TRANSCRANIAL DIRECT CURRENT STIMULATION: THE EFFECT ON

FUNCTIONAL OUTCOMES IN THE PAIN AND MOTOR DOMAINS

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Entities should not be multiplied unnecessarily.

- William of Ockham (1287-1347)

Contents

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LIST OF RESEARCH REPORTS

Report I:

Aslaksen PM, Vasylenko O, Fagerlund AJ. (2014). The effect of transcranial direct current stimulation on experimentally induced heat pain. *Experimental Brain Research, 232*(6), 1865-1873.

Report II:

Fagerlund AJ, Danielsen T, Freili J, Aslaksen PM. No effect of 2mA anodal tDCS over the M1 on performance and practice effect on Grooved Pegboard Test and Trail Making Test B. Submitted, *eNeuro,* December 2014.

Report III:

Fagerlund AJ, Hansen OA, Aslaksen PM. (2015). Transcranial direct current stimulation as a treatment for patients with fibromyalgia: a randomized controlled trial. *Pain, 156*(1), 62-71.

ABSTRACT

The physiological effects of transcranial direct current stimulation (tDCS) in the living human brain were verified experimentally in the early 2000's. A series of studies from Göttingen, Germany, shows that consistently, anodal stimulation lead to increased cortical excitability, while cathodal stimulation leads to increased cortical inhibition. Since then, the effect of tDCS has been further explored, both in terms of basic physiology, and on functional outcomes. The method, when applied according to existing protocols, is associated with no serious safety concerns. Early clinical studies has shown that tDCS stimulation can lead to symptom relief, or improved rehabilitation, in a number of conditions assumed to be associated with devious brain function. The results from early phase clinical studies on chronic pain has yielded encouraging results, but in order to conclude on the clinical efficacy of tDCS in its current application, there is a need for larger, rigorously designed studies. In healthy volunteers, the effects of tDCS has been tested on various outcomes. In experimentally induced pain, the effects appear to be less consistent then in clinical pain. In the motor domain, some studies indicate that in healthy volunteers, motor performance and motor learning can be facilitated by tDCS. However, the effects appear to be sensitive to how the stimulation is conducted, and how and when the outcomes are measured.

This thesis describes two experiments and one clinical trial that investigated the effect of anodal tDCS over the primary motor cortex (M1) on functionally relevant outcomes, namely experimentally induced and clinical pain, and motor learning and performance on two neuropsychological tests that are commonly employed in clinical practice. The aim of Report I was to test the effect of a single session of anodal tDCS with a duration of 7 minutes and a current intensity of 2 milliampere (mA) on experimentally induced heat pain in healthy volunteers. In order to estimate the placebo effect, a no treatment condition was included in addition to active and sham tDCS. Thus, 75 healthy volunteers were randomized into 3

groups. At pretest, during stimulation and at posttest, pain stimuli were presented as thermode heat at temperatures of 43ºC, 45ºC and 47ºC. Additionally at each time point, heat pain thresholds were measured. Pain intensity was measured with a computerized visual analog scale (COVAS). Subjective stress was measured with adjective pairs from the Stress/Arousal Adjective Check List (SACL) and rated with a 0-10 numeric rating scale (NRS), and blood pressure, an indicator of objective stress, were measured with an automatic blood pressure monitor. The results indicated that, at the highest temperature, the active tDCS group reported greater pain reduction from pretest to posttest. However, the repeated measures data indicated that the response of the sham tDCS group consistently had a response pattern that were more similar to the active tDCS group than the no treatment group, indicating that the tDCS procedure might induce placebo responses that influenced the pain ratings.

The aim of the experiment in Report II was to test the effect of 20 minutes 2 mA anodal tDCS over the M1 on performance and practice effect on two commonly used neuropsychological tests measuring fine motor (Grooved Pegboard Test, GPT) and psychomotor (Trail Making test B, TMT-B) speed. In order do so, a similar study design as in Report II was employed, but with longer stimulation duration. A total of 60 healthy volunteers were randomized into 3 groups, and the neuropsychological tests were administered before, during and after stimulation. Control variables were registered to investigate the effect of overt anatomical and behavioral characteristics on the outcomes. The results indicated no effect of active tDCS on motor learning and performance. In fact all groups performed similarly at each time point. Interestingly, and uniquely for the active tDCS group, higher caffeine intake and lower inter electrode impedance predicted improved motor learning.

The aim of the randomized controlled trial in Report III was to investigate the effect of anodal tDCS on pain in fibromyalgia (FIM). A total of 48 patients, receiving active or sham tDCS, completed the study. Stimulation was administered in a similar fashion as in Report II, but

over 5 consecutive days. Thus the study design was a between group design with 7 repeated measures (pretest, treatment x 5, posttest). Pain intensity, pain unpleasantness, stress, and tension (the latter 2 derived from the SACL used in Report I) were measured with short message service (SMS) text messages 3 times daily for 30 days before stimulation (mean of 30 days: pretest), during the treatment days, and for 30 days after stimulation (mean of 30 days: posttest). In addition, daily function and psychiatric symptoms were measured before and after the stimulation. The results indicated that active tDCS statistically reduced pain in the patients compared to sham tDCS. However, the effect sizes were small, and the results might indicate that the achieved pain reduction was of limited clinical importance.

The overall conclusions from the experiments involving healthy volunteers (Report I and II) is that anodal tDCS over the M1 is ineffective in reducing acute pain and improving motor learning and performance. In FIM patients (Report III) 5 consecutive sessions of tDCS is capable of inducing statistically significant pain relief, and improved stimulation protocols should be investigated in order to make the treatment clinically effective.

INTRODUCTION

Systematic investigations on the behavioral effects of non invasive direct current techniques date back at least 30-40 years (Priori, 2003). Since the physiological effects were verified using Transcranial Magnetic Stimulation (TMS), demonstrating that overall, anodal stimulation increases neuronal excitability, while cathodal stimulation reduces it (Nitsche and Paulus, 2000, 2001), transcranial direct current stimulation (tDCS) has gained considerable interest from researchers. The method is safe (Nitsche et al., 2003b) and can induce excitability changes in the human cortex that outlasts the stimulation itself by altering the membrane resting potential of neurons, and acting on Long Term Potentiation (LTP)-like mechanisms (Stagg and Nitsche, 2011). The weak direct current, originating from a variable voltage stimulator that ensures constant current intensity, is usually transferred using moisturized sponge pads or rubber electrodes with conductive gel directly on the skin. While a substantial part of the current is shunted across the scalp, about 50% of the current penetrates into the brain (Dymond et al., 1975; Miranda et al., 2006).

In tDCS research, the primary motor cortex (M1) has been widely used as model system in order to study modulation of cortical excitability by tDCS, since it has a minimal distance to the scalp surface, and can thus be reached with TMS pulses (Nitsche et al., 2015). TMS has been a valuable tool for verifying the excitatory and inhibitory effects of tDCS on both intracortical neurons and cortical output neurons (Hallett, 2007), for example by assessing changes in Motor Evoked Potential (MEP) thresholds as an effect of tDCS. Building on the experimentally verified evidence that tDCS changes excitability in the M1, the region has often been targeted in studies with behavioral and clinical outcomes. The reports included in this thesis are all based on tDCS with the anode placed over the M1, and the cathode placed over the contralateral supra orbital area (M1-SO). This M1-SO montage is likely the most commonly employed tDCS electrode arrangement, thus making comparison between the

obtained results in the present thesis and previous studies possible. While TMS induces a pulsed magnetic field that can temporarily excite or inhibit specific areas (Hallett, 2000), tDCS can be considered a neuromodulatory intervention, as the electric fields generated does not lead to the rapid depolarization required to produce action potentials in neuronal membranes (Nitsche et al., 2008). Thus, the stimulation can be administered without overt immediate effects, such as muscle contractions or intense sensations of the stimulation itself, making it possible to conduct blinded experiments with relative ease. Furthermore, the administration of tDCS is easy and does not require a large infrastructure. Not surprisingly, this accessible and safe method for altering functional properties of the brain has spurred research on the effect of tDCS on both behavioral and clinical outcomes.

