches to several disorders [Arendt-Nielsen and Yarnitsky, 2009, Cruz-Almeida and Fillingim, 2014].

The implementation and standardization of QST protocols have been developed immensely over the last few decades, and is now widely used in basic research (e.g. proof-of-concept studies) and in the clinic for assessing pain and sensory deficits [Arendt-Nielsen and Yarnitsky, 2009, Moloney et al., 2012]. However, to this end, QST remains a semi-objective test at best, heavily influenced not only by instruction of subjects and test performance, but also subject cooperation and attention as well as environmental factors such as temperature [Moloney et al., 2012]. Therefore, the test-retest reliability of various QST protocols have been scrutinized in several different pain paradigms such as atypical odontalgia (trigeminal neuropathic pain) [Baad-Hansen et al., 2015], chronic pancreatitis (visceral pain) [Olesen et al., 2012], knee osteoarthritis (musculoskeletal disorder) [Wylde et al., 2011] and more. Emerging evidence on the reliability on thermal QST parameters has mainly found fair-to-excellent rates, however, with considerable variability and call for improvement (for further information on thermal QST reliability studies from the period 1990-2010, see Moloney et al. [2012]). Similarly, mechanical thresholds have been shown to obtain high reliability when employing the QST protocol proposed by DFNS in patients with different sensory disturbances, however, the short duration of the study should be considered [Geber et al., 2011]. Together, utilizing QST in the clinical assessment of different pain conditions seems feasible. In contrast to this notion, a recent review highlighted several flaws in the reporting of reliability of QST in multiple published papers [Werner et al., 2013]. Regardless of discrepancy in reliability measures, the vast amount of published literature on the reliability of QST in clinical populations indicates that QST remains a powerful complementary tool in assessing gain-and-loss of sensory function in patients suffering from a variety of pain conditions [Arendt-Nielsen and Yarnitsky, 2009].

In summary, acupuncture and vibration are both alternative treatment modalities for pain. Moreover, the introduction of standardized QST protocols in relation to pain research, offers a powerful mechanism-based approach to evaluate the effect of newly developed devices targeted for treating chronic pain. In view of adding to our current understanding of acupuncture and its wide range of application in pain disorders, a new technique, vibro-acupuncture (VA), has been developed. For this specific purpose, a novel acu-vibrator (Appendix I) has been developed. The small vibration motor can be connected to the acupuncture

needles with a metal clip and produce vibrations with different frequencies (0-110 Hz) and amplitudes (0-200 μm) according to demand. This allows for transmission of vibrations into the deep muscle through the acupuncture needles at specific acupuncture points. This is, to our knowledge, the first attempt to combine acupuncture and vibration stimuli, thereby conducting high frequency vibration into the deep muscle. The novelty of this study will investigate human peripheral sensory responses to this combination, and possibly provide new information on neural analgesic mechanisms of acupuncture, and information on treatment improvement of acupuncture in chronic elbow pain patients.

2. Aims and hypothesis

The overall aim for the current thesis was to examine the local sensory responses to the newly developed VA compared with conventional MA, and placebo acupuncture (PA) in healthy subjects and chronic pain patients. Moreover, we sought to elucidate local, segmental, and central effects on sensory function between PA, MA, and VA. Finally, the analgesic effects of VA were investigated and compared to that of MA and PA, in view of pinpointing a possible clinical application in managing chronic elbow pain.

The specific hypotheses of the current thesis are: (1) VA is superior to PA and MA in increasing pain thresholds, i.e. thermal pain threshold, cutaneous mechanical pain threshold (MPT), pressure pain threshold (PPT), and mechanical pain suprathreshold (SPS). (2) VA has markedly different effects on different local responses such as light tactile detection threshold when compared to PA and MA. (3) VA provides better analgesic effects in chronic elbow pain subjects than PA and MA.

3. Materials and Methods

3.1. Subjects

3.1.1. Healthy subjects

Healthy subjects, aged 20-60 years and free from any ongoing pain or chronic pain, were recruited. The gender ratio was not limited during recruitment. Exclusion criteria for the healthy subjects involved pregnancy or intent of becoming pregnant; regular use of analgesics (non-steroid anti-inflammatory drugs (NSAIDs)) or paracetamol within the last week; frequent recreational drug or alcohol use; acupuncture treatment within the last week; and previous history of neurologic, musculoskeletal, or mental illnesses.

3.1.2. Chronic elbow pain subjects

Chronic elbow pain subjects, aged 20-60 years and suffering from tennis elbow, were recruited with no limitations to gender ratio. Diagnosis criteria have been described earlier [Tosti et al., 2013]. Briefly, subjects presenting with tenderness over the common extensor origin, anterior and distal to the lateral humeral epicondyle, were included if they rated ongoing pain > 2 (0-10 VAS) in the previous week. Exclusion criteria included pregnancy or intent to become pregnant; breast feeding; regular use of analgesics (including use of simple analgesia and NSAIDs within the last week); frequent recreational drug or alcohol use; acupuncture treatment within the last week; and previous neurologic, musculoskeletal, or mental illnesses.

3.1.3. Recruitment and ethics

All recruitment was done through advertising at Aalborg University, University College Nordjylland, acupuncture clinics, and the internet (i.e. www.forsog.dk and social media).

The study was approved by the local ethics committee (VN-20140005) and carried out in accordance with the Helsinki Declaration of October 2013. Written informed consent was obtained after information on the setup of the study and prior to participation. Each subject as subsequently identified only by ID numbers.

3.2. Experimental design

In view of fulfilling the stated aims (refer to section 2), the current study was set up as a randomized, placebo-controlled, double-blinded, cross-over study. Random allocation to the order of treatment (PA, MA, or VA) yielded three randomized sessions for each participant with every session lasting approximately two hours. In order to assess the different parameters pertaining to local, segmental, and central responses of the acupuncture treatments, sensory perception before and after acupuncture (PA, MA, and VA) was tested by applying a standardized QST protocol [Rolke et al., 2006a] on the testing site (lateral epicondyle of the humerus). The local effect was tested on the ipsilateral forearm of the acupuncture treatment. In addition, the segmental effect was tested by assessing PPT and SPS in the contralateral forearm (at the same testing site as the ipsilateral forearm), and a possible central effect was investigated by assessing both parameters on the contralateral leg (tibialis anterior muscle). Following the QST application, one of three acupuncture treatments was performed for 25 mins by another investigator according to a randomization code that was not accessed until all three sessions had been completed. Moreover, to add to the treatment profiles, subjects were asked to rate the pain perception during the acupuncture treatment on a 0-10 visual analogue scale (VAS), complete a modified MGH Acupuncture Sensation Scale (MASS) (Appendix II) and McGill Pain Questionnaire (MPQ) (Appendix III). Immediately after, the QST assessments were performed again. Furthermore, chronic elbow pain subjects were instructed to fill out additional MPQ and VAS charts before and after the treatment, describing the pain in the affected arm. Figure 3 depicts the study setup.

All side effects of the three acupuncture treatments were recorded with the acupuncture credibility scale (Appendix IV), and the double-blinded nature of the experimental setup was tested with an indication chart (Appendix V), where participants indicated the type of acupuncture they had received and the reasoning behind their choice within five pre-determined answers.

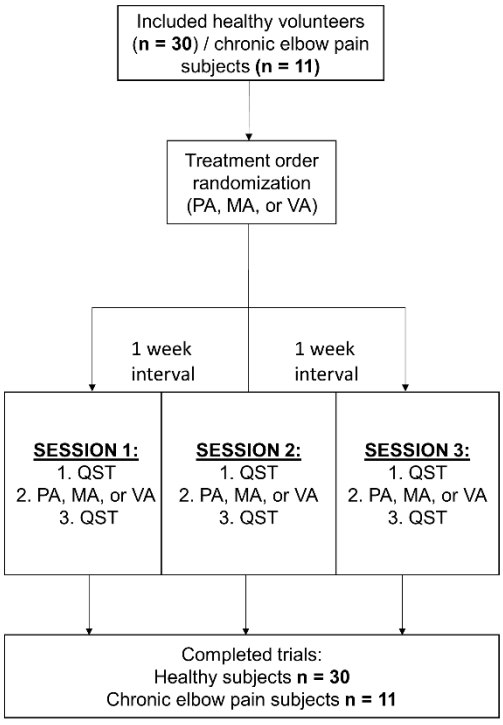

Figure 3. Flow chart illustrating the study setup. Following inclusion, treatment order was randomized for each subject, ensuring all three treatments were employed. Each treatment session was conducted with at least one week interval. *PA: Placebo acupuncture; MA: Manual acupuncture; VA: Vibro-acupuncture; QST: Quantitative Sensory Testing*

3.3. Methods

3.3.1. General information

The randomization for treatment order was done by Tanja Kim Jensen (TKJ). All procedures were carried out in a quiet room with consistent temperature (20°C to 24°C). All subjects were relaxed and sitting in a dental chair, with arms placed at the armrests. All QST assessments were performed by Dennis Boye Larsen (DBL; the author), whereas the acupuncture treatments were carried out by Kelun Wang (KW) or TKJ.

3.3.2. Acupuncture treatments

All subjects received treatment with MA, VA, or PA, for 25 mins on the right forearm of healthy subjects and the affected forearm of chronic elbow pain subjects. The acupuncture procedures will be described according to guidelines described in the Standards for Reporting Interventions in Controlled Trials of Acupuncture [MacPherson et al., 2001]. Briefly, sterile single-use acupuncture needles (0.25 x 25 mm, Hwato, Jiangsu, P.R. China) were used for all treatments. For all three procedures, the skin was cleaned with alcohol swabs before needle insertion. Needles were inserted 20 mm into the deep tissue layers of the dorsum of the hand (Hegu point; LI-4, between first and second metacarpal bones, approximately in the middle of the second metacarpal bone of the radial side) and three finger widths below the lateral epicondyle of the humerus (Shousanli point; LI-10). When a subject received MA, the needles would be placed and turned for *Deqi* sensation, and left for 25 mins without further stimulation. During VA, the acupuncture needles were connected to the acu-vibrator microcontroller by metal clips, which exerted continuous mechanical vibrations (frequency 100 Hz; amplitude 150 μm) for the entire duration of the acupuncture. The intensity was adjusted to match the maximum sensation below pain threshold, if the vibration amplitude was found excessive for the subjects. Placebo acupuncture sessions were carried out by applying a half-cut needle with blunt tip through a cube-shaped foam. This yielded a pricking sensation upon "insertion", but did not puncture the skin, and has been shown to elicit the feeling of penetration [Streitberger and Kleinhenz, 1998]. During all treatments, the vision of the subjects to the treatment procedure was blocked by a pillow. During PA and MA, the acu-vibration microcontroller was placed adjacent to the subject with power "on" in order to ensure the power light and sound of vibration, but with no connection to the needles.

3.3.3. Indications and subjective sensations

3.3.3.1. Blinding

As described in the general information (refer to section 3.3.1.), all data during the acupuncture section of each session (i.e. MASS, MPQ, VAS, and acupuncture credibility) were obtained by KW or TKJ. In view of testing the double-blinded nature of the study setup (outcome assessor and participants), each subject was asked to indicate which type of acupuncture treatment one had received. Four different options were available; PA, MA, VA, or do not know based on five pre-determined answers: (1) The manner, attitude, or words of the acupuncturist; (2) the manner, attitude, or words of the assistant; (3) the sensation of the acupuncture stimulation; (4) the results of the acupuncture treatment (e.g. changes in pain threshold or rating); and 5) the experience of the acupuncture procedure (e.g. what the acupuncturist did and how it felt).

3.3.3.2. MGH Acupuncture Sensation Scale and McGill Pain Questionnaire

Immediately following each acupuncture treatment, subjects were asked to rate their sensations during treatment at LI-4 and LI-10, by means of a modified MASS which comprises perceptive descriptors including soreness, aching, deep pressure, heaviness, fullness, tingling, numbness, sharp pain, dull pain, warmth, cold, and throbbing [Kong et al., 2007] with vibration added to account for the sensation elicited by the newly developed acu-vibrator. Each sensation was rated from 0-10, with anchor words "none" (0), "mild" (2), "moderate" (5), "strong" (8), and "unbearable" (10) evenly spaced out. Moreover, each subject filled out the MPQ, which describes the quality of pain during acupuncture treatment, allocated to sensory, affective, evaluative, and miscellaneous dimensions of pain [Melzack, 1975]. Additionally, VAS scores were obtained to rep-

resent the pain intensity during the acupuncture stimulation.

3.3.3.3. Adverse events

Adverse events (AEs) were recorded for the subjects in each treatment paradigm, and denoted as "dizziness", "fatigue", "pain", "bruising", and "infection". Each AE was scored using a six-point scale (0 = none, 1 = minimal, 2 = mild, 3 = moderate, 4 = severe, and 5 = extremely severe). A blank field was left for subjects to report any AE, which did not categorize as either of the denotations mentioned above.

3.3.4. Quantitative Sensory Testing

3.3.4.1 Thermal detection and thermal pain threshold

Thermal detection and thermal pain thresholds tests were performed using a TSA 2001-II (MEDOC, Israel). A thermal probe with a 3x3 cm contact area was placed on the testing site of the right arm (healthy subjects), or on the affected arm (chronic elbow pain subjects). The baseline temperature was set to 32°C, with cut-off temperatures of 0°C and 50°C [Rolke et al., 2006a]. Temperature increase/decrease rate was set to 1°C per second. All subjects were instructed to click a mouse button as soon as any perception of cold, warm, or pain was felt. The tests were measured in a specific order, starting with cold detection threshold (CDT), warm detection threshold (WDT), cold pain threshold (CPT), and heat pain threshold (HPT) [Rolke et al., 2006a]. For the CDT, subjects would click as soon as the change in temperature towards 'cold' or 'colder' was felt. The WDT was measured as soon as the subjects felt a change in temperature towards 'warm' or 'warmer'. When measuring the CPT and HPT, subjects were instructed to click the button at the first painful sensation caused by either cold or heat. Subjects were made aware that each test would be repeated three times. The three consecutive measurements were averaged as the final value for each parameter.

3.3.4.2. Mechanical detection threshold

Mechanical detection threshold (MDT) was tested by employing a standardized set of Semmes Weinstein Von Frey Aesthesiometer with 20 different diameters (20 piece full kit, Touch-Test® Sensory Evaluators, North Coast Medical, US). The range of sizes of the filaments was 1.65 to 6.65 mm corresponding to forces ranging from 0.008 g to 300 g via logarithmic function. The threshold was calculated by using the method of limits in which series of ascending and descending stimulus intensities were applied to the testing site of each subject. During the test, filaments were applied at 90° angle against the skin until they bend, and were held in place for ~1.5 seconds. The subjects were instructed to look away and say 'yes' as soon as the stimulus was felt. Each test started with the 1.65 mm filament and increased in size until the first positive response, at which point decreasing sizes of filaments were applied until the subject did not respond to the stimulus. The MDT was calculated as the geometric mean of five series of ascending and descending stimulus sizes.

3.3.4.3. Cutaneous mechanical pain threshold

Mechanical pain threshold was measured by applying seven custom-made weighted pinprick stimulators with a flat contact area of 0.2 mm in diameter, exerting forces ranging from 8 to 512 mN with a common ratio of 2. The stimulators were applied in a 90° angle on the testing site and were held for ~2 seconds. Subjects were instructed to look away and say 'yes' as soon as they felt pricking pain. Using the "method of limits", series of five ascending and five descending stimulus intensities were recorded. The final MPT was calculated as the geometric mean of five ascending and descending stimulus intensities.

3.3.4.4. Stimulus-response functions

The stimulus-response functions test yields

two important measures. First, mechanical pain sensitivity (MPS) is used to detect pinprick hyperalgesia, in which the same seven custom-made weighted pinprick stimulators from the MPT test was used. Second, dynamic mechanical allodynia (ALL) is tested in combination with the MPS test, by employing three light tactile stimulators as innocuous moving stimuli (a single stroke of approximately 1 cm in length at the testing site). The light tactile stimulators included a cotton wisp exerting a force of ~3 mN, a cotton tip with a force of ~100 mN, and a brush exerting forces ranging from 200-400 mN. These light stimuli were intertwined with the pinprick stimuli and applied in a random order. In total, each stimulator was applied five times at the testing site (i.e. 15 tactile and 35 pinprick stimuli). For each stimulus, the subjects were instructed to give a pain rating between 0-100 on a numerical rating scale (NRS; '0' representing no pain; '100' indicating the most intense pain imaginable). The MPS was calculated as the geometric mean of all numerical ratings for the pinprick stimuli and ALL was calculated as the geometric mean of all numerical ratings across the three tactile stimulators.

3.3.4.5. Temporal summation

The wind-up ratio was used to represent temporal summation in which spinal cord neurons become increasingly excited [Herrero et al., 2000]. A single pinprick stimulator, exerting a force of 128 mN, was employed. The test was repeated five times where a single stimulus was applied to the testing site, followed by 10 consecutive applications (1/s applied within a small area of ~1 cm^2) of the same pinprick stimulator at the site. The subjects were instructed to rate the pain on a 0-10 NRS after the initial single stimulus, and an estimated mean of the whole series of 10 stimuli. Windup-ratio (WUR) was calculated as the mean rating of the 10 repetitive stimuli divided by the mean rating of the five single stimuli.

3.3.4.6. Vibration threshold

A Vibrameter (100 Hz / 0-400 µm, Somedic, Sweden) was used for obtaining the vibration detection threshold (VDT). The vibrator (weight: 650 g) was placed, without any additional forces pressing, at the skin of the testing site. The vibration amplitude was gradually increased, and the subjects were instructed to say 'yes' as soon as they felt the vibration at the local point, followed by immediate cessation of the amplitude increase. The VDT was calculated as the mean of three consecutive measurements.