Previous studies has shown promising results (see Background for a summary of relevant fields) with the M1-SO electrode montage on clinical conditions, especially chronic pain. However, larger clinical trials are needed in order to accumulate sufficient evidence to implement tDCS in clinical practice. In Report I, the aim was to test the effect of tDCS on experimentally induced heat pain in healthy subjects in a laboratory setting, and thus provided evidence for the potential to reduce acute pain. In Report III the aim was to test the clinical efficacy of the M1-SO montage on patients with fibromyalgia (FIM), a chronic pain condition. The primary outcome was pain. Additionally, the effect on psychiatric symptoms associated with the condition, and daily function was also investigated. The trial was conducted in a hospital setting, and thus provide results that can be relevant for questions regarding future clinical implementation of the method.

In healthy subjects, there are some encouraging results (see Background) regarding the ability of tDCS to enhance performance on motor tasks. This has generated interest in the public, where tDCS often is perceived as a tool for "brain boosting". Although the evidence for the neuroenhancing features of tDCS are built on partially inconsistent evidence from laboratory

tests, the technology is already commercially exploited and available to customers aiming to improve their athletic and computer game performance. In Report II the aim was to test whether tDCS can improve performance and practice effect on two neuropsychological tests whose results have external validity. The results provided evidence whether it is likely that tDCS in a M1-SO setup can improve motor function in healthy subjects.

Overall, the reports in the present thesis investigated whether anodal tDCS over the M1, in a M1-SO application, can alter functionally important outcomes in the pain and motor domains. The purpose was to supplement the existing literature of tDCS research with high quality evidence. In order to do so, we have aimed to maintain a methodology that at some points are innovative, and in sum are likely to have reduced confounds. For example, all reports are based on data from trials that used a state of the art stimulator that enabled computerized double blinding to reduce experimenter bias. Furthermore, we have emphasized a method for moistening the electrodes that provide low electrode impedance and subject skin sensation to reduce the risk of un-blinding. Innovatively, in the clinical trial we used short message service (SMS) messages for pain assessment, that both increases the number of data points, and reduces experimenter influence on the patients' pain evaluations. Finally, in the experiments (Report I and II), a no-treatment condition was included, in addition to sham control, to estimate the placebo effect.

BACKGROUND

Immediate physiological effects of anodal tDCS

In animals, anodal stimulation produces a sub threshold depolarization of neurons (Creutzfeldt et al., 1962). The immediate effect of anodal tDCS over the M1 in humans appears to be solely dependent on changes in neuron membrane potential (Stagg and Nitsche, 2011). In order to induce relevant changes, the direction of current flow has to be along the longitudinal axis, along the soma and axon, of a given neuron in order to induce relevant effects on membrane polarity (Roth, 1994), thus the position of the cathode is critical because it determines the direction of the current flow (Nitsche et al., 2015). For instance, placing the anode over the M1 and the cathode at the contralateral upper arm produces significantly less excitatory effects than the more common M1-SO montage (Moliadze et al., 2010), possibly due to changes in the direction of the current flow. In neurons, the axon and soma has a higher density of receptors and ion-channels than the dendrites. Thus, changes in the polarity in the soma and axon result in increased effect of the stimulation. Therefore, it is likely that the result of tDCS is at least partially a product of dominant neuron orientation in the stimulated area, and the direction of the current (Nitsche et al., 2015). Voltage-gated sodium and calcium channels generate action potentials by opening and allowing an inward influx of sodium and calcium that depolarizes the neuron by changing the electrochemical gradient. Pharmacologic blocking of sodium channels with carbamazepine selectively eliminates the excitability enhancement normally induced by anodal tDCS, and the calcium channel blocker flunarizine yields a similar effect (Nitsche et al., 2003a). Furthermore, Nitsche and colleagues (2005) have suggested that the modulatory activity of tDCS is predominantly restricted to intracortical neurons, and not cortico-spinal neuron polarization. Taken together, the immediate effect of anodal tDCS appears to be neuromodulatory, predominantly affecting interneurons, and depending on neuronal orientation and the direction of the electric field.

Physiological after effects of anodal tDCS

The after effects of tDCS is dependent on the depolarization of neuronal membranes, as the reduced immediate excitatory effect produced by sodium and calcium channel blockers, also translates into reduced after effects. However, antagonizing the glutamate receptor N-methyl-D-aspartate (NMDA) with dextromethorphane does not affect immediate changes in neuronal excitability, but specifically abolishes the after effects (Nitsche et al., 2003a). Furthermore, the partial NMDA agonist D-Cycloserine selectively potentiates the duration of excitability changes induced by anodal tDCS (Nitsche et al., 2004). The NMDA-receptor is the predominant molecular device for controlling synaptic plasticity and memory function (Li and Tsien, 2009), and the specific effect of drugs that manipulates the NMDA-receptors on the after effects of tDCS indicates that the long term effects of the stimulation is driven by glutaminergic neuroplasticity mechanisms. Furthermore, during tDCS, local concentrations of the neurotransmitter gamma-Aminobutyric acid (GABA) concentrations under the anode are reduced, and the effects are stable for at least 20 minutes (Stagg et al., 2009). GABA is the primary inhibitory neurotransmitter in the central nervous system that, along with dopamine, acetylcholine and adrenaline, is likely to have modulating effects on the NMDA-related plasticity effects of tDCS (Nitsche et al., 2015). Additionally, citalopram, a selective serotonin reuptake inhibitor (SSRI), increase and prolong anodal tDCS induced facilitation in the motor cortex (Nitsche et al., 2009b). Finally, amphetamine, a catecholaminergic reuptake-blocker, has NMDA-dependent facilitation effects on the after effects. In sum, the after effects of anodal tDCS appear to be highly reliant on glutaminergic neuroplasticity, and are affected by neuromodulators.

Application of tDCS in clinical and experimental pain studies

Results from early phase clinical trials indicate that tDCS may affect symptoms in conditions such as epilepsy (Fregni et al., 2006c), depression (Boggio et al., 2008a; Nitsche et al., 2009a), drug addiction (Boggio et al., 2008b; Boggio et al., 2010; Fregni et al., 2008), stroke (Boggio et al., 2007; Hummel et al., 2005), and Alzheimer disease (Boggio et al., 2012). In addition, tDCS have gathered substantial interest as a potential treatment for chronic pain, leading to several clinical trials. Results from early trials provide evidence that tDCS with the anode placed over the M1 can lead to substantial pain relief in fibromyalgia (FIM) (Fregni et al., 2006b), chronic pain after traumatic spinal cord injury (Fregni et al., 2006a), and in various chronic pain conditions (Antal et al., 2010). Other studies found more modest effects on patients with neurogenic arm pain (Boggio et al., 2009), and no effect on patients with spinal cord injury (Soler et al., 2010), nonspecific low back pain (O'Connell et al., 2013) and human T-lymphotropic virus type I (HTLV-1) related chronic pain (Gonçalves et al., 2013). Among the non-pain outcomes in chronic pain, anodal tDCS over the M1 has been shown to increase sleep efficiency, decrease arousal and increase delta activity in non rapid eye movement (REM) sleep (Roizenblatt et al., 2007). Interestingly, in the study by Fregni and colleagues (2006) , anodal tDCS over the M1 induced large pain reduction, and improved daily functioning measured with fibromyalgia impact questionnaire (FIQ), and physical functioning and bodily pain measured with short form 36 (SF36) (see Methods for a description of FIQ and SF36), but had no effect on depression and anxiety. Findings from these clinical trials are not uniform, and larger more rigorously designed clinical trials are sought for, as indicated by a Cochrane review by O'Connell and colleagues (2014). While tDCS has the potential to be a cost effective treatment option for chronic pain compared to other brain stimulation methods (Zaghi et al., 2009), the premise for clinical implementation is more high-quality evidence for the clinical efficacy of the method.

Regarding chronic pain, the considered background literature in this thesis are limited to studies and theory based on anodal tDCS over the M1, as it is most relevant for the methodology in the reports this thesis is based on. However, the studies involving experimentally induced pain in healthy subjects are less numerous than clinical studies, and often use different electrode positions or polarity for comparison. For instance, a study has shown that cathodal, but not anodal tDCS over the M1 reduces laser evoked mild pain perception in the contralateral hand, and that anodal tDCS increases warm (sub pain threshold) sensation (Csifcsak et al., 2009). Furthermore, other studies that also applied anodal and cathodal stimulation of the M1 found no effects on neither mechanoreceptive detection nor heat pain thresholds (Jürgens et al., 2012), or pain ratings (Ihle et al., 2014). Additionally, anodal tDCS over both the M1 and the dorsolateral prefrontal cortex (DLPFC) has been shown to reduce pain thresholds in electrically induced peripheral pain (Boggio et al., 2008c). Furthermore, anodal stimulation of the DLPFC both increases tolerance to heat pain and working memory performance, but in an uncorrelated fashion, suggesting that the analgesic effects of tDCS in healthy subjects are not associated with cognitive processing (Mylius et al., 2012). In sum, the results in the published literature regarding the effect of anodal tDCS over the M1 on experimentally induced pain in healthy subjects appear to less consistent than studies involving clinical pain in patients. The findings that cathodal, but not anodal stimulation over the M1 increases pain perception (Csifcsak et al., 2009) seem to contradict clinical studies where pain reductions following anodal tDCS over the M1 often are reported. Nonetheless, a recent meta-analysis concluded that, overall, anodal tDCS over the M1 increases sensory and pain threshold in healthy individuals, and decreases pain level in patients with chronic pain (Vaseghi et al., 2014). However the authors of this meta-analysis state that the results should be interpreted with caution, as the included studies had small sample sizes, and that they did not consider the level of blinding.

While pain perception might differ between patients and healthy subjects (see below), the methodology in the studies are also different. For example the clinical studies that found the largest effect of anodal M1 tDCS (Antal et al., 2010; Fregni et al., 2006a; Fregni et al., 2006b) administered the stimulation protocol over 5 consecutive sessions, but none of the experimental studies repeated the same stimulation. Thus, the two categories of studies might be too methodologically different to yield comparable results.

Rationale and possible mechanisms in tDCS induced chronic pain relief

Chronic pain can be defined as a continuous, long term pain of more than 12 weeks, or after the time that healing would have been thought to have occurred in pain after trauma or surgery (BritishPainSociety, 2012). Hyperalgesia, an increased sensitivity to pain, and allodynia, pain due to a stimulus that does not normally provoke pain, are common components in chronic pain, and are examples of peripheral and central sensitization that affect the thresholds for action potentials of nociceptors. (Fregni et al., 2007). Imaging studies have shown that patients with chronic pain processes pain differently than healthy controls (Burgmer et al., 2009; K. B. Jensen et al., 2009). For instance, patients with FIM have reduced regional cerebral blood flow (rCBF) in the right thalamus compared to healthy controls (Kwiatek et al., 2000). Furthermore, in areas of the brain typically associated with pain perception (primary and secondary somatosensory cortex, insular, anterior cingulate and prefrontal cortices) (Apkarian et al., 2005), patients with FIM display disrupted functional connectivity at rest (Cifre et al., 2012). Up-regulation of motor cortex excitability might modulate pain perception through indirect effects via neural networks and pain modulating areas (Fregni and Pascual-Leone, 2007; Lima and Fregni, 2008). This has recently been supported by an imaging study that demonstrated reduced rCBF during experimentally

induced heat pain in several brain regions that are distant to the site of stimulation site when comparing anodal to cathodal stimulation (Ihle et al., 2014). In addition to indirect effects on distant brain structures, the M1 can itself be an important component in endogenous pain modulation. Recently, is has been suggested that the M1, while not a part of the typical pain network in the brain, is connected to pain related neural areas through a feedback loop (Castillo Saavedra et al., 2014). Thus, it is possible that the neuromodulatory effects of tDCS in the M1, and indirect effects on brain areas more distant to the electrodes, can affect the abnormal pain processing known to occur in patients with chronic pain, and as a consequence, reduce perceived pain.

tDCS in studies investigating motor learning and performance

In behavioral studies, it is generally suggested that anodal tDCS over an area involved in a task facilitates the learning of the task (Antal et al., 2014), and the results from a meta-analysis (Jacobson et al., 2012) do indeed indicate that, overall, the facilitation effect of anodal tDCS is more consistent than the inhibitory effect of cathodal tDCS in motor and cognitive domains. However, the results from this field are complex, and that in addition to polarity, other aspects of the stimulation such as laterality, timing, and stimulation intensity might also be important. For instance, on a finger sequencing task, anodal tDCS over the left M1 improves right hand performance, but with the opposite effect for the left hand (Vines et al., 2006). Another study (Stagg et al., 2011) has demonstrated that the timing of the stimulation is important, as anodal tDCS during an explicit learning task, in accordance with the overall theory in the field, increases the rate of learning, but if the stimulation is applied prior to the task, the rate of learning is decreased. The intensity of the stimulation might also be important. Experimental evidence suggests a dose-response relationship between intensity

and both neural excitation (Nitsche and Paulus, 2000) and after effects (Nitsche and Paulus, 2001). Furthermore, preliminary evidence suggests that the effect of anodal tDCS on learning tasks can be facilitated by increasing the current intensity of the stimulation (Leenus, 2013).

Rationale and possible mechanisms in tDCS induced improved motor learning

It is likely that a neurophysiological correlate of motor skill resides in the M1 for several days after acquisition (Nudo et al., 1996), and that this brain region plays an important role in motor skill learning (Ungerleider, 1995). The acquisition of a new motor skill is accompanied by changes in neuronal activity and excitability (Nitsche et al., 2003c). Motor learning within the M1 is, like the general facilitation after effect of tDCS, found likely to occur via LTP-like mechanisms dependent on modulation of NMDA receptors, with modification thresholds altered by prior experience (Stagg and Nitsche, 2011). This seems to indeed be the case in the visual cortex, where the change in the efficacy of a given synapse depends not only on current pre- and post-synaptic activities, but also on a slowly varying time averaged value of the post-synaptic activity (Bienenstock et al., 1982; Kirkwood et al., 1996). In the mice M1, direct current stimulation coupled with repeated synaptic co-activation induces a long lasting synaptic potentiation which is NMDA-dependent. This experimental evidence from rodents indicate that both the time averaged mean status of synapses and the neuronal activation pattern during motor learning might be relevant for the effect of tDCS. In humans, timing dependent effects on motor learning have been observed with anodal tDCS over the M1 (Kuo et al., 2008; Stagg et al., 2011), indicating that tDCS induced increased excitability of the M1 prior to learning a motor task might reduce motor learning. Thus, in order to enhance learning, tDCS is most effective when applied during practice, not before. In sum, the conceptual background for tDCS as a method for enhancing motor learning is anchored in

evidence from imaging and animal studies, and supported by results from human studies with behavioral outcomes.