3.3.4.7. Deep pressure pain threshold and mechanical pain suprathreshold

The PPT was measured by the use of an algometer (Somedic, Sweden). A probe (area: 1 cm^2; diameter 1.1 cm) was pressed against the testing site with ramping rate of ~30 kPa/second. The subjects were instructed to push a button as soon as they felt pain on the testing site. The PPT was calculated as the average of three consecutive measurements. For the SPS, 130% of the PPT was applied to the testing site, and subjects were asked to rate the pain intensity using a 0-10 NRS

3.4. Statistical analyses

According to the protocol, log-transformation (base 10) was done for all appropriate QST measures (CDT, WDT, MDT, MPT, MPS, ALL, WUR, and PPT) [Rolke et al., 2006a]. Additionally, VDT data was log-transformed in order to obtain normal distribution for healthy subjects and chronic elbow pain subjects. Normal distribution was tested for all data with Shapiro-Wilk's normality test. All QST parameters were analyzed with a two-way RM ANOVA with treatment type (MA, VA, and PA) and time (baseline and post-treatment measures) as within-subjects factors. To test the assumption of normality of residuals, the studentized residuals for each QST parameter were obtained. Mauchley's test of Sphericity for

treatment and treatment × time interaction was applied, and if failed, a Greenhouse-Geisser correction to the degrees of freedom was employed. To avoid increased type I error rate during *post hoc* multiple comparisons, Bonferroni correction (critical α-value/*n* of comparisons) was employed for any multiple comparisons based on significant main effects (treatment and/or time) and simple main effect (SME) analysis *post hoc* tests (repeated measures ANOVA on each level of the two factors) for significant interaction effects. Additionally, in view of testing the local, segmental, and central effects of the three treatment types, the relative percentage change (baseline measure divided by post-treatment measure) of PPT and SPS measures was calculated, and tested with a one-way RM ANOVA (within-subjects factor: treatment type) and Friedman's test for repeated measures of ranks, respectively.
Differences in distribution of ranks for MASS descriptors, MPQ, and VAS scores (for pain quality and intensity during acupuncture) were tested with Friedman's test for repeated measures on ranks with Bonferroni *post hoc* Wilcoxon signed-rank tests. MPQ and VAS scores (for pain in the affected arm at baseline and post-treatment; chronic elbow pain subjects) were analyzed using a two-way repeated measures analysis of variance (two-way RM ANOVA) with the same within-subjects factors as described for the QST data.
All results are reported as mean ± standard error of the mean (SEM) unless otherwise stated. The statistical calculations were carried out using the Statistical Package for Social Sciences version 22 (SPSS, IBM). *P*-values < 0.05 (Bonferroni correction applied where appropriate; 0.05/3 = 0.0167) were considered statistical significant. Figures were made in Microsoft Excel (Microsoft Office 365, 2013), and Microsoft PowerPoint (Microsoft Office 365, 2013)

4. Results

4.1. Subjects

4.1.1. Healthy subjects: Characteristics and exclusion

Thirty healthy subjects (21 men and 9 women; mean age ± standard deviation: 23.47 ± 2.87) completed all three sessions designed to determine possible differences in treatment effects of MA, VA, and PA. None of the included subjects had any ongoing or chronic pain, history of neurologic, musculoskeletal, or mental illnesses and complied with the inclusion criteria at the time of testing.
Since WUR is a ratio-based measure, any subject with five consecutive "0" ratings in single pinprick sessions had their data removed from the main analysis (subjects 12, 14, 20, 25, 26, 28, and 29).

4.1.2. Chronic elbow pain subjects: Characteristics and exclusion

Eleven chronic elbow pain subjects (six men and five women; mean age ± standard deviation: 47.45 ± 8.81) were included and completed all three sessions. Three of the included subjects had their left arm tested, whereas the remaining eight were tested on their right arm. The pain period was 24.27 ± 27.49 (mean period ± standard deviation) months with a pain intensity of 4.77 ± 1.75 (mean intensity ± standard deviation) (VAS) at the first session for all chronic elbow pain subjects. All included subjects complied with the inclusion criteria at the time of testing. For WUR, all subjects except subject 8 had at least one session where the single stimulation series was rated "0" five consecutive times distributed both at baseline and post-treatment measurements. Therefore, the WUR parameter could not be tested in the treatment × time two-way RM ANOVA for chronic elbow pain subjects.
Furthermore, since subject 7 had several "0" ratings in SPS, the relative percentage change could not be calculated for the affected arm (VA

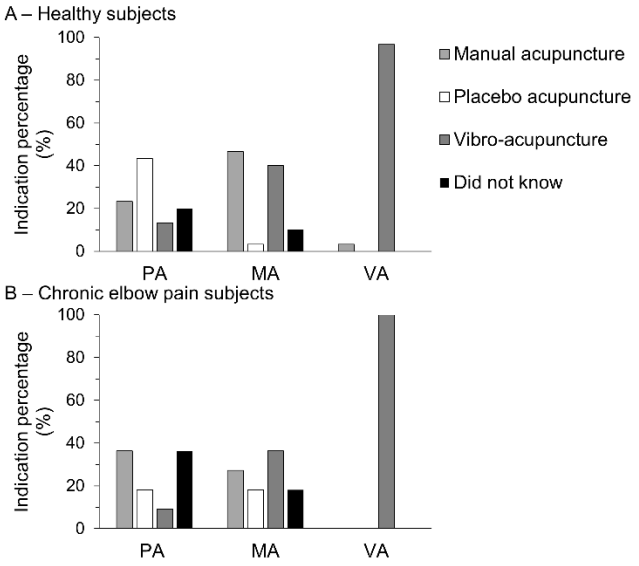

Figure 4. Distribution of indications for healthy subjects and chronic elbow pain subjects. As depicted, a clear uncertainty towards treatment mode was present for PA and MA for each subject group. For VA, virtually all subjects correctly indicated VA as treatment mode, indicating that double-blinding was not achieved. *PA: Placebo acupuncture; MA: Manual acupuncture; VA: Vibro-acupuncture.*

and MA) and the non-affected arm (MA and VA), and was therefore excluded.

4.2. Blinding; acupuncture credibility scale and indication

For the healthy subjects during PA, 7/30 (23.3%) of the subjects indicated MA as the treatment mode, 13/30 (43.3%) correctly denoted PA, 4/30 (13.3%) reported VA, and the remaining 6/30 (20%) did not know which treatment type they had received. During MA, 14/30 (46.7%) of the subjects reported the correct treatment (MA), 1/30 (3.3%) indicated PA, 12/30 (40%) marked VA, and 3/30 (10%) did not know. Finally, 1/30 (3.3%) and 29/30 (96.7%) of the subjects indicated MA and VA, respectively, during VA. Two pre-defined answers as to why subjects chose the treatment type were given: (1) "the sensation of the acupuncture stimulation" and (2) "the experience of the acupuncture procedure (e.g. what the acupuncturist did and how it felt)". After MA, 15/24 (62.5%) subjects answered (1), whereas 9/24 (37.5%) answered (2). When treated with MA, 21/27 (77.7%) answered (1) and 6/27 (22.3%) answered (2). Lastly, when subjected to VA, 25/30 (83.3%) answered (1), and the remaining 16.7% (5/30) answered (2).

When chronic elbow pain subjects received PA, 4/11 (36.36%) indicated MA as the mode of treatment, 2/11 (18.18%) correctly reported PA, 1/11 (9.09%) said VA, and the remaining 4/11 (36.36%) did not know. During MA, 3/11 (27.27%) chronic elbow pain subjects correctly indicated MA, 2/11 (18.18%) reported PA, 4/11 (36.36%) indicated VA, and the remaining 2/11 (18.18%) did not know. Finally, all chronic elbow pain subjects (11/11; 100%) denoted VA as the treatment mode during VA. The only pre-defined answer to why the treatment mode was indicated was (1). Figure 4 depicts the distribution of indication as to which treatment mode the subjects received in each of the three sessions.

4.3. Subjective sensations associated with acupuncture; MASS descriptors

The MASS descriptors for healthy subjects, used to describe *Deqi* sensation during acupuncture treatment at LI-4, showed significant differences for aching (p = 0.012), deep pressure (p = 0.001), sharp pain (p = 0.014), dull pain (p = 0.002), and vibration (p < 0.0001) between the three treatment types. Bonferroni *post hoc* analyses revealed decreased scores when comparing PA to MA and VA for descriptors aching (p = 0.004 and 0.006, respectively), deep pressure (p = 0.002 and 0.003, respectively), and dull pain scores (p = 0.016 and 0.005, respectively) (Figure 5, A). Moreover, sharp pain was significantly lower during PA when compared to MA (p = 0.007) (Figure 5, A). Vibration scores were significantly lower for PA and MA when compared to VA (p < 0.005 for both comparisons) (Figure 5, A). At

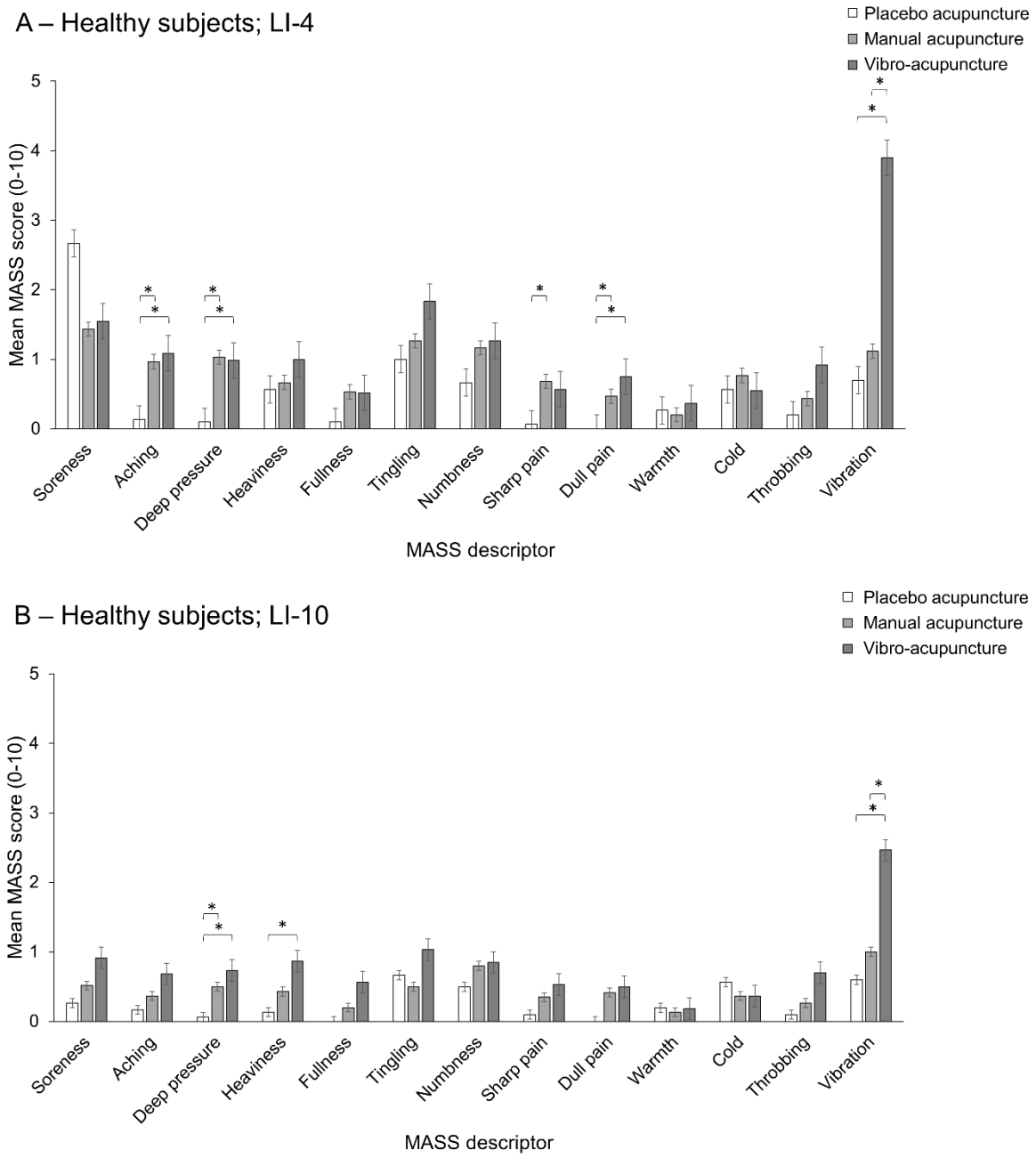

Figure 5. MASS scores for healthy subjects at LI-4 and LI-10 (mean ± SEM). (A) At LI-4, significantly lower scores were found for aching, deep pressure, and dull pain, when comparing PA with MA and VA. Sharp pain was significantly lower when comparing PA to MA, and vibration scores were significantly lower for PA and MA, when compared to VA. (B) At LI-10, PA induced significantly lower scores in deep pressure when comparing PA to MA and VA, whereas heaviness was decreased for PA when compared to VA. Vibration scores were significantly lower for PA and MA when compared to VA. *, $p < 0.0167$. *MASS: MGH acupuncture sensation scale; PA: Placebo acupuncture; MA: Manual acupuncture; VA: vibro-acupuncture.*

LI-10, significant differences were found for MASS descriptors soreness (p = 0.018), deep pressure (p = 0.003), heaviness (p = 0.03), fullness/distention (FD) (p = 0.008), dull pain (p = 0.021), throbbing (p = 0.017), and vibration

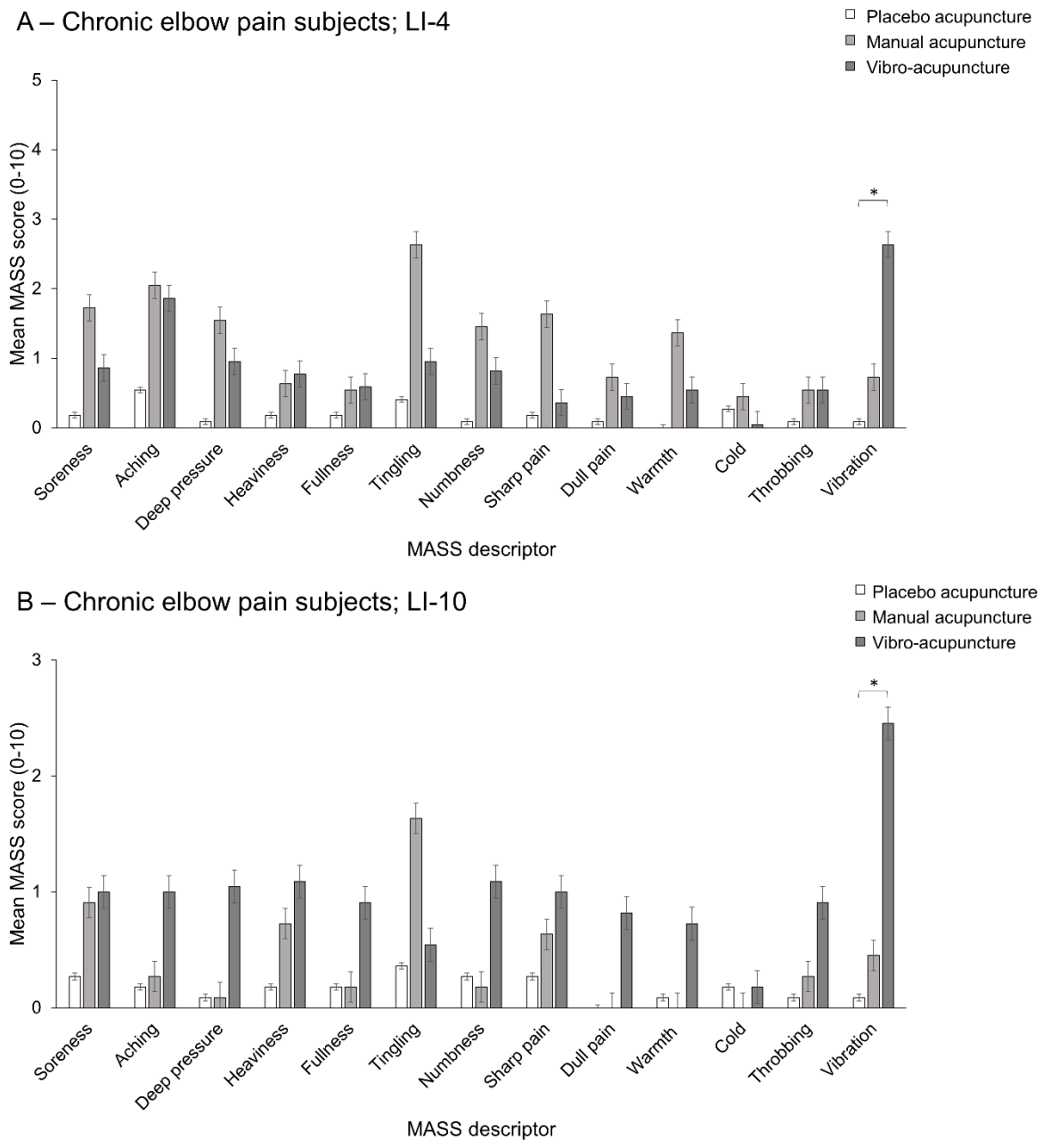

Figure 6. MASS scores for chronic elbow pain subjects at LI-4 and LI-10 (mean ± SEM). (A) At LI-4, a significantly lower score for vibration was found, when comparing PA with VA. (B) At LI-10, PA induced a significantly lower score in vibration, when comparing PA to VA. *, $p < 0.0167$. *MASS: MGH acupuncture sensation scale; PA: Placebo acupuncture; MA: Manual acupuncture; VA: vibro-acupuncture.*

($p < 0.001$). The Bonferroni *post hoc* tests showed lowered scores associated with deep pressure when comparing PA with MA and VA ($p = 0.008$ and 0.004, respectively) (Figure 5, B), and increased scores for VA compared to PA for heaviness ($p = 0.011$) (Figure 5, B). Similar to LI-4, vibration scores were significantly lower for PA and MA when compared to VA ($p < 0.0005$ and $p = 0.002$, respectively) (Figure 5, B). Due to Bonferroni correction, *p*-values

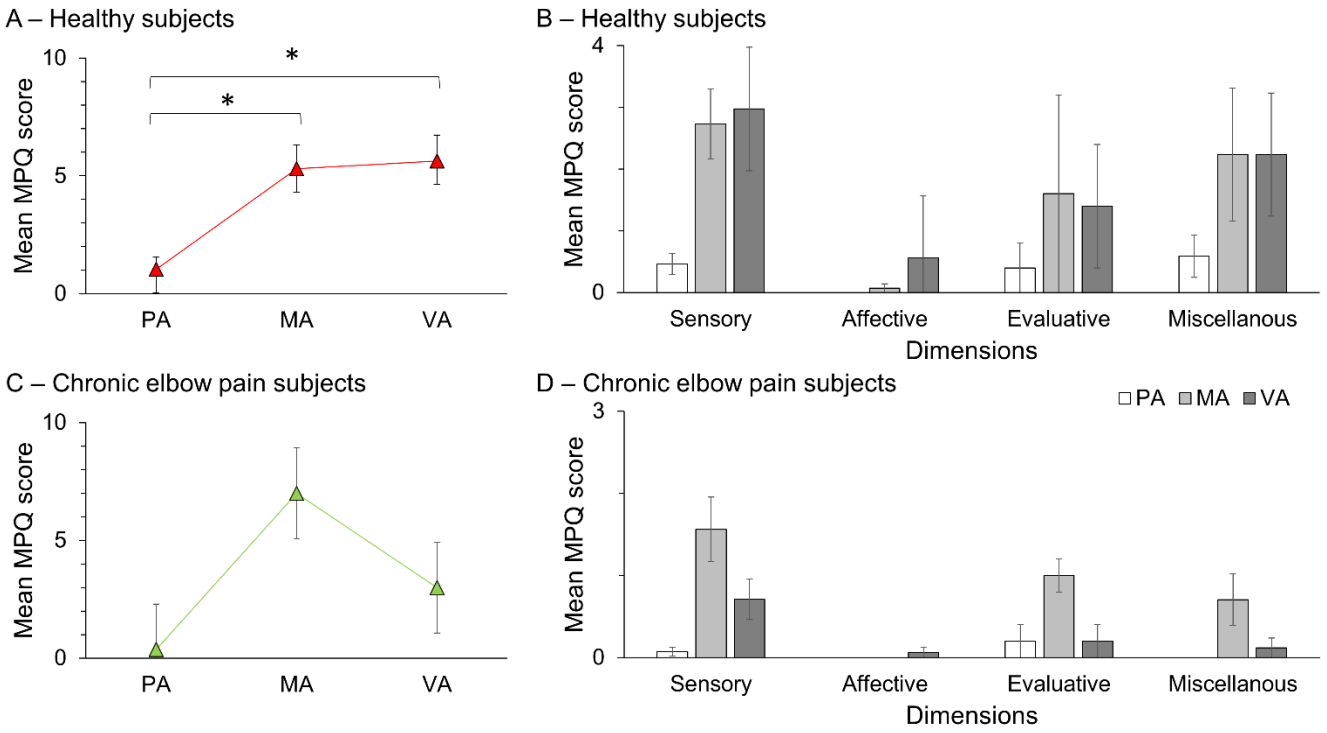

Figure 7. MPQ scores for healthy subjects and chronic elbow pain subjects (mean ± SEM). (A) Significant differences in MPQ scores were found for healthy subjects when comparing PA to MA and VA. The distribution of MPQ descriptors in the four pain dimensions are depicted in (B). For chronic elbow pain subjects, no significant differences were found when comparing PA to MA and VA, or MA with VA (C), albeit differences were observed in the four pain dimensions (D). *, $p < 0.05$. *MPQ: McGills Pain Questionnaire; PA: Placebo acupuncture; MA: Manual acupuncture; VA: Vibro-acupuncture.*

for differences in soreness, FD, dull pain, and throbbing did not reach significance between the three treatments.

For the chronic elbow pain subjects, significant differences in MASS descriptors for *Deqi* at LI-4 were found for tingling (p = 0.006), sharp pain (p = 0.04) and vibration (p = 0.011). For vibration, VA showed significantly higher scores than PA (p = 0.016), but application of Bonferroni correction to the Wilcoxon signed-rank tests, resulted in non-significant differences for tingling and sharp pain (Figure 6, A). At LI-10, only vibration was significantly different across the three treatments (p = 0.004), where VA yielded significantly elevated vibration scores compared to PA (p = 0.011) (Figure 6, B).

4.4. Subjective sensations associated with acupuncture; MPQ and VAS

The healthy subjects most frequently chose MPQ descriptors "pricking", "annoying", "tingling", "cool", and "tender/sharp" for pain during acupuncture across all three treatments. Within PA, the most frequently chosen descriptors were "cool", "pricking", and "annoying". For MA, the five most reported MPQ descriptors were "pricking", "annoying", "sharp", "tingling", and "tender". Lastly, the most often used MPQ words for VA were "pricking", "tingling", "annoying", "stinging", and "sharp/tender/piercing/cool".

Friedman's test for repeated measures on ranks showed a significant difference in MPQ scores dependent on treatment session, χ^2 (2) = 19.50, $p < 0.0005$. Bonferroni corrected *post hoc* Wilcoxon rank signed tests revealed significant differences between PA vs. MA ($p < 0.001$) and PA vs. VA ($p < 0.001$). No differences were found between MA and VA (p = 1)

(Figure 7, A). The quality of the pain associated with acupuncture was distributed across four distinct dimensions of pain; sensory (S), affective (A), evaluative (E), and miscellaneous (M) pertaining to the different descriptors used to describe the sensation during acupuncture. Placebo acupuncture had lower mean scores in all four dimensions compared to MA (S: 0.46 ± 0.17 vs. 2.73 ± 0.57; A: 0 vs. 0.07 ± 0.07; E: 0.4 ± 0.4 vs. 1.6 ± 1.6 M: 0.59 ± 0.34 vs. 2.24 ± 1.07, respectively) and compared to VA (S: 0.46 ± 0.17 vs. 2.98 ± 0.63; A: 0 vs. 0.56 ± 0.14; E: 0.4 ± 0.4 vs. 1.4 ± 1.4; M: 0.59 ± 0.34 vs. 2.24 ± 1.07, respectively) (Figure 7, B). Similarly, the obtained VAS scores across the three treatment groups differed significantly, χ^2 (2) = 19.756, p < 0.0005. Bonferroni *Post hoc* analysis showed a significant difference in reported VAS scores between PA and MA (p = 0.003) and between PA and VA (p < 0.0001) (Figure 8, A).

Chronic elbow pain subjects described the pain associated with acupuncture as "pricking", "stinging", "quivering", "tingling", and "shooting/hot/annoying". For PA, the most used descriptors were "flickering", "itchy", and "annoying", whereas MA yielded "pricking", "quivering", "hot", "stinging", and "shooting/tingling/tender/radiating/tender/cool". Lastly, VA was described with "pricking", "tingling", stinging", and "flickering/quivering/shooting/sharp/dull/aching/heavy/taut/tiring/annoying/numb".

Friedman's test for repeated measures on ranks showed a significant difference in MPQ scores across the three treatment sessions, χ2 (2) = 8.36, p = 0.015. Due to Bonferroni correction, no significant differences were found between PA and MA (p = 0.018), PA and VA (p = 0.042), or MA and VA (p = 0.183) (Figure 7, C). The quality of acupuncture pain was different between treatment PA and MA (S: 0.46 ± 0.17 vs. 2.73 ± 0.57; A: 0 vs. 0.07 ± 0.07; E: 0.4 ± 0.4 vs. 1.6 ± 1.6; M: 0.59 ± 0.34 vs. 2.24 ± 1.07, respectively) and PA and VA (S: 0.46 ± 0.17 vs. 2.97 ± 0.63; A: 0 vs. 0.56 ± 0.14; E: 0.4 ± 1.4 vs. 1.4 ± 1.6; M: 0.59 ± 0.34 vs. 2.24 ± 1.07, respectively) (Figure 7, D). Furthermore, significant differences in VAS scores between the three treatments were found, χ^2 (2) = 6.08, p = 0.048, however, due to Bonferroni correction, the *post hoc* analyses yielded no significant differences between PA and MA (p = 0.027), PA and VA (p = 0.138), or MA and VA (p = 0.461) (Figure 8, B). Additionally, chronic elbow pain subjects were asked to describe their pain using the same MPQ and VAS score for their pain before and after treatment. The two-way RM ANOVA revealed a significant main effect for time on MPQ (p < 0.001) and VAS (p < 0.001) scores, but no main effect of treatment (p = 0.76 and 0.95, respectively) or treatment × time interaction (p = 0.68 and 0.67, respectively) (Figure 9, A and C). The four dimensions

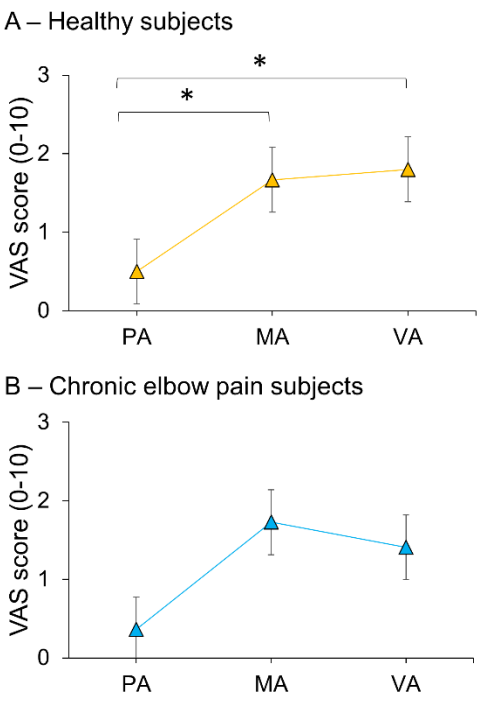

Figure 8. VAS scores associated with each acupuncture treatment (mean ± SEM). (A) For healthy subjects, pain intensity was significantly increased when treated with MA and VA compared to PA. (B) No differences in VAS scores were found for chronic elbow pain subjects. *, p < 0.05. *VAS: Visual analogue scale; PA: Placebo acupuncture; MA: Manual acupuncture; VA: Vibro-acupuncture.*

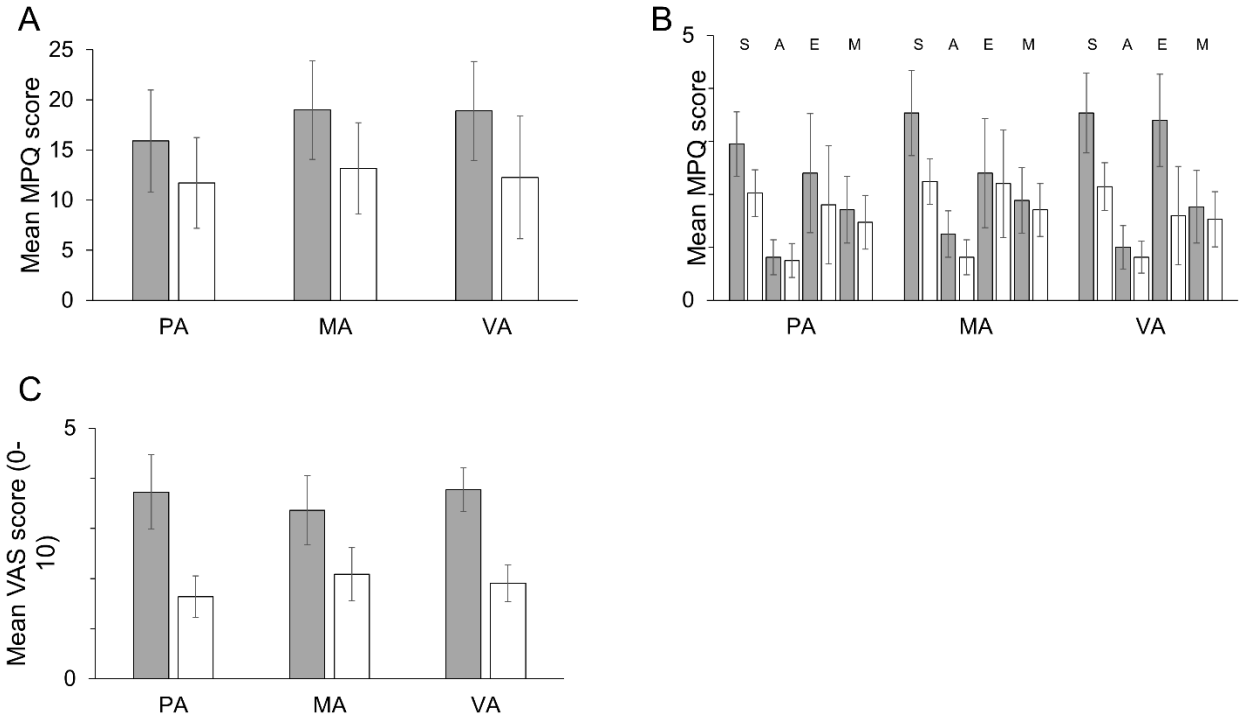

Figure 9. MPQ and VAS scores for chronic elbow pain subjects at baseline vs. post-treatment (mean ± SEM). Grey bars represent baseline measures; white bars represent post-treatment measures. S A E M: Sensory, Affective, Evaluative, and Miscellaneous, respectively. A time-dependent decrease in both parameters was found (A and C), indicating that subjects felt less pain at post-treatment measures during PA, MA, and VA. The dimension distribution of MPQ descriptors for each treatment at baseline vs. post-treatment is shown in (B). *PA: Placebo acupuncture; MA: Manual acupuncture; VA: Vibro-acupuncture.*

of pain were as follows at baseline compared to post-treatment for PA (S: 2.95 ± 0.6 vs. 2.02 ± 0.4; A: 0.81 ± 0.33 vs. 0.75 ± 0.32; E: 2.4 ± 1.12 vs. 1.8 ± 1.11; M: 1.71 ± 0.63 vs. 1.47 ± 0.51, respectively), MA (S: 3.54 ± 0.8 vs. 2.24 ± 0.43; A: 1.25 ± 0.44 vs. 0.81 ± 0.33; E: 2.4 ± 1.02 vs. 2.2 ± 1.02; M: 1.88 ± 0.62 vs. 1.71 ± 0.49, respectively), and VA (S: 3.54 ± 0.75 vs. 2.15 ± 0.45; A: 1 ± 0.41 vs. 0.81 ± 0.3; E: 3.4 ± 0.87 vs. 1.6 ± 0.93; M: 1.76 ± 0.69 vs. 1.53 ± 0.52, respectively), (Figure 9, B).

4.5. Adverse events

All AEs explored in this study were reported at least once, with "needling pain after treatment", "needling/bruising", and "drowsiness/lethargy" being the three most commonly reported for healthy subjects, whereas chronic elbow pain subjects reported "needling/bruising" and "needling pain after treatment". The severity was rated "mild" to "moderate". Other AEs described by the subjects included "sleeping hand", "cold fingers", and "tightening in fingers" with the severity rated similar to the pre-defined AEs.

4.6. Main effects of treatment and time on QST parameters

The two-way RM ANOVA for the QST data of healthy subjects revealed a significant main effect of time with increases in CDT ($p < 0.0001$) and WDT ($p = 0.029$), and decreases in CPT ($p = 0.032$), HPT ($p < 0.00001$) (Figure 10, A-D). Similarly, main effects of time with decreases in MPT ($p < 0.00001$) (Figure 10, F), and increases in PPT for the left arm ($p = 0.019$) and

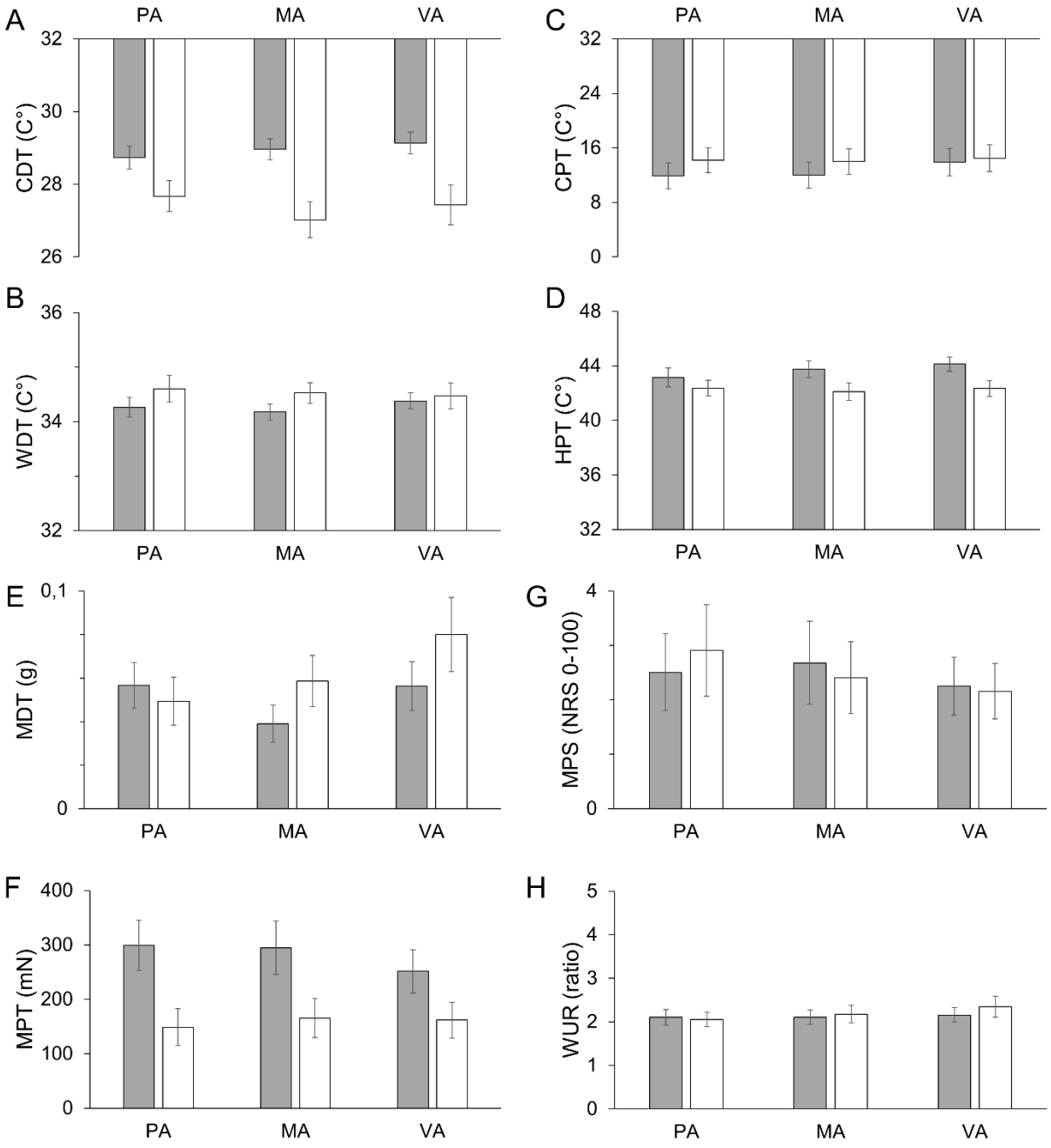

Figure 10. QST parameters for healthy subjects (mean ± SEM). Grey bars represent baseline measures; white bars represent post-treatment measures. Significant time-dependent increases were found for CDT and WDT (A-B), whereas CPT and HPT (C-D) were decreased. In addition, a significant time-dependent decrease in MPT was found (F). *QST: Quantitative Sensory Testing; CDT: Cold detection threshold; WDT: Warm detection threshold; CPT: Cold pain threshold; HPT: Heat pain threshold; PA: Placebo acupuncture; MA: Manual acupuncture; VA: Vibro-acupuncture.*

tibialis (p = 0.016) were found (Figure 10, J) J). In contrast, treatment had no significant main effect on any QST parameter. For chronic elbow pain subjects, a significant main effect of