Fibromyalgia

Fibromyalgia (ICD-10 M79.7) is a chronic pain syndrome with a prevalence of 2% to 5% that occurs more often in women (Neumann and Buskila, 2003; Wolfe et al., 2013). The diagnostic criteria for FIM was established by the American College of Rheumatology (ACR) in 1990. According to the ACR-90 criteria, the condition is defined as widespread pain for at least 3 months, and tenderness in 11 or more out of 18 tender points during digital palpation with an approximate force of 4 kg (Wolfe et al., 1990). A more recently proposed diagnostic criteria based on self report, and not manual tender point examination, provide a scale that can be useful in providing longitudinal data on symptom severity (Wolfe et al., 2011; Wolfe et al., 2010). Patients in Report III were recruited in a Norwegian hospital that employed manual tender point examination as diagnostic criteria for the condition. FIM is associated with fatigue, disturbed sleep, depression, and reduced quality of life (Häuser et al., 2010). The most common treatment guidelines recommend aerobic exercise, pharmacological treatment, cognitive behavioral treatment, and various multi-component treatments (Häuser et al., 2010). Following the recommended methods, treatment effects on pain caused by FIM are usually modest (Marcus et al., 2014). The patophysiology of FIM is not yet entirely known (Desmeules et al., 2003). There is strong evidence that central sensitization plays a major role in the generation of FIM symptoms (Woolf, 2011). The association between FIM and abnormal central nervous system (CNS) function are further supported by imaging studies (K. B. Jensen et al., 2009; Kwiatek et al., 2000). However, FIM might not be a primary disorder of the brain, in the sense that CNS alterations might not be at the beginning in the chain of

events leading to FIM (Schweinhardt et al., 2008). Individual vulnerability and prolonged

severe stress might play a role in the development of chronic widespread pain (McBeth et al.,

2007). As the cause of FIM remains unknown, the condition in clinical practice is often

treated with regards to biological, psychological and social factors.

GENERAL RESERCH QUESTIONS

The major question underlying the present thesis was to investigate the effect of anodal tDCS over M1 on functionally important outcomes in the pain and motor domains. The outcome measures were chosen for their predictive value on phenomena relevant for human functioning rather than for their known particular sensitivity to the excitability changes induced by electric stimulation. This approach is meant to supplement the existing literature that concerns the effect of the relatively simple M1-SO montage on outcome measures that can be considered the product of a long, and partially unknown, physiological chain of evidence.

The principal research questions addressed in this thesis are as follows:

1) Can tDCS reduce acute heat pain perception in healthy volunteers?

2) Can tDCS enhance motor performance and motor learning on two neuropsychological tests that predict functionally relevant outcomes, and what are the individual differences that predict the functional effect of tDCS?

3) Can tDCS induce clinically relevant pain reduction in patients with fibromyalgia? Can the stimulation affect other clinically relevant outcomes such as daily function and psychiatric symptoms?

METHODS

Overview of study design

	n (females)	Groups	RM	mA	Duration	Sessions
Report I	75 (37)	3	3	2	7	1
Report II	60 (29)	3	3	2	20	1
Report III	48 (45)	2	7	2	20	5

Table shows number of participants, number of randomized groups, number of repeated measures (RM), current intensity (mA), duration of stimulation in minutes, and number of stimulation sessions in the reports included in the present thesis. All reports used the M1-SO electrode montage, with the anode over the M1. All studies were conducted double blind with regards to the active/sham conditions. The no-treatment conditions in Report I and II were conducted single blind.

tDCS

Studies that use tDCS to manipulate cortical excitability are typically sham controlled. That is, subjects in the control group undergo an identical procedure, but the component considered to be therapeutically effective is removed. The most common way of administering sham tDCS is to perform a similar electrode montage on the control participants as on the active tDCS participants, and then perform stimulation with a duration that is insufficient to induce lasting excitability changes in the cortex. Experimental evidence suggests that a minimum of 3 minutes of 1mA tDCS are required to induce after effects of the stimulation (Nitsche and Paulus, 2000). For sham stimulation in this thesis, Report I used a 20 seconds fade-in followed by 10 seconds of 2mA tDCS, and Report II and III used a 8-seconds fade in, followed by a 30 seconds 2mA tDCS terminated by a 5 seconds-fade out. Thus, it is likely that all conducted sham stimulation had the therapeutically effective component removed, but

mimicked the skin sensation of electric stimulation under the electrodes. While the relative convenience of administering a sham condition (Gandiga et al., 2006) likely has contributed to the growing popularity of tDCS as a research tool since the early 2000's, the efficacy of the patient blinding, especially at high current intensities has recently been questioned (O'Connell et al., 2012). Even with a setup that enables sufficient patient blinding, experimenter blinding might be compromised by observed differences on the skin surface after stimulation (Palm et al., 2013). Considering these findings, tDCS studies that aim to achieve experimental control should emphasize optimal electrode preparation, as both skin sensation from electric stimulation, and skin redness origins from the electrode-skin interface.

The most common set up for electrode preparation is to dampen the sponge electrodes in saline (NaCl). While subject discomfort has been shown to correlate with higher electrolyte concentration in the solution, advantageous conductive properties can be achieved (Dundas et al., 2007). On the other hand, using tap water to prepare the electrodes has been shown to produce skin lesions under the electrodes, possibly due to small concentrations of diverse substances in the water (Frank et al., 2010; Palm et al., 2008). In Report I, saline and conducive paste designed for electroencephalography (EEG) electrodes were used. Based on pilot tests prior to conducting the clinical trial (Report III), it was found that a combination of medical grade sterile water and conductive paste designed for EEG devices held similar conductive properties as saltwater, while producing less discomfort. Thus, we employed this method of electrode preparation in the subsequent (Report II and III) trials. We did not investigate the efficacy of the blinding condition in the trials, but the distribution of reported adverse effects, for instance scalp pain, tingling, itching, burning sensation, and skin redness between the groups might relate to the efficacy of patient blinding (Brunoni et al., 2011a). In Report II, after a single session of tDCS, burning sensations under the electrodes occurred more frequently after active tDCS compared to sham tDCS. However, in Report III, after an

identical stimulation protocol but with 5 consecutive sessions, and a larger sample receiving stimulation, acute mood change occurred more often after sham tDCS, otherwise there were no differences between the groups. There were no consistent tendency in the between group differences in reported adverse effects reported in Report II and Report III, indicating that active tDCS did not systematically induce increased patient discomfort compared to sham. Thus, assuming that reported between group differences in adverse effects can predict the efficacy of the blinding procedure, the adverse effect data did not indicate that participant blinding was compromised in Report II and Report III. Furthermore, in Report II, the inter electrode impedance after 1 minute of stimulation indicated that the voltage needed to drive the 2mA was relatively low ($\approx 10V$), indicating that the conductive properties of the sterile water and conductive paste were acceptable.

Pain Stimuli

Noxious heat stimuli are a common method for inducing experimental pain. Conductive heating of nociceptive nerve endings allows control over the temperature at the stimulator-tissue interface (Baumgärtner et al., 2005). Imaging studies have consistently shown that heat thermode induced experimental pain produces increased rCBF in the second somatic (S2) and the insular regions, and in the anterior cingulate cortex (ACC) (Peyron et al., 2000), concordant with the regions associated with pain processing in the brain (Ploghaus et al., 1999). In Report I, we used computer controlled conductive heat as pain stimuli, which enabled precise control over the temperature as well as the temporal aspects of the stimulation.