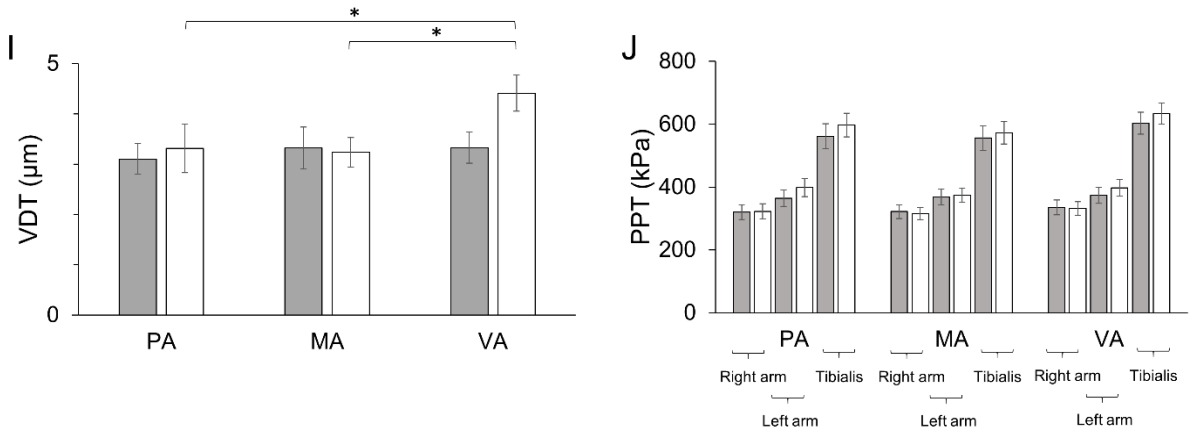

Figure 10-continued11. QST parameters for healthy subjects (mean ± SEM). Grey bars represent baseline measures; white bars represent post-treatment measures. A significant treatment × time interaction was found for VDT, with increased VDT for VA at post-treatment measures, compared to PA and MA. Significant time-dependent increases in PPT was found for the left arm and tibialis. *, $p < 0.05$. *QST: Quantitative Sensory Testing; VDT: Vibration threshold; PPT: Pressure pain threshold; PA: Placebo acupuncture; MA: Manual acupuncture; VA: Vibro-acupuncture.*

time was found for thermal parameters, with increases in CDT ($p < 0.0001$) and WDT ($p = 0.04$), and decreases in CPT ($p = 0.049$) and HPT ($p < 0.001$) (Figure 11, A-D).

4.7. Treatment × time interaction on QST parameters

For the healthy subjects, a significant treatment × time interaction was found for VDT

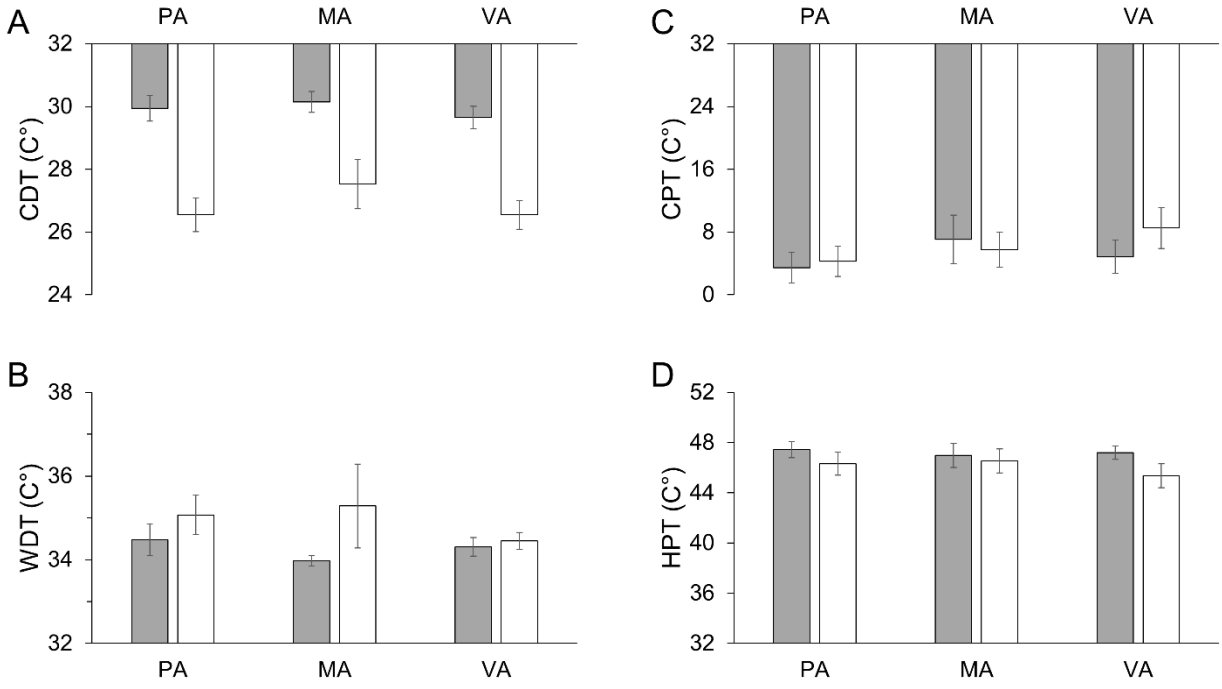

Figure 11. QST parameters for chronic elbow pain subjects (mean ± SEM). Grey bars represent baseline measures; white bars represent post-treatment measures. Significant time-dependent decreases were found for CDT and WDT (A-B), whereas CPT and HPT (C-D) were decreased. *QST: Quantitative Sensory Testing; CDT: Cold detection threshold; WDT: Warm detection threshold; CPT: Cold pain threshold; HPT: Heat pain threshold; PA: Placebo acupuncture; MA: Manual acupuncture; VA: Vibro-acupuncture*

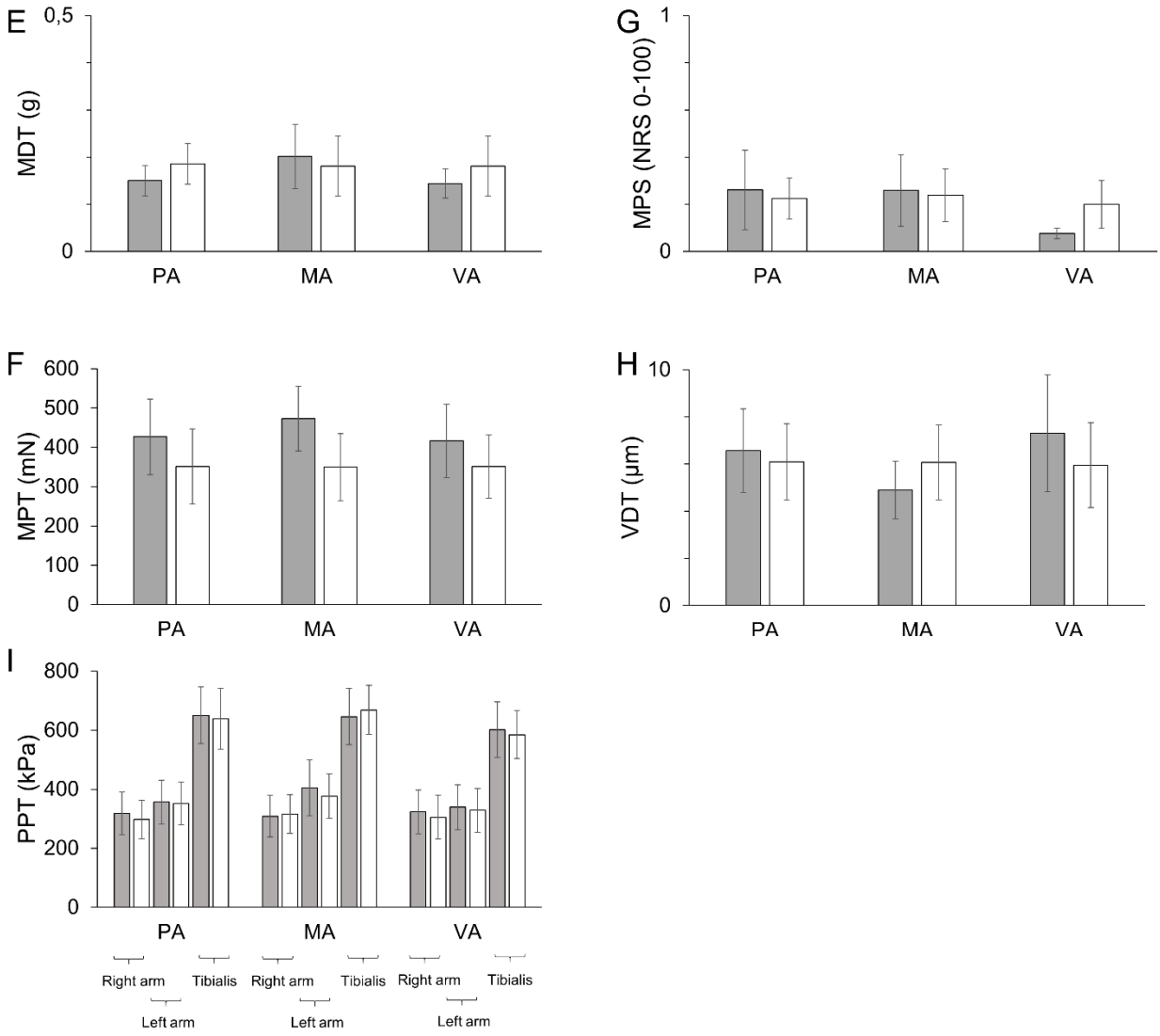

Figure 11-continued. QST parameters for chronic elbow pain subjects (mean ± SEM). Grey bars represent baseline measures; white bars represent post-treatment measures. No significant main effects or interactions were found for MDT (E), MPT (F), MPS (G), VDT (H), or PPT (I). *PA: Placebo acupuncture; MA: Manual acupuncture; VA: Vibro-acupuncture.*

measurements (p = 0.004). The *post hoc* analyses showed no significant differences between the three treatments at baseline (p = 0.699). Conversely, post-treatment measurements were significantly different (p < 0.001), with an increase in VDT at post-treatment measurements after VA (p < 0.001), but not PA (p = 0.717) or MA (p = 0.571) (Figure 10, I). No significant treatment × time interactions were found for any other QST parameter for healthy subjects or chronic elbow pain subjects.

4.8. Relative percentage change for PPT and SPS scores

The one-way RM ANOVA for the relative percentage changes for PPT scores in healthy subjects, showed no significant differences between the three treatment sessions for right

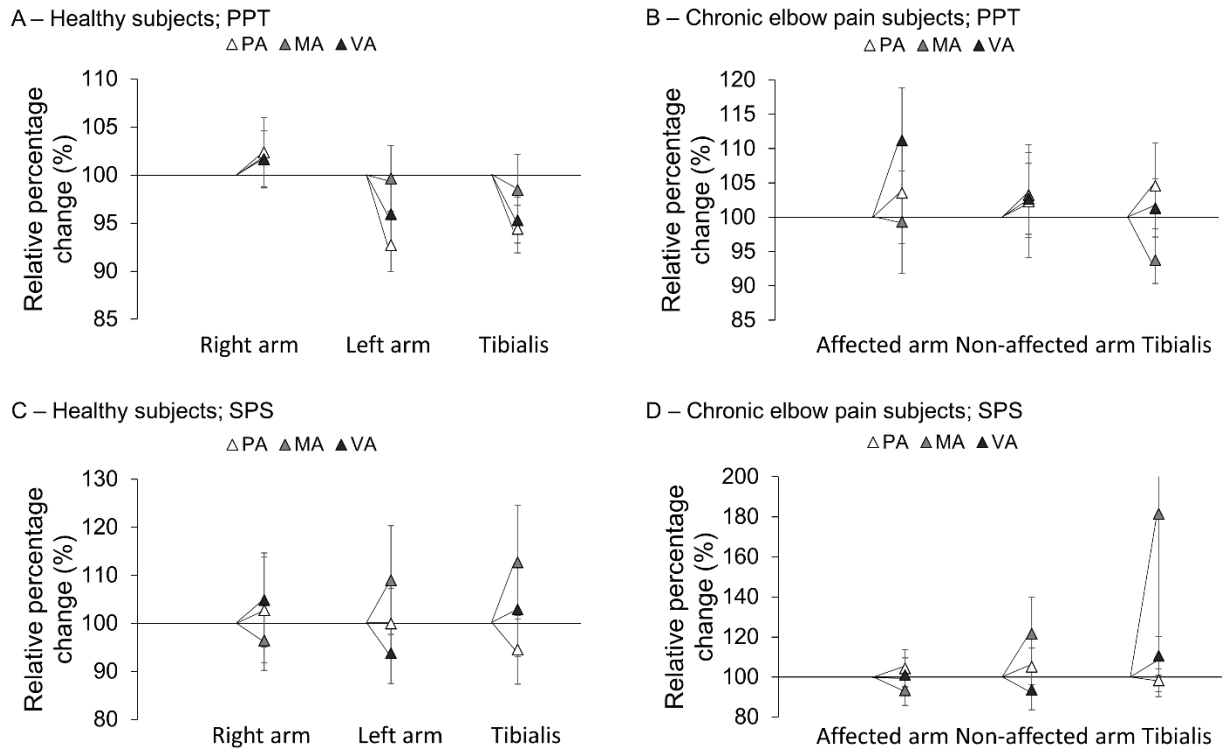

Figure 12. Relative percentage changes in PPT and SPS for healthy subjects and chronic elbow pain subjects (mean ± SEM). No significant differences in the relative percentage changes in PPT or SPS were found for healthy subjects (A-B, respectively) or chronic elbow pain subjects (C-D). *PPT: Pressure pain threshold; SPS: Mechanical suprathreshold; PA: Placebo acupuncture; MA: Manual acupuncture; VA: Vibro-acupuncture.*

arm (p = 0.98), left arm (p = 0.23), or tibialis (p = 0.48) (Figure 12, A), indicating that no treatment type changed the relative percentage change of PPT scores differently in either site. Similarly, the relative percentage changes for PPT scores in chronic elbow pain subjects did not differ between the three treatment sessions for the affected arm (p = 0.35), the non-affected arm (p = 0.99) or tibialis (p = 0.16) (Figure 12, B). Additionally, Friedman's test for repeated measures on ranks for the relative percentage changes in SPS scores in healthy subjects revealed no significant differences between treatment sessions for the right arm (p = 0.84), left arm (p = 0.62), or tibialis (p = 0.39) (Figure 12, C). There were no significant differences in the relative percentage change of SPS scores for chronic elbow pain subjects, between the three treatment sessions, in the affected arm (p = 0.89), the non-affected arm (p = 0.43), or tibialis (p = 0.51) (Figure 12, D).

5. Discussion

The current study applied commonly used subjective sensation scales in relation to acupuncture, MASS, MPQ, and VAS [Kong et al., 2007, Melzack, 1975, Huskisson, 1974], and the standardized QST protocol proposed by DFNS [Rolke et al., 2006b], for testing the sensory response to the novel VA treatment compared to MA and PA in healthy subjects and chronic elbow pain subjects. The primary findings showed a significantly increased VDT for healthy subjects after receiving VA. Thermal parameters for healthy subjects and chronic elbow pain subjects showed significant time-dependent increases (CDT and WDT) and decreases (CPT and HPT). Moreover, for healthy subjects, a significant time-dependent decrease in MPT and increases in PPT in the left

arm and tibialis were found. Elevated scores for *Deqi* sensations (MASS) during acupuncture were found for MA and VA when compared to PA in healthy subjects (aching, deep pressure, dull pain; heaviness for VA compared to PA; sharp pain for MA compared to PA). The sensation of vibration was increased for VA when compared to PA and MA in healthy subjects and for VA compared to PA in chronic elbow pain subjects. In line with the notion that MA and VA introduced elevated sensory responses upon needling, MPQ and VAS scores were significantly elevated for healthy subjects when exposed to MA and VA compared to PA. Interestingly, the same tendencies were seen for chronic elbow pain subjects but due to sample size and statistical considerations, these findings were not significant. Furthermore, a significant time-dependent decrease in both MPQ and VAS scores were found at post-treatment measures in chronic elbow pain patients. These findings and their importance in describing the potential effects of VA in relation to possible analgesic effects and perspectives will be discussed.