Measures of subjective pain

According to the International Association for the Study of Pain (IASP), pain can be defined as "An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage" (1994). This definition implies that both sensory and emotional components are integral parts of the construct, and thus, both should be measured. Commonly in studies that investigate pain, the sensory and emotional components are operationalized as "intensity" and "unpleasantness". The magnitude of pain is usually measured with anchored scales, where the subjects are to indicate the level of pain on a range between two defined extremes. The scales within this family of tests tend to yield relatively high inter-test reliability (Jensen et al., 1986; Kremer et al., 1981), and the specific scale should be selected based on the study design and practicality. In order to quantify the subjective experience of pain, the Visual Analog Scale (VAS) is a convenient tool for measuring both experimental and chronic pain (Price et al., 1983). While the analog nature of the VAS scale makes it suitable in a hospital or laboratory setting, the 11-point (0-10) Numeric Rating Scale (NRS) holds similar psychometric characteristics as the VAS scale (Ferreira-Valente et al., 2011), and is well suited for digital pain reports.

In Report I, we measured pain intensity with Computerized Visual Analog Scale (COVAS). The participants were instructed to move a mechanical slider along a line in order to indicate their pain between "no pain" and "most intense pain imaginable". The COVAS converted the position of the slider to a 0-100 scale and recorded the report. In Report III, we measured pain intensity and pain unpleasantness on a 0-10 NRS scale with SMS on mobile phones (see "Methods" in Report III" for details). To our knowledge, no previous randomized controlled trial (RCT) on chronic pain have employed SMS as a mean to obtain pain reports. However, SMS has shown to yield high compliance when monitoring pain levels in children (Alfvén, 2010) and to obtain weekly pain reports from patients with low back pain (Axén et al., 2012).

The experience regarding the use of SMS in Report III suggests that it is a highly suitable method for obtaining longitudinal pain data.

Adverse effects

tDCS is still a relatively new method, and a standard for reporting adverse effects is not yet present. Direct comparison of the frequency and severity of adverse effects between studies is therefore difficult. Brunoni and colleagues (2011a) suggested a standard form for registering adverse effects. In this structured interview, both occurrence and intensity of perceptions commonly associated with tDCS, and the degree to which the subjects consider the experienced adverse effect related to the stimulation, are quantified. I translated this form into Norwegian, and employed it in Report II and Report III. In these samples, the side effects included in the interview were mostly relevant, and considering the low frequency of reports in the category "others", they sufficiently covered the participant perceptions of tDCS. However, the items that covered the degree of which the perceived adverse effects were related to the stimulation appeared to be not well suited in our samples. The 5-point scale on adverse effect relatedness to tDCS (1, none; 2, remote; 3, possible; 4, probable; 5, definite) were in practice treated as a binary "yes-no" by many subjects. Secondly, the lack of a "don't know" item made some subjects reluctant to answer. Finally, the distinction between "remote", "possible" and "probable" seemed difficult, leading to arbitrary ratings. These aspects were present both in healthy subjects (Report II) and patients with FIM (Report III). Subsequently, the aforementioned shortcomings of the adverse effects probability ratings led to poor data quality, and violation of the statistical assumption that the data consisted of interval entities. Thus, the results from the "relatedness" scale were not analyzed. Regardless of the shortcomings with this aspect of the interview in our sample, we found the implication

of a standardized method for obtaining adverse effects in Report II and Report III to be valuable, as it enabled comparison of adverse effects between studies. In the future, in order to compare adverse effects across different stimulation protocols, a uniform quantifiable system for registering adverse effects are required. The structured interview by Brunoni (2011a) can be a viable starting point.

Neuropsychological tests

Neuropsyhological tests are paper or computerized tests that explore cognitive performance (Brunoni et al., 2012). By observing behavior (test performance), it is possible to draw hypotheses about brain function, both in healthy and clinical populations depending on the type of test. The Grooved Pegboard Test (GPT) assesses eye-hand coordination and motor speed, and is considered a relatively complex task compared to other motor tasks such as Grip Strength and Finger Tapping (Merker and Podell, 2011). Trail Making Test B (TMT-B) is a measure of attention, processing speed and mental flexibility that requires complex visual scanning and has a motor component (Meyers, 2011).

In Report II, GPT and TMT-B were used as outcome measures. Both tests were considered interesting to investigate facilitated practice effect following tDCS. Both GPT and TMT-B have a motor component, and the tDCS anode was placed over the motor cortex. Additionally, GPT is known to be sensitive to lateral brain damage, and it was hypothesized that it could possibly be sensitive to laterality effects of the stimulation. GPT was therefore administered with both the dominant and non-dominant hand, while the stimulation was uni-lateral. Furthermore, performance on the GPT is gender and age dependent (Ruff and Parker, 1993), performance on TMT is known to be age and IQ dependent (Meyers, 2011). Therefore, the tests were considered to have predictive value for daily functioning in healthy subjects, and

therefore an interesting target for tDCS mediated facilitation. Finally, none of the tests have randomized components. That is, they are administered in the same manner every time, and subjects perform consistently better after the first trial. This inherent practice effect made the tests suitable to investigate differences between active tDCS, sham tDCS and no-treatment groups.

Psychological questionnaires

In Report III, computerized questionnaires were administered at the start of the pretest period and at the end of the posttest period to investigate the effect of tDCS on daily function, anxiety and depression, psychiatric symptoms and distress, and general physical and mental health. The Fibromyalgia Impact Questionnaire (FIQ) (Bennett, 2005) was used to measure fibromyalgia related daily function. The Norwegian translation was based on the validated Swedish version (Hedin et al., 1995), and was assumed to hold similar test characteristics due to the semantic and phonetic similarities between the languages. The Hospital anxiety and depression scale (HADS), in a Norwegian translation known to have similar test characteristics as other translations (Olsson et al., 2005), was used to measure the level of anxiety and depression in the patients. The Symptom Checklist 90R in an official Norwegian translation (© 2009 by NCS Pearson, Inc) was used to measure psychiatric symptoms and distress. Additionally in Report III, the Short Form 36 (SF36v2) was used to measure general physical and mental health. The employed Norwegian translation have similar psychometric properties as other translated versions of the survey (Loge et al., 1998). Finally, in Report I, subjective stress was measured by having the participants rate two adjective pairs from the Stress/Arousal Adjective Check List (SACL) (Mackay et al., 1978) on a 0-10 NRS. The

Norwegian translation and experimental application of this scale has previously been used in our laboratory (Aslaksen et al., 2011; Aslaksen and Flaten, 2008).

SUMMARY OF RESERCH REPORTS

Report I (Aslaksen PM, Vasylenko O, Fagerlund AJ. (2014). The effect of transcranial direct current stimulation on experimentally induced heat pain. *Experimental Brain Research, 232*(6), 1865-1873.)

The aim of this experiment was to test whether 7 minutes 2mA anodal tDCS over the M1 reduced experimentally induced heat pain intensity in healthy subjects. We hypothesized that the group that received active tDCS would display reduced heat pain intensity, and that the group that received sham tDCS would display a significant placebo response compared to the no treatment group that received no tDCS montage or stimulation, but received similar pain stimulation as the active and sham groups. The no treatment group was included to estimate the placebo effect (Benedetti et al., 2003), as the true placebo effect is represented as the difference between sham and no treatment conditions (Fields and Levine, 1984) The active and sham conditions were double blind.

A total of 75 (37 females) healthy volunteers were randomized into 3 groups: active tDCS, sham tDCS, and no treatment. The active tDCS group received 7 minutes of stimulation with an intensity of 2mA. The anode was placed over the left M1(C3 position in the 10-20 system for EEG electrode placement), and the cathode was placed on the contralateral forehead in a similar fashion as Fregni and colleagues (2006). The sham tDCS group received a similar montage and a stimulation that mimicked the skin sensation of active tDCS, but with a duration that were insufficient to induce excitability changes in the cortex. The no treatment group received no electrode montage, but otherwise underwent the same experimental procedure. All 3 groups received pain stimulation procedure in 3 blocks: pretest, treatment and posttest. Each block consisted of 3 pain stimuli that were presented in the same order for each block: 43ºC, 45ºC and 47ºC.

Pain intensity was measured with a COVAS. The pain scale ranged from 0-100 and were anchored at "no pain" (0) and "most intense pain imaginable" (100). Subjective stress was measured with two adjective pairs from the SACL that were rated on an 11-point NRS. Blood pressure was measured with an automatic blood pressure monitor. The experiment was conducted at the University of Tromsø.

The results indicated that for the 43ºC heat stimuli, there was no main effect of group. For the 45ºC heat stimuli, the pain reports were lower in the active tDCS group compared to the natural history group, but not different from the sham tDCS group. For the 47ºC heat stimuli, there was an interaction between group and time. During treatment and at posttest, the pain reports were higher in the no treatment group compared to active and sham tDCS groups. When investigating the pretest - posttest NRS scores, the results indicated no difference between the groups at 43ºC. At 45ºC, the active tDCS group reported larger pain reduction than the no treatment group. At 47ºC the active tDCS group reported larger pain reduction than both the sham tDCS and the no treatment groups. Regarding pain thresholds, there were an increase from pretest to posttest regardless of group, and no specific effects of the tDCS stimulation. Consistently, males reported lower pain intensity at all temperatures compared to females. Subjective stress decreased from pretest to posttest regardless of group, and was lower in the active tDCS group compared with the no treatment group. Blood pressure was higher in the no treatment group compared to both active and sham tDCS groups, but no significant interaction between group and time.

The results from Report I revealed mixed findings. The effect of tDCS on heat pain intensity differed between the temperature settings of the heat stimuli, with larger effects at higher temperatures. The sham tDCS group consistently had a response pattern that were more similar to the active tDCS group than the no treatment group across all temperatures and time points, indicating that tDCS procedure might induce placebo responses that influenced the

pain ratings. The finding that 7 minutes of tDCS had no effect on changes in pain thresholds from pretest to posttest were in line with the finding of Jurgens et al. (2012), possibly because a single session of 7 minutes tDCS were insufficient to excitability changes that lasted long enough to affect the pain thresholds that were measured at posttest.

Report II (Fagerlund AJ, Danielsen T, Freili J, Aslaksen PM. No effect of 2mA anodal tDCS over the M1 on performance and practice effect on Grooved Pegboard Test and Trail Making Test B. Submitted *eNeuro* December 2014.)

The aim of this experiment was to test the effect of 20 minutes 2 mA anodal tDCS over the M1 on performance and practice effect on two commonly used neuropsychological tests measuring fine motor (GPT) and psychomotor (TMT-B) speed. We hypothesized that the group who received active tDCS would have increased performance on the tests during stimulation, compared to the sham tDCS and no treatment group. Furthermore, we hypothesized that the practice effects, operationalized as the difference in time to complete the tests would be larger in the active tDCS group. Additionally, we included control variables to investigate the influence of overt individual differences on the stimulation outcome.

A total of 60 healthy volunteers (29 females) were randomized into 3 groups: active tDCS, sham tDCS, and similarly to Report I, we included a no treatment condition to investigate the placebo response. The active tDCS group received 2 minutes of stimulation with an intensity of 2mA. The anode was placed over the M1 contralateral to the dominant hand, and the cathode was placed on the contralateral forehead. The sham tDCS group received a similar montage and a stimulation that mimicked the skin sensation of active tDCS, but with a duration that was insufficient to induce excitability changes in the cortex. The no treatment

group did not receive electrode montage, but the timing of the tests were synchronized with the tDCS groups. The test were administered at pretest (before stimulation), after 7 minutes of stimulation (during stimulation) and at posttest (after stimulation). At each time point GPT were administered with the dominant and non-dominant hand, and the TMT with the dominant hand only. The bi-lateral GP testing was included to investigate lateral effects of the stimulation on fine motor speed. To control for the influence of overt anatomical and behavioral individual differences on the effect of tDCS, we registered data on BMI, head circumference, sleep status and stimulant use (caffeine and nicotine). Additionally, inter electrode impedance after 60 seconds of stimulation were measured for the active tDCS group. Adverse effects were registered with a structured interview form (Brunoni et al., 2011a).

The results indicated that the groups performed similarly on pretest, and that the tDCS had no effect on neither performance or practice effect on the GP for the dominant or non-dominant hand or the TMT. A regression analysis with practice effect as dependent variable and control variables as predictors indicated that BMI was a significant predictor for practice effect on the TMT for all participants. Interestingly, and uniquely for the active tDCS group, both lower electrode impedance and higher caffeine intake prior to the experiment significantly predicted increased practice effect on the GPT with the dominant hand.

While the results from this experiment suggested that the null hypothesis regarding the effect of tDCS on GPT and TMT should be retained, the observed predictive value of control variables on the practice effect of GPT in the active tDCS group was novel. Impedance values are rarely reported in the literature, but might provide valuable information. Not only may it predict the skin sensation of electric stimulation under the electrodes, subject discomfort, and adverse effects, but as our results suggested, also affect the effect of tDCS on behavioral outcomes.

Report III (Fagerlund AJ, Hansen OA, Aslaksen PM. (2015). Transcranial direct current stimulation as a treatment for patients with fibromyalgia: a randomized controlled trial. *Pain, 156*(1), 62-71.)

The aim of this RCT was to test the effect of 5 consecutive 20 minutes sessions of 2mA anodal tDCS over the M1 on pain in fibromyalgia (FIM) in a hospital setting, using a procedure that facilitated patient blinding and reduced experimenter influence on endpoint ratings. We hypothesized that patients that received active tDCS should report better improvement in FIM-related symptoms (pain, stress, daily functioning, depression, psychiatric symptoms and general mental and physical health) compared with patients that received sham tDCS. Furthermore, we hypothesized that other clinically relevant aspects such as daily function and psychiatric symptoms would be positively affected by the stimulation.

In total, 48 (45 females) patients met the inclusion criteria and completed the stimulation protocol. They were randomized into 2 groups (active tDCS and sham tDCS). The active tDCS group received 5 consecutive sessions (Monday - Friday) of 20 minutes 2mA tDCS with the anode placed over the left M1 and the cathode on the contralateral forehead. The sham tDCS was administered similarly as in Report II. The patients reported pain intensity, pain unpleasantness, tension, and stress values on a 0-10 NRS with their mobile phones. The reports were obtained 3 times daily (morning, afternoon, evening) for 30 days prior to stimulation (mean value of 30 days: pretest), during stimulation (treatment x 5) and after stimulation (mean value of 30 days: posttest), and thus the RCT was between group design with 7 repeated measures. Additionally, Fibromyalgia Impact Questionnaire (FIQ), Hospital Anxiety and Depression Scale (HADS), Symptom Checklist 90 (SCL-90-R) and Short Form 36 (SF-36v2) were administered before the pretest period and after the posttest period. The

active and sham tDCS underwent an identical procedure from recruitment to completion, and the trial was double blinded. Adverse effects were registered using a standardized form (Brunoni et al., 2011a).