5.1. Was double-blinding achieved in the current study?

The assessment of blinding showed a higher percentage of uncertainty or wrong answers towards treatment mode with PA and MA compared to VA in healthy subjects and chronic elbow pain subjects. The successful blinding of a trial necessitates a large percentage of participants indicating the wrong type of treatment, or at best, not knowing what type of treatment mode they received [Kolahi et al., 2009]. Such answers were only given during treatment sessions with PA and MA, whereas for VA, virtually all subjects correctly guessed VA. This suggests that PA and MA sessions were successfully blinded, whereas VA sessions should be considered unblinded. The relatively high percentages of MA and VA indications during treatment with PA and MA, imply an indistinguishable sensation associated with these treatments. This is further supported by the underlying reason for indicating MA and VA: "the sensation of the acupuncture stimulation" and "the experience of the acupuncture procedure; actions of the acupuncturist and how it felt", both pertaining to the subjective perception of the treatment procedure. In contrast, the correct and mainly uniform indication pattern observed for VA, suggests that the sensation perceived during this treatment inhibits the aim for successful double-blinding. Unfortunately, it remains consequently difficult to obtain blinding during acupuncture trials given the strong perceptual sensations related to the needling and subsequent manipulation [Lin et al., 2012, Kim et al., 2014]. There is an apparent need for placebo acupuncture methods where the physiological effect is inert and challenging to distinguish from the true treatment(s), which in turn would increase internal validity and blinding of studies [Moroz et al., 2013]. In their original paper, Streitberger and Kleinheinz [1998] described the PA needle utilized in the present study, as being successful in inducing a penetrating sensation similar to MA. These findings are largely in accordance with the current results, since a majority of subjects was unable to distinguish PA from MA and VA when the placebo needle was employed, and MA from PA and VA when MA was applied. This also supports the notion that the placebo needle is an effective tool for, at least partly, blinding subjects. However, such blinding effect was not evident during the sessions with VA, where the acu-vibrator was directly attached to the needles, indicating that the vibration introduced by the device supersedes the masking of treatment mode. The importance of needling sensation was recently investigated in a study where both participants and acupuncturists were asked to indicate the treatment (active acupuncture vs. placebo acupuncture; non-penetrating needles, similar in

procedure as the current study), in view of elucidating possible factors detrimental to successful blinding [Vase et al., 2015]. The authors concluded that the feeling of *Deqi* may be a strong indicator for the perceived treatment mode, which ultimately results in unsuccessful blinding, given the high return of correct identifications of treatment from both acupuncturists and patients [Vase et al., 2015]. Therefore, coupled with a sensation not related to *Deqi* (i.e. vibration), this may partly explain why VA was evidently difficult to blind in the current study. The adjacent placement of the acu-vibrator device during PA and MA may have adequately introduced the belief that vibration was transmitted through the needles, and therefore promoted answers differing from the actual treatment. However, this notion is a double-edged sword, since this same vibration was generally too distinct to yield incorrect answers during the VA treatment. As such, the present results warrant optimization of the VA treatment if it is to be tested in clinical settings, since the importance of participant blinding is essential for yielding unbiased data [Walji and Boon, 2006]. Such optimization could potentially be obtained through a pilot study, using different frequencies and amplitudes for the acu-vibrator device, to test the minimum and maximum effect at various settings. This would allow for a broader analysis of the impact of the vibration, and if this can in fact be disguised in a more sufficient matter.

Taken together, the current study seemingly failed to achieve successful double-blinding in the sense of subjects being blinded towards treatment mode throughout all three sessions. This could introduce bias during the measurements (QST, SPS, and subjective sensation scales), and should be considered when appraising the results presented. On the other hand, the outcome assessor (the author; DBL) of QST measures, the subjective sensations/indications, and relative percentage changes of PPT and SPS remained blinded throughout the entire study period, until all statistical analyses were carried out in accordance with section 3.4. Several reviews have touched upon the subject of placebo-groups for acupuncture trials throughout the last decade, and it seems that no gold standard is yet available [Lin et al., 2012, White et al., 2001]. In view of increasing the internal validity and minimize potential bias, it is crucial to overcome this detrimental part of acupuncture research in the future. Moreover, it seems that blinding is commonly misconstrued in the sense of correctly identifying the overall success [Kolahi et al., 2009]. This does not become any less important when aiming for double-blinding as the current study proposes. Several statistical analyses have been suggested to account for the lack of evidence with regards to blinding, notably the James' and Bang's blinding index (BI) [Bang et al., 2004]. These BIs approach blinding in different ways, where James' BI deals with the level of disagreement (modified kappa-statistics) with 'not knowing' being the primary drive for statistics, whereas Bang's BI relies on the balance of correct vs. incorrect guesses [Bang et al., 2004]. Thus, complementary application of these statistical methods may prove to be integral and allow for more in-depth analysis and correct estimation of blinding success of future acupuncture trials testing newly invented devices such as the acu-vibrator.

5.2. Subjective sensations

5.2.1. *Deqi* sensations

The present results indicate that all three treatments induced some degree of *Deqi*. In addition, when assessing the MASS scores at LI-4, significant decreases for MASS descriptors aching, deep pressure, and dull pain were found for healthy subjects when comparing PA with MA and VA. At LI-10, deep pressure was rated significantly lower for PA compared to MA and VA, and heaviness was increased for VA compared to PA. Moreover, the sensation of sharp pain was elevated during MA sessions

compared to PA, however, a recent review highlighted that sharp pain should not be considered a part of *Deqi* [Zhu et al., 2013]. The modified MASS included the vibration descriptor as a mean of testing the sensation of vibration elicited by the acu-vibrator device during acupuncture, and for healthy subjects, increased scores were found at both LI-4 and LI-10, when comparing VA with PA and MA. For chronic elbow pain subjects, vibration was only significantly increased during VA when compared to PA. In contrast, no other *Deqi* sensations were different between the three treatments.

Several studies have investigated the sensations associated with *Deqi*, and while controversy still remains, sensations such as soreness, aching, heaviness, distention, tingling, numbness, and dull pain have all been described [MacPherson and Asghar, 2006, Park et al., 2002a, Leung et al., 2006]. Moreover, other sensations such as cold and warm have been used to characterize *Deqi* [Zhu et al., 2013, Kong et al., 2007]. An early study demonstrated that different afferent fiber types are implicated in conveying the sensations for *Deqi*, with soreness mainly carried by C-fibers, numbness by Aβ-fibers, and aching and fullness (heaviness/distention) by Aδ-fibers [Wang et al., 1985]. In addition, pressing and dull sensations have been reported to be conducted by C-fibers [Beissner et al., 2010]. On a central level, the activation of these afferent fibers have been shown to induce activity in several brain regions, dependent on the *Deqi* sensation. In a series of fMRI studies, Hui and colleagues reported a distinct difference in brain areas associated with the cortical and paralimbic-limbic system during needle manipulation (*Deqi*), with decreased activity in several areas associated with the perception of pain, indicating an analgesic effect [Hui et al., 2000, Hui et al., 2005]. In support, an association between the analgesic effect of acupuncture and *Deqi* has been suggested. For instance, Chiang et al. [1974] reported correlation between *Deqi* descriptors numbness, distention, and soreness and acupuncture analgesia. Moreover, Kong et al. [2005] showed a significant correlation between analgesia and *Deqi* descriptors soreness and numbness at LI-4, ST-36, and SP-6, whereas other common descriptors for *Deqi* such as throbbing, tingling, and distention were not associated. Together, this indicates that the specific activation of peripheral afferent fibers by acupuncture and *Deqi* yields an analgesic response, albeit controversial evidence exists [Takakura and Yajima, 2009, Shi et al., 2014]. The lack of treatment effect on pain parameters in the current study will be discussed in section 5.3.

In support of the increased sensory response to needle penetration and manipulation, Hui and colleagues [2007] conducted a study in which they characterized *Deqi* sensations such as aching, soreness, dull pain, and tingling as frequent descriptors associated with MA compared to non-invasive tactile stimulation. They further expanded on the relative differences in frequency and intensity of *Deqi* felt at distinct acupoints, notably LI-4, ST-36, and LV-3, indicating a divergence in afferent fiber types between the three sites of testing, with Aβ-, Aδ- and C-fibers all attaining an essential role in *Deqi* [Hui et al., 2007]. The present results from healthy subjects augments this notion, with an elevated *Deqi* response for acupuncture (MA/VA) compared to the non-invasive placebo. Interestingly, at LI-4, healthy subjects exhibited a tendency towards increased soreness when treated with PA compared to MA and VA (non-significant). This same tendency was not seen for LI-10, further supporting the concept of fiber type diversity dependent on the target site. Moreover, the significant findings in *Deqi* sensations between treatments at LI-4 (comprising all three fiber types) compared to LI-10 (C- and Aβ-fiber conveyed sensations), indicate a difference in afferent fiber density at the two sites tested, however, this remains a

speculation as of now [Hui et al., 2007]. A logical explanation as to why subjects generally scored lower in *Deqi* descriptors when receiving PA could be the non-invasive nature. Choi et al. [2013] reported that the depth of the needle penetration is important when aiming for a substantial acupuncture sensation. This supports the finding that *Deqi* sensations were not felt at the same magnitude when subjected to PA.

An intriguing observation is the non-significant differences in MASS scores for PA compared to MA and VA across the different *Deqi* descriptors (except aching, deep pressure, heaviness, and dull pain), indicating that the placebo needle induced sensations comparable to that of the penetrating needles, and may partly explain why PA obtained a large degree of uncertainty towards indication. This is especially true for the chronic elbow pain subjects, where no significant differences were found for *Deqi* sensations between the three treatments, although this may be ascribed to the low sample size (n = 11) and therefore increased variance, which should be taken into consideration. Arbitrary appreciation of the results indeed stipulates a need for including more subjects in view of understanding the full range of sensations associated with *Deqi* in the chronic elbow pain subjects.

Returning to the notion of *Deqi* attaining an adverse role in blinding, a recent study reported that three acupuncture procedures considered placebos were not successful in blinding subjects from actual punctuation of the skin [Wong et al., 2015]. The widely used term 'sham-acupuncture' has been used as a placebo control in several studies, and comprise distinctly different types such as superficial needling at acupoints, insertion of a needle in acupoints irrelevant for treatment of the condition, and needling outside acupoints [Dincer and Linde, 2003]. This type of intervention (and placebo in general) serves to address issues with measuring the specific effects of acupuncture as opposed to measuring placebo effects, however, its validity has been challenged and ascribed to e.g. the ubiquitous distribution of fibers and consequently activation during acupuncture [Moffet, 2009, Lund and Lundeberg, 2006]. Therefore, in accordance with the points discussed in section 5.1., the impact of *Deqi* and the needling sensation seem to be essential factors during acupuncture [Lundeberg, 2013] (and the lack of blinding hereof), which possibly could influence the psychophysical response of the subjects included. This is further exemplified when appraising the increased sensation of vibration during VA, which suggests that *Deqi* together with vibration yield a very distinct sensory response, which cannot be concealed or mistaken for PA or MA. It could be speculated that the afferent fibers conveying the many different *Deqi* sensations and vibration, together forms an amplified perception of vibration, which could explain the very one-sided indication after VA treatment. It is, however, much more likely that since vibration is not a classical sensation of *Deqi* [MacPherson and Asghar, 2006], the perception introduces a prominent sensation for the subjects. Given the nature of the treatments, vibration played an essential role both as direct stimuli for VA and as a perceptual illusion during PA and MA. Based on the results, the adjacent placement of the acu-vibrator device may have been insufficient in serving this intended purpose. Therefore, optimization of the study protocol in terms of masking the sensation of vibration may be warranted.

Together, the present results of the MASS scores demonstrate a collective activation of all three afferent fiber types during the acupuncture treatments, with significant increases in Aδ- (aching), C-fiber (deep pressure, heaviness, and dull pain) and Aβ-fiber (vibration) conveyed sensations when comparing MA and VA to PA. Furthermore, the similar ratings in

important *Deqi* sensations for MA and VA indicates that VA yields sensations similar to MA, despite the different approach of stimulation. This is an important conclusion for future researches involving VA, since *Deqi* is a common goal for any study undertaking the effects of acupuncture [Zhu et al., 2013].

5.2.2. Subjective sensation scales; MPQ and VAS

In relation to the findings from the MASS scores, the results from the VAS (pain intensity) and MPQ (quality of pain) employed for assessing the pain associated with the acupuncture treatments support the notion of elevated sensory response to MA and VA compared to PA. The healthy subjects had increased MPQ scores allocated across the sensory, evaluative, and miscellaneous dimensions of pain when treated with MA and VA, corroborated with increased VAS scores. Similarly, the chronic elbow pain subjects also showed increases in MPQ and VAS scores with a comparable distribution in the dimensions of pain and pain intensity, however, due to sample size (n = 11) and statistical considerations, these were not significant.

The original paper describing the placebo needle utilized in the present study, demonstrated a small difference in VAS scores between MA and PA, and the authors concluded that the difference did not reveal what type of acupuncture the subjects had received [Streitberger and Kleinhenz, 1998]. In support, the Park's sham device [Park et al., 2002b], which is similar in procedure as the Streitberger needle, was shown to elicit pain intensity in the same magnitude as the penetrating needles. The presented results are in sharp contrast to this notion. The observed difference between the mean VAS scores between PA and MA was less than was found in the original description, and was still significantly elevated for MA. However, where Streitberger and Kleinheinz [1998] only tested at LI-4 and Park et al. [2002b] needled at TE-5, the current study inserted needles at both LI-4 and LI-10, which could potentially lead to reduction in reported VAS scores, when the subjects reported the pain intensity based on the sensation at both sites. The underlying reason for discrepancies in pain intensity between the studies, await further clarification but may be ascribed to differences in afferent fiber allocation at the sites tested and/or subjective differences in pain perception.

The present findings also advocate that VA induced a similar experience as MA in healthy subjects with regards to pain quality and pain intensity, suggesting that these two distinctly different approaches may be perceived alike. Returning to the elevated sensations of *Deqi* for MA and VA compared to PA, this notion is supported by the fact that significant differences in pain quality and pain intensity for the healthy subjects, were mainly between PA and MA/VA, but not MA and VA. This is, to the best of our knowledge, the first time similarities between MA and the novel VA in relation to *Deqi* sensation, pain quality, and pain intensity in healthy subjects have been demonstrated. This warrants for the introduction of VA into more extensive research in view of elucidating potential analgesic effects, since the present results indicate that it can be readily included as a treatment group with features similar to MA.

5.3. Acupuncture effects on QST and pain

5.3.1. Treatment × time interaction

In the current study, VDT was significantly increased at post-treatment measurements when the healthy subjects were treated with VA compared to PA and MA. In relation to acupuncture, controversial evidence on the impact on VDT is available and has mainly been conducted in diabetic patients exhibiting peripheral neuropathy. In a study including 42 diabetic patients, a significant increase in VDT

was found following 15 days acupuncture treatment when compared to a sham-acupuncture group [Tong et al., 2010]. In contrast, Abuaisha et al. [1998], reported that a 10 week study with 46 diabetic patients who responded to acupuncture treatment, did not find any significant changes in VDT throughout the period. However, these two contrasting findings may be ascribed to differences in the site of measurement (medial malleolus for the Tong study, and the great toe for the Abuaisha study), length of the study (15 days vs. 10 weeks), or duration of the neuropathy. An earlier study supported the lack of impact on VDT in healthy subjects, after treating with MA, EA (low and high frequency), and superficial placebo acupuncture [Lundeberg et al., 1989]. The present results are in accordance with the reported findings that MA did not affect VDT, however, considering the discrepancies in the literature, this call for further investigations. In addition, the current findings suggest that VA induces significant sensory loss for vibration compared to PA and MA in healthy subjects. Vibration is primarily conveyed by large myelinated Aβ-fibers [Devor, 2009], and a plausible reason could be that the local afferents affected by VA became desensitized during the treatment. This novel finding suggests that VA can induce changes in sensory perception, although, in view of unravelling the potential of desensitization of Aβ-fibers, further research is needed.

5.3.2. The main effect of time on QST and pain parameters

Significant time-dependent differences were found for thermal QST parameters, with significant increases for CDT and WDT, and decreases for CPT and HPT in both healthy subjects and chronic elbow pain subjects, indicating an involvement of Aδ- and C-fibers.

Existing evidence regarding the effect of MA and EA on thermal sensations is somewhat controversial. A study utilizing the same QST protocol for thermal testing as the current together with Park's sham device [Park et al., 2002b] for placebo, found no significant differences between the verum acupuncture group, the placebo group, and a non-treated control-group in terms of thermal detection thresholds and thermal pain thresholds [Downs et al., 2005]. These results are in agreement with the findings from the current study, where no significant differences between PA, MA, and VA on thermal QST parameters were found. In contrast, several other authors have shown significant effects of MA and EA on different thermal parameters. For instance, a study using the cold-pressor test found that acupuncture at sites LI-4, TE-5, and SI-4 significantly increased CPT in healthy subjects when compared to sham acupuncture and a non-treated control group [Amand et al., 2011]. Moreover, Leung et al. [2008], demonstrated an increase in cold detection threshold, with sustained warm threshold elevation, as a result of longer duration EA (i.e. 15 minutes > 30 minutes), suggesting a shift in peripherally mediated spinal analgesia, to supraspinal modulation of thermal pain. Lang and colleagues [2010] reported significant increases in HPT in the lower limbs following MA and high-frequency EA at SP-6 and 9, ST-36, and GB39, with MA introducing segmental effects (i.e. bilateral increase of HPT). This was further expanded upon, when another study tested the CPT in the lower limbs, following EA at SP-6 and ST-36 with different durations (0 min, 20 min, 30 min, and 40 min), with the 30 mins duration yielding a significantly reduced CPT [Wang et al., 2009]. It is important to note that the different methodologies and stimulation points employed in a large majority of studies investigating the effect of acupuncture on QST parameters, inhibits comparisons and overall yields an unclear effect of acupuncture [Baeumler et al., 2014].