Analysis of the repeated measures data on pain indicated a significant Time by Group interaction term, indicating that patients who received active tDCS had better improvement in pain intensity compared to patients who received sham tDCS. From pretest to posttest, the active tDCS group had a mean NRS reduction in pain intensity of 13.6% (0.66 NRS) versus 1.70% (0.09 NRS) pain reduction in the sham tDCS group. On pain unpleasantness, stress and tension levels, there were no effects of the stimulation. There were significant interactions between type of stimulation (active/sham) and fibromyalgia related daily functioning on the FIQ, and total numbers on symptoms on the SCL90, but not on anxiety and depression measured with HADS, and on general physical and mental health measured with SF36v2. However on the surveys, the effect sizes were small, and there were lower compliance on the posttest measures. Thus, the data were analyzed as randomized, and should be interpreted with caution. The stimulation was well tolerated by the patients, and the adverse effects were overall equal between the active and sham groups.

Overall, the results from this RCT indicated that tDCS statistically reduced pain in patients with FIM, but the effect sizes were small and the method of stimulation should be further improved in order to achieve clinically relevant pain relief. Compared to a previous study that employed an identical stimulation protocol (Fregni et al., 2006b), the results from this study regarding pain reduction were modest, and more in line with the latest update on a Cochrane review on the effect of tDCS on pain (O'Connell et al., 2014a).

In this RCT, several measures were taken in order to reduce confounders in the study design. By employing mobile phone text messages (SMS) as a mean to obtain pain reports, the

number of pain reports were high. For instance, the individual patients reported pain and stress 90 times at pretest, and 90 times at posttest. The response rates on SMS were high (94%), giving relatively robust mean values for the pretest and posttest periods. Furthermore, by physically separating the assessment from the treatment situation, experimenter influence on the pain reports were likely reduced. Double blinding was done using an integrated study mode in the stimulator (see: Methods). The patients were allocated to individual treatment codes at inclusion. The codes were compatible with the stimulator, and associated with either active or sham tDCS, and the experimenters were naive to the nature of the codes. Additionally, the person in possession of the key to the stimulation codes had no interaction with the patients at any point in the participation. Thus, patients in the active and sham groups underwent an identical procedure, and the decoding of the treatment codes were done after the study was completed.

DISCUSSION

The results regarding the ability of anodal tDCS over the M1 to alter functionally important outcomes in the pain and motor domains are mixed. In both clinical and experimental pain, anodal tDCS over the M1 were statistically effective in reducing pain when comparing pretest and posttest scores, compared to sham tDCS. In report I, tDCS did reduce pain intensity, but only at the most painful temperatures in experimentally induced heat pain, but had no effect on heat pain thresholds. However the interaction terms in the repeated measures data in Report I indicated that active tDCS was not different from sham tDCS. In report III, the repeated measures data suggested an effect of the stimulation on reported pain intensity in FIM patients. Moreover, the pretest minus posttest scores in this clinical trial were calculated from the mean reported pain during the pretest period of 30 days (14 in some instances), and during the 30 days posttest period. Interestingly, the pain reduction after active tDCS was 0.66 NRS points (13.6%) versus 0.09 NRS points (1.7%) in the sham group. As both the pretest and posttest scores are calculated from 90 unique pain reports per patient, they can be regarded as founded on robust data with low degree of randomness. Although the relatively small mean pain reduction achieved in this trial can be considered clinically unimportant, Report III provides support for that tDCS is a method that can be worth developing further for clinical use. In Report II, there was no effect of the stimulation. The groups performed similarly both before, during and after the stimulation, regardless of whether they were in the active tDCS, sham tDCS or no-treatment condition. Motor learning was also equal between the groups. In the motor domain, the literature regarding the effect of M1 tDCS is less consistent than in the clinical pain domain. The timing of stimulation, laterality effects and type of test appears to be more important than in clinical studies. In order to establish tDCS as a viable tool for improving performance in healthy people, the method should be proven to either induce changes in real life outcome, or more empirically convenient, change the

outcomes on tests whose results can be predict real life outcomes. In that regard, Report II only provides evidence that an anodal tDCS over the M1, when applied with this particular timing relative to practice (after the initial practice test, during the second practice test, and before the last test) is ineffective. Overall, the results from the reports included in the present thesis provide stronger evidence for the clinical effect of tDCS, than for the effect on healthy volunteers in the pain and motor domains. However, the difference in number of tDCS sessions between Report III (5 sessions) and the other reports (1 session) is likely not trivial for the effect on the outcomes, and this should be kept in mind when comparing the results.

All reports in the present thesis are based on the same relatively simple M1-SO electrode montage. This montage is based on the experiments in Göttingen, Germany (Nitsche and Paulus) in the early 2000's that physiologically verified the excitatory and inhibitory effects of anodal and cathodal tDCS. Presently, the M1-SO arrangement with 2 relatively large electrodes can be considered prototypical (Edwards et al., 2013), and modeling has shown that the resulting distribution of electric field in the brain is not focal (Mendonca et al., 2011). However, low focality is not necessarily a problem for application in clinical syndromes, where modulation of altered excitability in larger regions might be preferable, or where the intended effects are thought to originate from an interaction of task- and stimulation-generated activity alternations (Nitsche et al., 2015). While the simplicity and subsequently low focality of the stimulation can be criticized, the simplicity can also be regarded as advantageous. The most appealing points of tDCS are the relative ease of administration and thereby low administration costs (Brunoni et al., 2011b; Zaghi et al., 2009), high safety (Brunoni et al., 2011a), and the potential for effects that endure for some time after the stimulation (Fregni et al., 2006b; Reis et al., 2009). While working towards improving the method through more focal stimulation, more accurate targeting and more sophisticated stimulation devices, these aspects should be preserved if possible. For example, evidence

from computational models suggests that individual differences in anatomy may affect the distribution of electric field in the brain, and that a uniform dose for all patients may not be the most efficient procedure (Datta et al., 2012). Anatomical differences in the brain are known to be age-related, but also to vary within a particular age group. Across 30 individuals (18-35 years), brain volume was shown to have 40% variation (Song et al., 2011). In addition to tissue volume, other anatomical aspects of the brain, such as contours, folding patterns and functional localization are also characterized by high inter individual variability (Mangin et al., 2004). This indicates that overt anatomical and demographic measures (weight, height, head circumference, gender) might be insufficient to determine the optimal dose of stimulation with regards to intensity and electrode position. A possible solution is to generate high-quality head models from MR images, and calculate the distribution of electric field resulting from a given electrode montage (Windhoff et al., 2013). This may assist in achieving a stimulation that affects the brain regions that are hypothesized to be relevant for the condition at interest, on an individual basis. However, the costs associated with individual modeling required to tailor the stimulation on an individual basis should be balanced against potential benefits (Truong et al., 2013), and the superiority of model assisted stimulation over conventional protocols in terms of clinical and functional outcomes is yet to be demonstrated. While the focality of the M1-SO montage is insufficient in basic studies aiming to explore the contribution of a specific brain area, it is the most commonly employed electrode arrangement in studies with functional outcomes, and has a theoretical rationale for its application in motor and pain domains. Thus, it is a well suited method for addressing the research questions in the present thesis. The M1-SO electrode montage can presently be considered the gold standard of tDCS, and is the protocol that other means of administrating stimulation should have their effect measured against.