Thermal perception is mediated by Aδ- and C-fibers, and the increased detection thresholds suggest that Aδ-fibers (cold) and C-fibers

(warm) became desensitized during the experimental sessions which supports findings from an earlier study [Leung et al., 2008]. In contrast, the CPT and HPT were significantly decreased when comparing baseline measures with post-treatment measures, indicating a sensitization of Aδ-fibers (cold pain) and C-fibers (heat pain). Such paradoxical effect may imply differences in peripheral and/or central processing of thermal detection and thermal pain, a notion that calls for further elucidation. It is, however, important to consider that a main effect of time removes the treatment factor from the equation, and the differences observed are merely absolute values (baseline vs. post-treatment across all three sessions), and could be a result of repeated testing. Indeed, Palmer and Martin [2005] reported significant changes in CDT, WDT, and HPT when running several cycles of thermal testing (i.e. repeated testing) within one hour, using the same procedure as the DFNS protocol promotes. However, these findings were not evident when testing the same parameters from day-to-day, and the small significant changes in CDT and CPT were still within normal range values [Agostinho et al., 2009]. The time frame of testing in the current study is close to the one hour mark, and as such, the findings from the aforementioned study should be taken into consideration. Such notion warrants further investigations, especially when repeated measures are an integral part of the study protocol.

Healthy subjects demonstrated a time-dependent significant reduction in MPT at post-treatment compared to baseline, indicating sensitization of Aδ-fibers. A small amount of studies has assessed MPT in healthy subjects with regards to acupuncture, mostly focusing on EA [Baeumler et al., 2014]. A desensitizing effect of EA was found in three studies [Pauser et al., 1975, Lynn and Perl, 1977, Lang et al., 2010], and the latter failed to show any effect of MA. In contrast, a recent investigation by Lee and colleagues [2014] found no significant changes in MPT following EA. The current results contradicts the findings from the aforementioned studies, since a significant decrease in MPT over time was found. Interestingly, a recent study investigated the order of the DFNS protocol, and the possible impact of thermal testing before mechanical testing [Grone et al., 2012]. They reported a factor two reduction of MPT, when tested after thermal QST parameters compared to before, indicating an possible flaw in the current DFNS protocol, since the mild heat stimulus (activation of nociceptors) may induce increased response in central neurons, yielding mechanical hyperalgesia [Grone et al., 2012]. This could partly explain the time-dependent decrease in MPT in the present study, and would further support the notion that neither PA, MA, nor VA had any significant effects on MPT.

For the healthy subjects, a time-dependent increase in PPT was found in the left arm and tibialis. This could indicate that Aδ- and C-fibers became desensitized during the experimental sessions, but not due to effects of the acupuncture treatments. These findings are in sharp contrast to several lines of evidence, reporting increases in PPT following both MA and EA, for healthy subjects [Schliessbach et al., 2011, Li et al., 2008], fibromyalgia patients [Targino et al., 2008], temporomandibular joint pain patients [Vicente-Barrero et al., 2012], and several other disorders [Baeumler et al., 2014]. It is therefore unexpected that the current study did not owe up to the analgesic potential of acupuncture, shown in other chronic pain disorders. Earlier evidences have shown that MA is effective in lowering pain, at least short-term, and improving the overall mobility for tennis elbow patients [Fink et al., 2002, Molsberger and Hille, 1994, Trinh et al., 2004], however, the present results show no significant improvement in MPQ or VAS scores based on treatment, when comparing baseline measures with post-treatment measures. Interestingly,

both parameters were reduced for each treatment, which could indicate a possible placebo effect of PA. Furthermore, other pain parameters such as PPT and SPS were tested in the current study, to investigate the possibility of segmental and central effects of acupuncture [White, 2009]. When testing the relative percentage changes for each site (right/affected arm; left/non-affected arm; and tibialis), no significant differences were found between the three treatments, suggesting that neither PA, MA, nor VA yielded any significant superior effect on either site. The low sample size (n = 11) may explain why no significant effects could be found in chronic elbow pain subjects. It is also possible, that segmental and central effects could be concealed by placebo effects. A recurrent discussion regarding placebo acupuncture has been the possible physiological impact such intervention introduces [Lin et al., 2012]. This issue is not confined to the lack of PPT increase, but may be applicable for the lack of overall treatment efficacy in relation to pain in the current study. In order to fulfill the definition of a credible placebo, the procedure must be physiologically inert and should imitate the verum treatment. However, there is currently no golden standard for credible placebo controls in acupuncture research, and controversial evidence exists. This yields two specific problems. First, placebo-control is necessary for distinguishing a probable effect of the treatment of interest, to ensure that the results are acupuncture-specific more so than non-specific, and second, any physiological intervention in which participants are presented to a stimuli may induce a physiological response, which ultimately reduces the observed effect of the treatment tested. Earlier evidence estimated the analgesic effect of placebo acupuncture to be 40%-50% of verum acupuncture [Lewith and Machin, 1983]. A more recent systematic review on the effect of acupuncture compared to placebo acupuncture and no-acupuncture, showed only a small analgesic effect with lack of clinical relevance (based on e.g. VAS scores and other pain scales) [Madsen et al., 2009]. This indicates that placebo groups implemented in accordance to current standards may not fully meet their intended purpose. This could potentially lead to misconception of study results, showing no treatment effect, when in fact the placebo group is not physiologically inert, and therefore induces responses similar to the treatment type of interest. If this applies to the current study, this would explain why the results do not show any significant superiority for MA and VA compared to PA. If this notion holds true, it would imply that both MA and VA show equal tendencies with regards to increasing e.g. PPT, SPS, and MPT measures, at least in the healthy subjects. It remains unknown whether PA had a therapeutical effect on both the healthy subjects and chronic elbow pain subjects, however, the findings from the MASS scores (*Deqi*) suggests that a possible placebo analgesic effect cannot be ruled out.

In summary, the current study did not achieve successful double-blinding as proposed, due to difficulties in masking the sensations during VA. This impact can be ascribed to several factors such as the increased *Deqi* response found for MA and VA when compared to PA, together with a significant perceptual response to vibration. Moreover, since pain quality and pain intensity were both significantly elevated during MA and VA, this further adds to the complexity in blinding the participating subjects. For the QST parameters, VA did not show a superior effect in increasing sensory or pain thresholds over MA and PA, except VDT. However, given the main effect of time on thermal thresholds, MPT, and PPT, it could be speculated that a placebo effect may have obscured the true analgesic potential of MA and/or VA, witnessed by e.g. the significantly lower pain quality and intensity for chronic elbow pain subjects following treatment with either acupuncture type. It is important to note, that VA was shown to

be similar to MA in both *Deqi* responses and pain quality/intensity, which warrants for further investigations into the analgesic properties of the novel combination of acupuncture and vibration.

5.4. Methodological considerations and limitations

The current study has several limitations and methodological considerations that should be addressed. First, the low number of chronic elbow pain subjects eligible in accordance with the inclusion criteria, naturally limits study power and ability to detect significant differences for the QST and pain parameters, and may partly explain why no significant effect of treatment was found for chronic elbow pain subjects. Given the self-limiting nature of tennis elbow, it was found to be quite comprehensive and difficult to fulfill the quota of 30 chronic elbow pain subjects in due time for the current thesis. In addition, since age and gender were not restricted during recruitment, it is not possible to draw comparisons across groups (healthy subjects vs. chronic elbow pain subjects). Another, unexpected limitation was the unsuccessful blinding of participants when treated with VA. It was clear from the results, that successful double-blinding was not achieved. Therefore, in order to obtain an increased internal validity excluded for bias, as well as gaining more confidence in the results presented, optimization of the VA treatment is warranted for future studies.

By employing the standardized QST protocol, the methodology itself limits the objectivity of the measurements, since the nature of psychophysical studies revolves around ratings and perception of the included subjects. It is therefore a protocol prone to bias through several psychological factors such as expectations, habituation, and coping strategies [Finniss et al., 2010, Lee et al., 2014]. Moreover, the DFNS protocol is specifically aimed at testing sensory gain and loss at local points, and in consideration of the possible segmental and central effects of acupuncture, the current study attempted to assess differences across three different sites. This was done without consideration of actual treatment × site interaction, but was merely tested as differences in the relative percentage changes for PPT and SPS at the three sites. Such statistical approach may not be suitable for the overall aim of testing for site differences, and should be addressed in the future.

Several subjects at the start of the sessions had experienced acupuncture before. The impact on the study results are not known, and introduces a methodological limitation to the current study setup, since this was not considered in relation to e.g. *Deqi* sensations, MPQ, or VAS. Therefore, the acupuncture experience should be recorded in future research and taken into consideration during the statistical analysis. However, a Korean study showed that expectations compared to actual sensations did not significantly differ between acupuncture naïve vs. acupuncture experienced participants [Park et al., 2005]. Whether this impacts the subjective ratings of *Deqi*, MPQ, and VAS in the current study remains unknown.

6. Conclusions

The current study investigated the analgesic effects of the novel VA treatment, which combines MA with vibration. Results obtained from 30 healthy subjects and 11 chronic elbow pain patients revealed a novel effect on VDT, suggesting that VA induces specific changes in Aβ-fibers. In contrast, VA did not prove superior to PA and MA in increasing pain thresholds or modulate sensory detection of thermal or mechanical stimuli. Moreover, there was no remarkable analgesic effect for VA compared to PA and MA, but a placebo effect cannot be ruled out. As such, based on the present findings, the specific hypotheses of the current thesis were disproven, however, warrants further

investigations with a larger sample size for chronic elbow pain patients. Lastly, VA was remarkably similar to MA in sensations associated with *Deqi* and pain quality and intensity, suggesting that it could attain a prominent role in future studies, in view of elucidating possible analgesic effects.

7. Acknowledgments

The author would like to express his deepest gratitude and appreciation to the study supervisor Kelun Wang for his indispensable guidance and advice in the laboratory when conducting the experiments, constructive criticism during the creation of the current thesis, and intellectual conversations. Moreover, special thanks go to Tanja Kim Jensen, for her assistance in performing acupuncture during the project period. Her help has been of utmost importance for the completion of the sessions required for the current project, and it would not have been possible to complete as many participants without her. This project was financially supported by Aalborg University, Center for Sensory-Motor Interaction and the bEir initiative.

8. Bibliography

ABRAIRA, V. E. & GINTY, D. D. 2013. The sensory neurons of touch. *Neuron,* 79**,** 618-39.

ABUAISHA, B. B., COSTANZI, J. B. & BOULTON, A. J. 1998. Acupuncture for the treatment of chronic painful peripheral diabetic neuropathy: a long-term study. *Diabetes Res Clin Pract,* 39**,** 115-21.

AGOSTINHO, C. M., SCHERENS, A., RICHTER, H., SCHAUB, C., ROLKE, R., TREEDE, R. D. & MAIER, C. 2009. Habituation and short-term repeatability of thermal testing in healthy human subjects and patients with chronic non-neuropathic pain. *Eur J Pain,* 13**,** 779-85.

AHMAD, Z., SIDDIQUI, N., MALIK, S. S., ABDUS-SAMEE, M., TYTHERLEIGH-STRONG, G. & RUSHTON, N. 2013. Lateral epicondylitis: a review of pathology and management. *Bone Joint J,* 95-B**,** 1158-64.

AMAND, M., NGUYEN-HUU, F. & BALESTRA, C. 2011. Acupuncture effect on thermal tolerance and electrical pain threshold: a randomised controlled trial. *Acupunct Med,* 29**,** 47-50.

ARENDT-NIELSEN, L. & YARNITSKY, D. 2009. Experimental and clinical applications of quantitative sensory testing applied to skin, muscles and viscera. *J Pain,* 10**,** 556-72.

BACKONJA, M. M., WALK, D., EDWARDS, R. R., SEHGAL, N., MOELLER-BERTRAM, T., WASAN, A., IRVING, G., ARGOFF, C. & WALLACE, M. 2009. Quantitative sensory testing in measurement of neuropathic pain phenomena and other sensory abnormalities. *Clin J Pain,* 25**,** 641-7.

BAEUMLER, P. I., FLECKENSTEIN, J., TAKAYAMA, S., SIMANG, M., SEKI, T. & IRNICH, D. 2014. Effects of acupuncture on sensory perception: a systematic review and meta-analysis. *PLoS One,* 9**,** e113731.

BANG, H., NI, L. & DAVIS, C. E. 2004. Assessment of blinding in clinical trials. *Control Clin Trials,* 25**,** 143-56.

BASS, E. 2012. Tendinopathy: why the difference between tendinitis and tendinosis matters. *Int J Ther Massage Bodywork,* 5**,** 14-7.

BAUMGARD, S. H. & SCHWARTZ, D. R. 1982. Percutaneous release of the epicondylar muscles for humeral epicondylitis. *Am J Sports Med,* 10**,** 233-6.

BEISSNER, F., BRANDAU, A., HENKE, C., FELDEN, L., BAUMGARTNER, U., TREEDE, R. D., OERTEL, B. G. & LOTSCH, J. 2010. Quick discrimination of A(delta) and C fiber mediated pain based on three verbal descriptors. *PLoS One,* 5**,** e12944.

BRUMMEL, J., BAKER, C. L., 3RD, HOPKINS, R. & BAKER, C. L., JR. 2014. Epicondylitis: lateral. *Sports Med Arthrosc,* 22**,** e1-6.

BAAD-HANSEN, L., PIGG, M., YANG, G., LIST, T., SVENSSON, P. & DRANGSHOLT, M. 2015. Reliability of intra-oral quantitative sensory testing (QST) in patients with atypical odontalgia and healthy controls - a multicentre study. *J Oral Rehabil,* 42**,** 127-35.

CAO, H., BOURCHIER, S. & LIU, J. 2012. Does Syndrome Differentiation Matter? A Meta-Analysis of Randomized Controlled Trials in Cochrane Reviews of Acupuncture. *Med Acupunct,* 24**,** 68-76.

CHANG, S. 2013. The meridian system and mechanism of acupuncture--a comparative review. Part 2: mechanism of acupuncture analgesia. *Taiwan J Obstet Gynecol,* 52**,** 14-24.

CHEN, L., HOUGHTON, M., SEEFELD, L., MALARICK, C. & MAO, J. 2010. Acupuncture in pain management. *Pain Med,* 11**,** 530-4.

CHIANG, C., CHANG, C. & CHU, H. 1974. The peripheral afferent pathway in acupuncture analgesia. *Zhonghua Yi Xue Za Zhi,* 6**,** 360-4.

CHOI, Y. J., LEE, J. E., MOON, W. K. & CHO, S. H. 2013. Does the effect of acupuncture depend on needling sensation and manipulation? *Complement Ther Med,* 21**,** 207-14.

CRUZ-ALMEIDA, Y. & FILLINGIM, R. B. 2014. Can quantitative sensory testing move us closer to mechanism-based pain management? *Pain Med,* 15**,** 61-72.

CUI, M., FENG, Y., MCADOO, D. J. & WILLIS, W. D. 1999. Periaqueductal gray stimulation-induced inhibition of nociceptive dorsal horn neurons in rats is associated with the release of norepinephrine, serotonin, and amino acids. *J Pharmacol Exp Ther,* 289**,** 868-76.

DELMAS, P., HAO, J. & RODAT-DESPOIX, L. 2011. Molecular mechanisms of mechanotransduction in mammalian sensory neurons. *Nat Rev Neurosci,* 12**,** 139-53.

DEVOR, M. 2009. Ectopic discharge in Abeta afferents as a source of neuropathic pain. *Exp Brain Res,* 196**,** 115-28.

DINCER, F. & LINDE, K. 2003. Sham interventions in randomized clinical trials of acupuncture--a review. *Complement Ther Med,* 11**,** 235-42.

DOWNS, N. M., KIRK, K. & MACSWEEN, A. 2005. The effect of real and sham acupuncture on thermal sensation and thermal pain thresholds. *Arch Phys Med Rehabil,* 86**,** 1252-7.

FACCO, E., LIGUORI, A., PETTI, F., ZANETTE, G., COLUZZI, F., DE NARDIN, M. & MATTIA, C.

2008. Traditional acupuncture in migraine: a controlled, randomized study. *Headache,* 48**,** 398-407.

FINK, M., WOLKENSTEIN, E., KARST, M. & GEHRKE, A. 2002. Acupuncture in chronic epicondylitis: a randomized controlled trial. *Rheumatology (Oxford),* 41**,** 205-9.

FINNISS, D. G., KAPTCHUK, T. J., MILLER, F. & BENEDETTI, F. 2010. Biological, clinical, and ethical advances of placebo effects. *Lancet,* 375**,** 686-95.

GADAU, M., YEUNG, W. F., LIU, H., ZASLAWSKI, C., TAN, Y. S., WANG, F. C., BANGRAZI, S., CHUNG, K. F., BIAN, Z. X. & ZHANG, S. P. 2014. Acupuncture and moxibustion for lateral elbow pain: a systematic review of randomized controlled trials. *BMC Complement Altern Med,* 14**,** 136.

GEBER, C., KLEIN, T., AZAD, S., BIRKLEIN, F., GIERTHMUHLEN, J., HUGE, V., LAUCHART, M., NITZSCHE, D., STENGEL, M., VALET, M., BARON, R., MAIER, C., TOLLE, T. & TREEDE, R. D. 2011. Test-retest and interobserver reliability of quantitative sensory testing according to the protocol of the German Research Network on Neuropathic Pain (DFNS): a multi-centre study. *Pain,* 152**,** 548-56.

GREEN, S., BUCHBINDER, R., BARNSLEY, L., HALL, S., WHITE, M., SMIDT, N. & ASSENDELFT, W. 2002. Acupuncture for lateral elbow pain. *Cochrane Database Syst Rev***,** CD003527.

GRONE, E., CRISPIN, A., FLECKENSTEIN, J., IRNICH, D., TREEDE, R. D. & LANG, P. M. 2012. Test order of quantitative sensory testing facilitates mechanical hyperalgesia in healthy volunteers. *J Pain,* 13**,** 73-80.

GRUCHOW, H. W. & PELLETIER, D. 1979. An epidemiologic study of tennis elbow. Incidence, recurrence, and effectiveness of prevention strategies. *Am J Sports Med,* 7**,** 234-8.