Due to ease of administration and no serious safety concerns in its current application, tDCS is appealing as a treatment tool for chronic pain. The method is not known to undermine the effects of other treatments. On the contrary, experimental evidence suggests that the physiological after effects can be facilitated by SSRI (Nitsche et al., 2009b). Chronic pain is known to have comorbidity with depression, and it is therefore possible that some of these patients receives medication that can facilitate the duration of the excitability changes induced by the stimulation, and possibly also the clinical effects of tDCS. With this in mind, tDCS can be considered for application as an add-on therapy in chronic pain. Consistent with the literature, we found that tDCS was more effective in ameliorating chronic rather than experimental pain. While the modality of heat pain is likely to differ from the pain experienced in a chronic pain condition, the outcome measure of subjectively reported pain is comparable between Report I and Report III. In an imaging study by Jensen and colleagues (2009), patients with Fibromyalgia, during provoked pain, exhibited reduced response compared to healthy subjects in the descending pain regulating system, but not in areas associated with sensory projections from the stimulated body part. It is therefore possible, that the effect of tDCS in chronic pain is due to the normalization of functionally abnormal endogenous pain processing systems, rather than altered function in sensor systems. This is supported by the finding that tDCS did not alter pain thresholds in healthy subjects in Report I, and that in another study (Csifcsak et al., 2009), warm sensation increased after anodal tDCS, in contrast to the often observed reduction in pain.

Placebo effects are present in almost all medical treatments (Enck et al., 2008), and thus also likely to be present in tDCS. In Report III, the placebo effect appears to be small, as the patients that received sham tDCS had small pain reduction compared to active tDCS. While the study design in Report III (active/sham) was sufficient to investigate the hypothesis, the treatment effect of tDCS on fibromyalgia in a hospital setting, it was insufficient to precisely

estimate the placebo effect, as it included no no-treatment condition (Benedetti et al., 2003). The placebo effect may vary between the treatment and placebo groups (Muthén and Brown, 2009), and the real psychobiological placebo response is represented by the difference between the sham and a natural history/no-treatment condition (Fields and Levine, 1984). Therefore, in order to precisely estimate the placebo effect, a no-treatment condition was included in Report I and II. The placebo effect was significant on pain perception at the highest temperature setting in Report I where the effect of active tDCS was no different from the effect of sham tDCS, while both where different from the no-treatment condition. In report II, all groups performed similarly at all time points, and thus no placebo effect was observed.

In report III, the stimulation resulted in a statistical difference in patient's pain intensity levels, but in order to draw conclusion with regards to whether these changes are sufficient to be considered clinically important, a defined threshold for what constitutes clinically important changes is needed. However, there is no clear consensus regarding what constitutes clinically relevant pain change. For instance, with the NRS scale, it has been suggested that in chronic pain, a 30 % reduction is needed (Farrar et al., 2001), while in acute pain a reduction of 1.39 constitute clinically relevant change (Kendrick and Strout, 2005). As the inter-test reliability between NRS and VAS scores are high (M. P. Jensen et al., 1986; Kremer et al., 1981), it is possible to consider studies that investigate clinically relevant VAS scores as relevant for NRS outcomes. It has been suggested that in acute pain, a difference of 9 mm (0.9 NRS) is a clinically relevant change regardless of gender, age, and cause of pain (Kelly, 1998), while in another study, is has been shown to vary with pain intensity (Bird and Dickson, 2001). Finally, this has been contradicted by a study that indicate that overall, the minimum clinically important difference in acute pain is 12 mm (1.2 NRS), and that it does not differ with the severity of pain being reported (Kelly, 2001). Given the inconsistency in

the results from these studies, and that all studies that present discrete thresholds are on patients with acute pain measured in emergency departments, the threshold to apply in clinical trials is not given. Thus, the conclusions regarding clinically significant pain reduction in clinical studies should consider both methodological aspects of the study, and whether the pain is acute or chronic. For example, in Report III, by defining the threshold for clinically relevant change as 1.2 NRS, 4 patients in the active group, and 1 patient in the sham group, had a clinically relevant effect of the stimulation. However, it is possible that the 1.2 threshold is conservative given the nature of the outcome measures in Report III. The difference in pain was in this study calculated from mean pain 30 days prior to, and 30 days after the treatment, in patients with chronic pain, and it is possible that the threshold for clinically important pain reduction under these circumstances is lower than for acute pain in an emergency department.

The field of tDCS is evolving regarding theoretical background and improved stimulation protocols. However there are some methodological aspects that could be standardized to enable comparison between studies. Building on the reports in the present thesis, two general recommendations for future research that employs tDCS can be made. Firstly, inter electrode impedance should be reported. This basic property of stimulation, given a constant stimulation intensity, determine the voltage required to drive the electric current as per Ohm's law (see Report II for a discussion). The voltage is one of the aspects that affect the skin sensation under the electrodes during stimulation. Thus, it is likely to affect patient discomfort and adverse effects, and also the participants' ability to discriminate between sham and active tDCS. Furthermore, as indicated in Report II, the impedance may also correlate with inter-individual differences that affect the efficacy of tDCS on functional outcomes. However, as impedance in tDCS typically is highest at the start of stimulation, and then decreases before becoming relatively stable, the temporal dimension of impedance registration is important for comparison value between studies, and remains to be determined. Secondly, adverse effects

should be uniformly registered and reported. While presently most evidence suggests that tDCS is associated with few safety concerns, future stimulation protocols that are individually tailored and more focal might also produce different patterns of adverse effects. Therefore, making adverse effects comparable between both present and future studies could yield valuable information, support in decision making regarding which protocols to employ clinically, and ultimately improve safety. In Report II and III, a standardized from for registering adverse effects was employed. While having some shortcomings (see Methods), this form produced comparable results, and can be a good template for further improvement. For example, in pain studies, outcome measures are commonly measured with the VAS/NRS family of scales. Therefore, it might be reasonable to increase the quantitative resolution by grading adverse effects with a 0-10 scale with anchored extremes, instead of 0-4. This way the grading is done in a fashion that pain patients are likely to be accustomed to, and provide a more continuous scale that might be more sensitive.

OVERALL CONCLUSIONS

The main findings in the present thesis can be summed up as follows:

1) Anodal tDCS over the M1 at 2mA for 7 minutes does not effectively reduce acute heat pain in healthy subjects, and can induce placebo effects that interact with the treatment effect. In Report I, a relatively short session of anodal tDCS over the M1 resulted in larger pain reduction compared to sham tDCS. However, the size of this effect was small, and the pain thresholds were unaffected. Furthermore, in the repeated measures data, the effects of active and sham tDCS could not be differentiated.

2) Anodal tDCS over the M1 at 2mA for 20 minutes does not enhance motor learning and performance on tests that can predict functionally relevant outcomes, but the conclusion is likely only relevant for instances where tDCS is administered in similar temporal fashion in relation to the practice task as in Report II. The timing and laterality of the stimulation is important, and it is likely that different results can be obtained with different stimulation-practice timing. Similarly, laterality relations (dominant hand, side of stimulation, hand performing the task) are also likely to affect the outcome. Interestingly, for the first time we demonstrate that electrode impedance, likely due to inter individual differences, can predict the functional outcome of the stimulation.

3) Anodal tDCS over the M1 at 2mA for 20 minutes over 5 consecutive sessions does statistically reduce pain in fibromyalgia, and improve daily functioning and total number of symptoms. In report III, both the repeated measures data, and the quantitatively robust pretest-posttest scores on pain intensity indicated better improvement in the active tDCS group

compared to the sham group. However, the results indicate that the M1-SO montage might be insufficient to produce clinically relevant pain reduction, and that improved stimulation protocols should be investigated to improve the treatment effect.

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