HAN, J. S. 2004. Acupuncture and endorphins. *Neurosci Lett,* 361**,** 258-61.

HAN, J. S. 2011. Acupuncture analgesia: areas of consensus and controversy. *Pain,* 152**,** S41-8.

HARRINGTON, J. M., CARTER, J. T., BIRRELL, L. & GOMPERTZ, D. 1998. Surveillance case definitions for work related upper limb pain syndromes. *Occup Environ Med,* 55**,** 264-71.

HERQUELOT, E., GUEGUEN, A., ROQUELAURE, Y., BODIN, J., SERAZIN, C., HA, C., LECLERC, A., GOLDBERG, M., ZINS, M. & DESCATHA, A. 2013. Work-related risk factors for incidence of lateral epicondylitis in a large working population. *Scand J Work Environ Health,* 39**,** 578-88.

HERRERO, J. F., LAIRD, J. M. & LOPEZ-GARCIA, J. A. 2000. Wind-up of spinal cord neurones and pain sensation: much ado about something? *Prog Neurobiol,* 61**,** 169-203.

HONG, Q. N., DURAND, M. J. & LOISEL, P. 2004. Treatment of lateral epicondylitis: where is the evidence? *Joint Bone Spine,* 71**,** 369-73.

HUI, K. K., LIU, J., MAKRIS, N., GOLLUB, R. L., CHEN, A. J., MOORE, C. I., KENNEDY, D. N., ROSEN, B. R. & KWONG, K. K. 2000. Acupuncture modulates the limbic system and subcortical gray structures of the human brain: evidence from fMRI studies in normal subjects. *Hum Brain Mapp,* 9**,** 13-25.

HUI, K. K., LIU, J., MARINA, O., NAPADOW, V., HASELGROVE, C., KWONG, K. K., KENNEDY, D. N. & MAKRIS, N. 2005. The integrated response of the human cerebro-cerebellar and limbic systems to acupuncture stimulation at ST 36 as evidenced by fMRI. *Neuroimage,* 27**,** 479-96.

HUI, K. K., NIXON, E. E., VANGEL, M. G., LIU, J., MARINA, O., NAPADOW, V., HODGE, S. M., ROSEN, B. R., MAKRIS, N. & KENNEDY, D. N. 2007. Characterization of the "deqi" response in acupuncture. *BMC Complement Altern Med,* 7**,** 33.

HUSKISSON, E. C. 1974. Measurement of pain. *Lancet,* 2**,** 1127-31.

HUTCHINS, H. S., JR., YOUNG, F. A., LACKLAND, D. T. & FISHBURNE, C. P. 1997. The effectiveness of topical anesthesia and vibration in alleviating the pain of oral injections. *Anesth Prog,* 44**,** 87-9.

HAAKE, M., MULLER, H. H., SCHADE-BRITTINGER, C., BASLER, H. D., SCHAFER, H., MAIER, C., ENDRES, H. G., TRAMPISCH, H. J. & MOLSBERGER, A. 2007. German Acupuncture Trials (GERAC) for chronic low back pain: randomized, multicenter, blinded, parallel-group trial with 3 groups. *Arch Intern Med,* 167**,** 1892-8.

JOHNSON, G. W., CADWALLADER, K., SCHEFFEL, S. B. & EPPERLY, T. D. 2007. Treatment of lateral epicondylitis. *Am Fam Physician,* 76**,** 843-8.

JULIUS, D. & BASBAUM, A. I. 2001. Molecular mechanisms of nociception. *Nature,* 413**,** 203-10.

KAKIGI, R. & SHIBASAKI, H. 1992. Mechanisms of pain relief by vibration and movement. *J Neurol Neurosurg Psychiatry,* 55**,** 282-6.

KAPTCHUK, T. J. 2002. Acupuncture: theory, efficacy, and practice. *Ann Intern Med,* 136**,** 374-83.

KIM, K. H., KANG, J. W., LEE, M. S. & LEE, J. D.

2014. Assessment of the quality of reporting in randomised controlled trials of acupuncture in the Korean literature using the CONSORT statement and STRICTA guidelines. *BMJ Open,* 4**,** e005068.

KITAI, E., ITAY, S., RUDER, A., ENGEL, J. & MODAN, M. 1986. An epidemiological study of lateral epicondylitis (tennis elbow) in amateur male players. *Ann Chir Main,* 5**,** 113-21.

KNIESEL, B., HUTH, J., BAUER, G. & MAUCH, F. 2014. Systematic diagnosis and therapy of lateral elbow pain with emphasis on elbow instability. *Arch Orthop Trauma Surg,* 134**,** 1641-7.

KOLAHI, J., BANG, H. & PARK, J. 2009. Towards a proposal for assessment of blinding success in clinical trials: up-to-date review. *Community Dent Oral Epidemiol,* 37**,** 477-84.

KONG, J., FUFA, D. T., GERBER, A. J., ROSMAN, I. S., VANGEL, M. G., GRACELY, R. H. & GOLLUB, R. L. 2005. Psychophysical outcomes from a randomized pilot study of manual, electro, and sham acupuncture treatment on experimentally induced thermal pain. *J Pain,* 6**,** 55-64.

KONG, J., GOLLUB, R., HUANG, T., POLICH, G., NAPADOW, V., HUI, K., VANGEL, M., ROSEN, B. & KAPTCHUK, T. J. 2007. Acupuncture de qi, from qualitative history to quantitative measurement. *J Altern Complement Med,* 13**,** 1059-70.

KONG, J., MA, L., GOLLUB, R. L., WEI, J., YANG, X., LI, D., WENG, X., JIA, F., WANG, C., LI, F., LI, R. & ZHUANG, D. 2002. A pilot study of functional magnetic resonance imaging of the brain during manual and electroacupuncture stimulation of acupuncture point (LI-4 Hegu) in normal subjects reveals differential brain activation between methods. *J Altern Complement Med,* 8**,** 411-9.

KUMAR, V. S., SHETTY, A. A., RAVIKUMAR, K. J. & FORDYCE, M. J. 2004. Tennis elbow--outcome following the Garden procedure: a retrospective study. *J Orthop Surg (Hong Kong),* 12**,** 226-9.

LABAN, M. M., IYER, R. & TAMLER, M. S. 2005. Occult periarthrosis of the shoulder: a possible progenitor of tennis elbow. *Am J Phys Med Rehabil,* 84**,** 895-8.

LANG, P. M., STOER, J., SCHOBER, G. M., AUDETTE, J. F. & IRNICH, D. 2010. Bilateral acupuncture analgesia observed by quantitative sensory testing in healthy volunteers. *Anesth Analg,* 110**,** 1448-56.

LEE, J., NAPADOW, V. & PARK, K. 2014. Pain and sensory detection threshold response to acupuncture is modulated by coping strategy and acupuncture sensation. *BMC Complement Altern Med,* 14**,** 324.

LEIBING, E., LEONHARDT, U., KOSTER, G., GOERLITZ, A., ROSENFELDT, J. A., HILGERS, R. & RAMADORI, G. 2002. Acupuncture treatment of chronic low-back pain -- a randomized, blinded, placebo-controlled trial with 9-month follow-up. *Pain,* 96**,** 189-96.

LEUNG, A. Y., KIM, S. J., SCHULTEIS, G. & YAKSH, T. 2008. The effect of acupuncture duration on analgesia and peripheral sensory thresholds. *BMC Complement Altern Med,* 8**,** 18.

LEUNG, A. Y., PARK, J., SCHULTEIS, G., DUANN, J. R. & YAKSH, T. 2006. The electrophysiology of de qi sensations. *J Altern Complement Med,* 12**,** 743-50.

LEUNG, L. 2012. Neurophysiological basis of acupuncture-induced analgesia--an updated review. *J Acupunct Meridian Stud,* 5**,** 261-70.

LEWITH, G. T. & MACHIN, D. 1983. On the evaluation of the clinical effects of acupuncture. *Pain,* 16**,** 111-27.

LI, W., COBBIN, D. & ZASLAWSKI, C. 2008. A comparison of effects on regional pressure pain threshold produced by deep needling of LI4 and LI11, individually and in combination. *Complement Ther Med,* 16**,** 278-87.

LIN, J. G., CHEN, C. H., HUANG, Y. C. & CHEN, Y. H. 2012. How to design the control group in randomized controlled trials of acupuncture? *Evid Based Complement Alternat Med,* 2012**,** 875284.

LIN, J. G. & CHEN, W. L. 2008. Acupuncture analgesia: a review of its mechanisms of actions. *Am J Chin Med,* 36**,** 635-45.

LUK, J. K., TSANG, R. C. & LEUNG, H. B. 2014. Lateral epicondylalgia: midlife crisis of a tendon. *Hong Kong Med J,* 20**,** 145-51.

LUND, I. & LUNDEBERG, T. 2006. Are minimal, superficial or sham acupuncture procedures acceptable as inert placebo controls? *Acupunct Med,* 24**,** 13-5.

LUNDEBERG, T. 1984. The pain suppressive effect of vibratory stimulation and transcutaneous electrical nerve stimulation (TENS) as compared to aspirin. *Brain Res,* 294**,** 201-9.

LUNDEBERG, T. 2013. To be or not to be: the needling sensation (de qi) in acupuncture. *Acupunct Med,* 31**,** 129-31.

LUNDEBERG, T., ERIKSSON, S., LUNDEBERG, S. & THOMAS, M. 1989. Acupuncture and sensory thresholds. *Am J Chin Med,* 17**,** 99-110.

LYNN, B. & PERL, E. R. 1977. Failure of acupuncture to produce localized analgesia. *Pain,* 3**,** 339-

51.
MACPHERSON, H. & ASGHAR, A. 2006. Acupuncture needle sensations associated with De Qi: a classification based on experts' ratings. *J Altern Complement Med,* 12**,** 633-7.
MACPHERSON, H., WHITE, A., CUMMINGS, M., JOBST, K., ROSE, K. & NIEMTZOW, R. 2001. Standards for reporting interventions in controlled trials of acupuncture: the STRICTA recommendations. *Complement Ther Med,* 9**,** 246-9.
MADSEN, M. V., GOTZSCHE, P. C. & HROBJARTSSON, A. 2009. Acupuncture treatment for pain: systematic review of randomised clinical trials with acupuncture, placebo acupuncture, and no acupuncture groups. *BMJ,* 338**,** a3115.
MELCHART, D., STRENG, A., HOPPE, A., BRINKHAUS, B., WITT, C., WAGENPFEIL, S., PFAFFENRATH, V., HAMMES, M., HUMMELSBERGER, J., IRNICH, D., WEIDENHAMMER, W., WILLICH, S. N. & LINDE, K. 2005. Acupuncture in patients with tension-type headache: randomised controlled trial. *BMJ,* 331**,** 376-82.
MELZACK, R. 1975. The McGill Pain Questionnaire: major properties and scoring methods. *Pain,* 1**,** 277-99.
MELZACK, R. & WALL, P. D. 1965. Pain mechanisms: a new theory. *Science,* 150**,** 971-9.
MOAYEDI, M. & DAVIS, K. D. 2013. Theories of pain: from specificity to gate control. *J Neurophysiol,* 109**,** 5-12.
MOFFET, H. H. 2009. Sham acupuncture may be as efficacious as true acupuncture: a systematic review of clinical trials. *J Altern Complement Med,* 15**,** 213-6.
MOLONEY, N. A., HALL, T. M. & DOODY, C. M. 2012. Reliability of thermal quantitative sensory testing: a systematic review. *J Rehabil Res Dev,* 49**,** 191-207.
MOLSBERGER, A. & HILLE, E. 1994. The analgesic effect of acupuncture in chronic tennis elbow pain. *Br J Rheumatol,* 33**,** 1162-5.
MOROZ, A., FREED, B., TIEDEMANN, L., BANG, H., HOWELL, M. & PARK, J. J. 2013. Blinding measured: a systematic review of randomized controlled trials of acupuncture. *Evid Based Complement Alternat Med,* 2013**,** 708251.
NAIK, P. N., KIRAN, R. A., YALAMANCHAL, S., KUMAR, V. A., GOLI, S. & VASHIST, N. 2014. Acupuncture: An Alternative Therapy in Dentistry and Its Possible Applications. *Med Acupunct,* 26**,** 308-314.
NANITSOS, E., VARTULI, R., FORTE, A., DENNISON, P. J. & PECK, C. C. 2009. The effect of vibration on pain during local anaesthesia injections. *Aust Dent J,* 54**,** 94-100.
NAPADOW, V., MAKRIS, N., LIU, J., KETTNER, N. W., KWONG, K. K. & HUI, K. K. 2005. Effects of electroacupuncture versus manual acupuncture on the human brain as measured by fMRI. *Hum Brain Mapp,* 24**,** 193-205.
NIRSCHL, R. P. & PETTRONE, F. A. 1979. Tennis elbow. The surgical treatment of lateral epicondylitis. *J Bone Joint Surg Am,* 61**,** 832-9.
OLESEN, S. S., VAN GOOR, H., BOUWENSE, S. A., WILDER-SMITH, O. H. & DREWES, A. M. 2012. Reliability of static and dynamic quantitative sensory testing in patients with painful chronic pancreatitis. *Reg Anesth Pain Med,* 37**,** 530-6.
OTTI, A. & NOLL-HUSSONG, M. 2012. Acupuncture-induced pain relief and the human brain's default mode network - an extended view of central effects of acupuncture analgesia. *Forsch Komplementmed,* 19**,** 197-201.
OTTOSON, D., EKBLOM, A. & HANSSON, P. 1981. Vibratory stimulation for the relief of pain of dental origin. *Pain,* 10**,** 37-45.
PALMER, S. T. & MARTIN, D. J. 2005. Thermal perception thresholds recorded using method of limits change over brief time intervals. *Somatosens Mot Res,* 22**,** 327-34.
PARK, H., PARK, J. & LEE, H. 2002a. Does Deqi (needle sensation) exist? *Am J Chin Med,* 30**,** 45-50.
PARK, J., PARK, H., LEE, H., LIM, S. & AHN, K. 2005. Deqi sensation between the acupuncture-experienced and the naive: a Korean study II. *Am J Chin Med,* 33**,** 329-37.
PARK, J., WHITE, A., STEVINSON, C., ERNST, E. & JAMES, M. 2002b. Validating a new non-penetrating sham acupuncture device: two randomised controlled trials. *Acupunct Med,* 20**,** 168-74.
PATESTAS, M. & GARTNER, L. P. 2006. *A Textbook of Neuroanatomy*, Wiley-Blackwell.
PAUSER, G., REICHMANN, C., BAUM, M., BENZER, H., HAIDER, W. & THOMA, H. 1975. [The influence of acupuncture analgesia on the sensation and feeling of pain and the autonomic state of the organism (author's transl)]. *Wien Klin Wochenschr,* 87**,** 25-8.
PFAU, D. B., GEBER, C., BIRKLEIN, F. & TREEDE, R. D. 2012. Quantitative sensory testing of neuropathic pain patients: potential mechanistic and therapeutic implications. *Curr Pain Headache Rep,* 16**,** 199-206.
PLASTER, R., VIEIRA, W. B., ALENCAR, F. A., NAKANO, E. Y. & LIEBANO, R. E. 2014. Immediate effects of electroacupuncture and

manual acupuncture on pain, mobility and muscle strength in patients with knee osteoarthritis: a randomised controlled trial. *Acupunct Med,* 32**,** 236-41.

ROLKE, R., BARON, R., MAIER, C., TOLLE, T. R., TREEDE, R. D., BEYER, A., BINDER, A., BIRBAUMER, N., BIRKLEIN, F., BOTEFUR, I. C., BRAUNE, S., FLOR, H., HUGE, V., KLUG, R., LANDWEHRMEYER, G. B., MAGERL, W., MAIHOFNER, C., ROLKO, C., SCHAUB, C., SCHERENS, A., SPRENGER, T., VALET, M. & WASSERKA, B. 2006a. Quantitative sensory testing in the German Research Network on Neuropathic Pain (DFNS): standardized protocol and reference values. *Pain,* 123**,** 231-43.

ROLKE, R., MAGERL, W., CAMPBELL, K. A., SCHALBER, C., CASPARI, S., BIRKLEIN, F. & TREEDE, R. D. 2006b. Quantitative sensory testing: a comprehensive protocol for clinical trials. *Eur J Pain,* 10**,** 77-88.

SALTER, M. W. & HENRY, J. L. 1990. Physiological characteristics of responses of wide dynamic range spinal neurones to cutaneously applied vibration in the cat. *Brain Res,* 507**,** 69-84.

SAYEGH, E. T. & STRAUCH, R. J. 2014. Does Nonsurgical Treatment Improve Longitudinal Outcomes of Lateral Epicondylitis Over No Treatment? A Meta-analysis. *Clin Orthop Relat Res*.

SCHLIESSBACH, J., VAN DER KLIFT, E., ARENDT-NIELSEN, L., CURATOLO, M. & STREITBERGER, K. 2011. The effect of brief electrical and manual acupuncture stimulation on mechanical experimental pain. *Pain Med,* 12**,** 268-75.

SHI, G. X., LI, Q. Q., LIU, C. Z., ZHU, J., WANG, L. P., WANG, J., HAN, L. L., GUAN, L. P. & WU, M. M. 2014. Effect of acupuncture on Deqi traits and pain intensity in primary dysmenorrhea: analysis of data from a larger randomized controlled trial. *BMC Complement Altern Med,* 14**,** 69.

SHIRI, R. & VIIKARI-JUNTURA, E. 2011. Lateral and medial epicondylitis: role of occupational factors. *Best Pract Res Clin Rheumatol,* 25**,** 43-57.

SHIRI, R., VIIKARI-JUNTURA, E., VARONEN, H. & HELIOVAARA, M. 2006. Prevalence and determinants of lateral and medial epicondylitis: a population study. *Am J Epidemiol,* 164**,** 1065-74.

SIMS, S. E., MILLER, K., ELFAR, J. C. & HAMMERT, W. C. 2014. Non-surgical treatment of lateral epicondylitis: a systematic review of randomized controlled trials. *Hand (N Y),* 9**,** 419-46.

SLUITER, J. K., REST, K. M. & FRINGS-DRESEN, M. H. 2001. Criteria document for evaluating the work-relatedness of upper-extremity musculoskeletal disorders. *Scand J Work Environ Health,* 27 Suppl 1**,** 1-102.

SMIDT, N., ASSENDELFT, W. J., AROLA, H., MALMIVAARA, A., GREENS, S., BUCHBINDER, R., VAN DER WINDT, D. A. & BOUTER, L. M. 2003. Effectiveness of physiotherapy for lateral epicondylitis: a systematic review. *Ann Med,* 35**,** 51-62.

STREITBERGER, K. & KLEINHENZ, J. 1998. Introducing a placebo needle into acupuncture research. *Lancet,* 352**,** 364-5.

SULLIVAN, R. 1968. Effect of different frequencies of vibration on pain-threshold detection. *Exp Neurol,* 20**,** 135-42.

SUN, Y., GAN, T. J., DUBOSE, J. W. & HABIB, A. S. 2008. Acupuncture and related techniques for postoperative pain: a systematic review of randomized controlled trials. *Br J Anaesth,* 101**,** 151-60.

TAKAKURA, N. & YAJIMA, H. 2009. Analgesic effect of acupuncture needle penetration: a double-blind crossover study. *Open Med,* 3**,** e54-61.

TARGINO, R. A., IMAMURA, M., KAZIYAMA, H. H., SOUZA, L. P., HSING, W. T., FURLAN, A. D., IMAMURA, S. T. & AZEVEDO NETO, R. S. 2008. A randomized controlled trial of acupuncture added to usual treatment for fibromyalgia. *J Rehabil Med,* 40**,** 582-8.

TITCHENER, A. G., FAKIS, A., TAMBE, A. A., SMITH, C., HUBBARD, R. B. & CLARK, D. I. 2013. Risk factors in lateral epicondylitis (tennis elbow): a case-control study. *J Hand Surg Eur Vol,* 38**,** 159-64.

TOMMERDAHL, M., DELEMOS, K. A., WHITSEL, B. L., FAVOROV, O. V. & METZ, C. B. 1999. Response of anterior parietal cortex to cutaneous flutter versus vibration. *J Neurophysiol,* 82**,** 16-33.

TONG, Y., GUO, H. & HAN, B. 2010. Fifteen-day acupuncture treatment relieves diabetic peripheral neuropathy. *J Acupunct Meridian Stud,* 3**,** 95-103.

TOSTI, R., JENNINGS, J. & SEWARDS, J. M. 2013. Lateral epicondylitis of the elbow. *Am J Med,* 126**,** 357 e1-6.

TRINH, K. V., PHILLIPS, S. D., HO, E. & DAMSMA, K. 2004. Acupuncture for the alleviation of lateral epicondyle pain: a systematic review. *Rheumatology (Oxford),* 43**,** 1085-90.

TSUI, P. & LEUNG, M. C. 2002. Comparison of the effectiveness between manual acupuncture and electro-acupuncture on patients with tennis elbow. *Acupunct Electrother Res,* 27**,** 107-17.

ULETT, G. A., HAN, S. & HAN, J. S. 1998. Electroacupuncture: mechanisms and clinical application. *Biol Psychiatry,* 44**,** 129-38.

VAN RIJN, R. M., HUISSTEDE, B. M., KOES, B. W. & BURDORF, A. 2009. Associations between work-related factors and specific disorders at the elbow: a systematic literature review. *Rheumatology (Oxford),* 48**,** 528-36.

VASE, L., BARAM, S., TAKAKURA, N., TAKAYAMA, M., YAJIMA, H., KAWASE, A., SCHUSTER, L., KAPTCHUK, T. J., SCHOU, S., JENSEN, T. S., ZACHARIAE, R. & SVENSSON, P. 2015. Can acupuncture treatment be double-blinded? An evaluation of double-blind acupuncture treatment of postoperative pain. *PLoS One,* 10**,** e0119612.

VICENTE-BARRERO, M., YU-LU, S. L., ZHANG, B., BOCANEGRA-PEREZ, S., DURAN-MORENO, D., LOPEZ-MARQUEZ, A., KNEZEVIC, M., CASTELLANO-NAVARRO, J. M. & LIMINANA-CANAL, J. M. 2012. The efficacy of acupuncture and decompression splints in the treatment of temporomandibular joint pain-dysfunction syndrome. *Med Oral Patol Oral Cir Bucal,* 17**,** e1028-33.

WADA, T., MORIYA, T., IBA, K., OZASA, Y., SONODA, T., AOKI, M. & YAMASHITA, T. 2009. Functional outcomes after arthroscopic treatment of lateral epicondylitis. *J Orthop Sci,* 14**,** 167-74.

WALJI, R. & BOON, H. 2006. Redefining the randomized controlled trial in the context of acupuncture research. *Complement Ther Clin Pract,* 12**,** 91-6.

WALKER-BONE, K., PALMER, K. T., READING, I., COGGON, D. & COOPER, C. 2004. Prevalence and impact of musculoskeletal disorders of the upper limb in the general population. *Arthritis Rheum,* 51**,** 642-51.

WALKER-BONE, K., PALMER, K. T., READING, I., COGGON, D. & COOPER, C. 2012. Occupation and epicondylitis: a population-based study. *Rheumatology (Oxford),* 51**,** 305-10.

WANG, K. M., YAO, S. M., XIAN, Y. L. & HOU, Z. L. 1985. A study on the receptive field of acupoints and the relationship between characteristics of needling sensation and groups of afferent fibres. *Sci Sin B,* 28**,** 963-71.

WANG, S. M., LIN, E. C., MARANETS, I. & KAIN, Z. N. 2009. The impact of asynchronous electroacupuncture stimulation duration on cold thermal pain threshold. *Anesth Analg,* 109**,** 932-5.

WASEEM, M., NUHMANI, S., RAM, C. S. & SACHIN, Y. 2012. Lateral epicondylitis: a review of the literature. *J Back Musculoskelet Rehabil,* 25**,** 131-42.

WERNER, M. U., PETERSEN, M. A. & BISCHOFF, J. M. 2013. Test-retest studies in quantitative sensory testing: a critical review. *Acta Anaesthesiol Scand,* 57**,** 957-63.

WHITE, A. 2009. Western medical acupuncture: a definition. *Acupunct Med,* 27**,** 33-5.

WHITE, A. R., FILSHIE, J. & CUMMINGS, T. M. 2001. Clinical trials of acupuncture: consensus recommendations for optimal treatment, sham controls and blinding. *Complement Ther Med,* 9**,** 237-45.

WONG, E. L., LEUNG, P. C. & ZHANG, L. 2015. Placebo acupuncture in an acupuncture clinical trial. How good is the blinding effect? *J Acupunct Meridian Stud,* 8**,** 40-3.

WYLDE, V., PALMER, S., LEARMONTH, I. D. & DIEPPE, P. 2011. Test-retest reliability of Quantitative Sensory Testing in knee osteoarthritis and healthy participants. *Osteoarthritis Cartilage,* 19**,** 655-8.

ZEISIG, E. 2012. Natural course in tennis elbow--lateral epicondylitis after all? *Knee Surg Sports Traumatol Arthrosc,* 20**,** 2549-52.

ZHU, S. P., LUO, L., ZHANG, L., SHEN, S. X., REN, X. X., GUO, M. W., YANG, J. M., SHEN, X. Y., XU, Y. S., JI, B., ZHU, J., LI, X. H. & ZHANG, L. F. 2013. Acupuncture De-qi: From Characterization to Underlying Mechanism. *Evid Based Complement Alternat Med,* 2013**,** 518784.

Appendices

Appendix I - Acu-vibrator

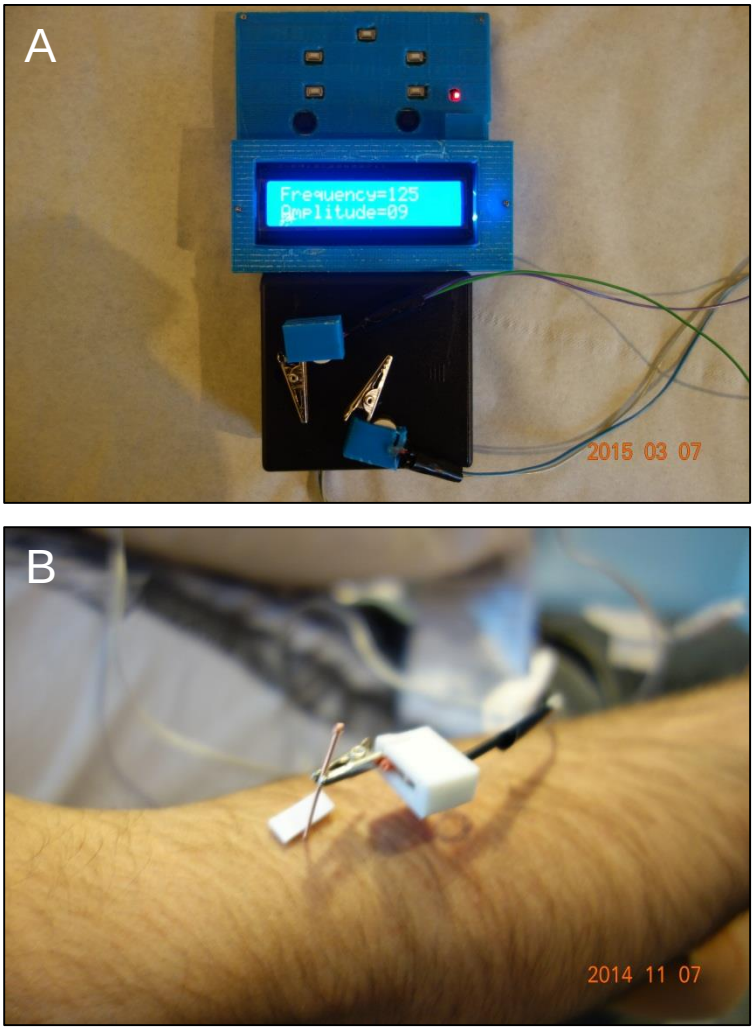

Figure AI. Application of the acu-vibrator through acupuncture needles. The novel acu-vibrator employed in the current study is able to transmit high-frequency vibrations into the deep muscle (A) . Clips were used to attach the device to the acupuncture needles following insertion into the target area (B) (LI-4/LI-10 in the current study), allowing for a broad range of applications.

Appendix II. Modified MGH Acupuncture Sensation Scale.

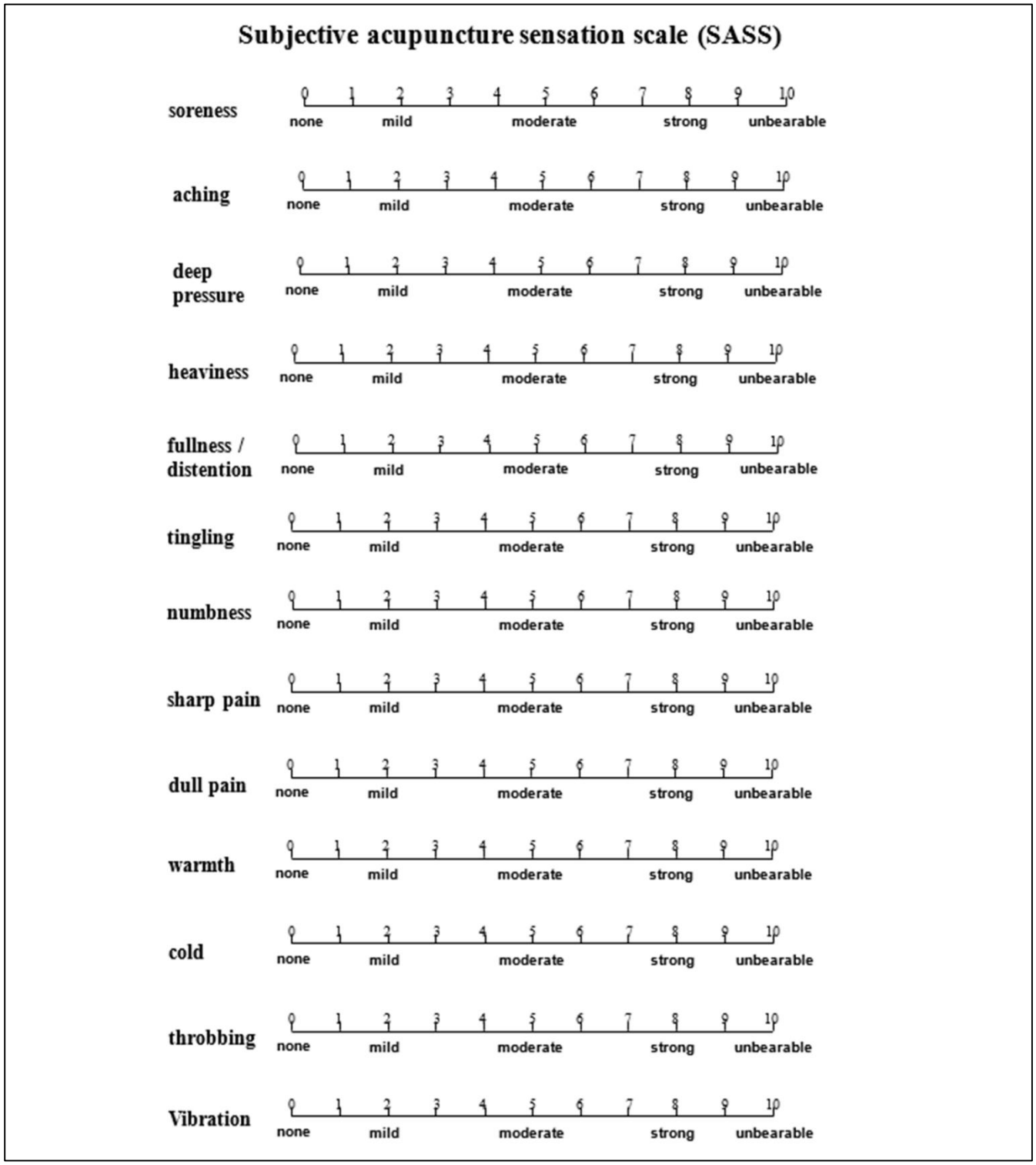

Figure AII. The modified MGH acupuncture sensation scale (MASS). The acupuncture sensation scale (MGH version) including common descriptors for *Deqi*, modified to add vibration (a non-*Deqi* descriptor) was used to assess the experience of *Deqi* between treatment types.

Appendix III. McGills Pain Questionnaire.

PRI: S_____ A _____ E _____ M _____ PRI(T) _____ PPI _____

(1-10) (11-15) (16) (17-20) (1-20)

The following words can describe the pain. Mark with an X next to word that best describes your pain.

1 ☐ Flickering ☐ Quivering ☐ Pulsing ☐ Throbbing ☐ Beating ☐ Pounding	**2** ☐ Jumping ☐ Flashing ☐ Shooting	**3** ☐ Pricking ☐ Boring ☐ Drilling ☐ Stabbing ☐ Lancinating	**4** ☐ Sharp ☐ Cutting ☐ Lacerating	**5** ☐ Pinching ☐ Pressing ☐ Gnawing ☐ Cramping ☐ Crushing
6 ☐ Tugging ☐ Pulling ☐ Wrenching	**7** ☐ Hot ☐ Burning ☐ Scalding ☐ Searing	**8** ☐ Tingling ☐ Itchy ☐ Smarting ☐ Stinging	**9** ☐ Dull ☐ Sore ☐ Hurting ☐ Aching ☐ Heavy	**10** ☐ Tender ☐ Taut ☐ Rasping ☐ Splitting
11 ☐ Tiring ☐ Exhausting	**12** ☐ Sickening ☐ Suffocating	**13** ☐ Fearful ☐ Frightful ☐ Terrifying	**14** ☐ Punishing ☐ Gruelling ☐ Cruel ☐ Vicious ☐ Killing	**15** ☐ Wretched ☐ Blinding
16 ☐ Annoying ☐ Troublesome ☐ Miserable ☐ Intense ☐ Unbearable	**17** ☐ Spreading ☐ Radiating ☐ Penatrating ☐ Piercing	**18** ☐ Tight ☐ Numb ☐ Drawing ☐ Squeezing ☐ Tearing	**19** ☐ Cold ☐ Cold ☐ Freezing	**20** ☐ Nagging ☐ Nauseating ☐ Agonizing ☐ Dreadful ☐ Torturing

VAS UNPLEASESANTNESS (UBEHAG)										
0	1	2	3	4	5	6	7	8	9	10

Figure AIII. McGills Pain Questionnaire (MPQ). The MPQ was employed to test the different dimensions of pain, associated with the three types of acupuncture treatments, and further indicate whether chronic elbow pain subjects felt a less degree of pain following treatment.

Appendix IV. Acupuncture credibility scale.

Code for Adverse Events (AE) of Acupuncture

(0 = none, 1 = minimal, 2 =mild, 3 = moderate, 4 = severe, and 5 = extremely severe)

Common AE	**0-5**	**Other AE**	
Bleeding/bruising			
Needling pain after treatment			
Symptom aggravation			
Fainting / dizziness			
Drowsiness/lethargy			
Sweating			

Figure AIV. Acupuncture credibility scale. The credibility scale was used for indicating adverse events, rated on a 0-6 scale (0 = none, 1 = minimal, 2 = mild, 3 = moderate, 4 = severe, and 5 = extremely severe).

Appendix V. Indication chart.

A. Please indicate which treatment you believe you had received.

(1) Acupuncture

(2) Placebo

(3) Acupuncture + vibration

(4) Don't know

B. If you answer either Acupuncture or Placebo/sham, what led you to that belief?

(1) The manner, attitude, or words of the acupuncturist

(2) The manner, attitude, or words of the assistant

(3) The sensation of the acupuncture stimulation

(4) The results of the acupuncture treatment (eg, changes in pain threshold or rating)

(5) The experience of the acupuncture procedure (eg, what the acupuncturist did and how it felt)

Figure AV. Indication. The indication chart was presented to the subjects following treatment with any of the three types of acupuncture treatments (A). Four options were available, and subjects answering 1-3 were further asked to indicate the reasoning behind their answer (B)