TRANSCRANIAL DIRECT CURRENT STIMULATION FOR THE REDUCTION OF CHRONIC NON-SPECIFIC LOW BACK PAIN

by

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ABSTRACT

Non-specific chronic low back pain has serious personal and socio-economic consequences. International guidelines recommend multimodal cognitive behavioural management (CBT). The effectiveness of CBT might be enhanced by directly targeting central nervous system pain processing. Transcranial direct current stimulation (tDCS) is a novel approach aiming to influence pain by altering cortical excitability.

An evaluation of existing reviews indicated the need for an up-to-date review of clinical and experimental pain trials.

A systematic review including 14 trials (published 2006-2012) evaluating tDCS for the reduction of clinical and experimental pain identified a low level of evidence for its effectiveness. Only 1 trial had a low risk of bias. A meta-analysis of trials on clinical pain identified a small pain reducing effect that just reached clinical importance.

To investigate the effectiveness of tDCS alone and in combination with CBT, a double-blind RCT was conducted; preceded by a feasibility study confirming practicability of trial procedures and patient acceptability of tDCS. Results indicated that tDCS alone or in combination with CBT did not significantly influence pain or disability.

An updated meta-analysis, including this trial's results, lowered the pain reducing effect of tDCS below clinical importance, and increased the level of evidence for its effectiveness to "high".

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LIST OF ABBREVIATIONS

AMSTAR	Assessement of Methodological Quality of Systematic Reviews
CBT	Cognitive Behavioural Therapy
CI	Confidence Interval
CLBP	Chronic low back pain
CNSLBP	Chronic non-specific low back pain
CONSORT	Consolidated Standards of Reporting Trials
DBS	Deep Brain Stimulation
DLPFC	Dorsolateral prefrontal cortex
FABQ	Fear Avoidance Beliefs Questionnaire
FfBH	Funktionsfragebogen Hannover (Hannover functional ability questionnaire)
fMRI	Functional magnetic resonance imaging
GABA	Gamma-aminobutyric acid
GCP	Good clinical practice
GRADE	Grading the quality of evidence and the strength of recommendations
HADS	Hospital Anxiety and Depression Score
ICC	intraclass coefficient
ICF	International Classification of Functioning, Disability, and Health
IMMPACT	Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials
ITT	Intention-to-treat
LEP	Laser-evoked potential
LBP	Low back pain
M1	Primary motor cortex
MCS	Invasive motor cortex stimulation
MEP	Magno-electric evoked potentials
MeSH	Medical subject headings
MCRC	Minimum clinically relevant change
MRI	Magnetic resonance imaging
NaCl	Sodium chloride
NMDA	N-methyl-D-aspartate receptor
NRS	Numerical rating scale
NSAIDs	Non-steroid anti-inflammatory drugs
NSLBP	Non-specific LBP
ODI	Oswestry Disability Index
PAG	Periaqueductal grey
PET	Positron emission tomography
PPSI	Patient-Perceived Satisfactory Improvement

PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-analyses
RAND36	36-Item Short Form Health Survey
RCT	Randomised controlled trial
RMDQ	Roland-Morris Disability Questionnaire
rTMS	Repetitive transcranial magnetic stimulation
tDCS	Transcranial direct current stimulation
TENS	Transcutaneus electrical nerve stimulation
TMS	Transcranial magnetic stimulation
S1	Primary somatosensory cortex
SD	Standard deviation
SE	Standard error
SEP	Somatosensory-evoked potential
SF-36	Short form quality of life questionnaire with 36 items
SOP	Standard operating procedure
SRM	Standardised response mean
V1	Visual cortex
VAS	Visual analogue scale

1. CHAPTER

INTRODUCTION

The research presented in this thesis investigates the effectiveness of transcranial direct current stimulation (tDCS) for the reduction of chronic non-specific low back pain (CNSLBP). CNSLBP is a prevalent condition, associated with personal and socio-economic risks and consequences, and with a range of management options. International guidelines recommend a multimodal approach to management. The efficacy of management programmes might be enhanced by interventions that target central nervous system pain processing, which is known to be altered in chronic pain states. tDCS is an intervention that electrically influences the function of areas of the brain from the outside of the skull and might influence pain processing non-invasively. This initial chapter provides background to CNSLBP and available management approaches; introducing tDCS as a new intervention. The main trial reported in this thesis was conducted in Germany, hence information presented in this introductory chapter describes the situation internationally with a focus on CNSLBP in Germany.

1.1 Low back pain (LBP)

LBP is defined as "pain, muscle tension, or stiffness localised below the costal margin and above the inferior gluteal folds, with or without pain referred to the leg(s)" (van Tulder et al., 2006, p.171). It is one of the most prevalent and expensive diseases in Western industrialised countries (Becker et al., 2010) and was the most frequent type of pain reported in a survey in the United States in 2002 (Deyo et al., 1994). A recent systematic review investigating the global prevalence of low back pain (Hoy et al., 2012), included 165 studies from 54 countries and estimated the mean point prevalence (percentage of persons currently experiencing LBP) of

activity-limiting LBP as 12% and the mean lifetime prevalence (percentage of persons that experience LBP once or more in their lifetimes) of LBP as 39%. The global mean lifetime prevalence was lower than anticipated by the authors due to very low rates reported in studies conducted in China, Nepal, Cuba, and Pakistan (Hoy et al., 2012). Publications from the United States indicated a much higher point prevalence of 20-30% (Deyo et al., 2006) and a 1 month prevalence of 30-68% was reported for different European countries (Nachemson, 2004). Estimates in Germany were particularly high, with reported values of 37% point prevalence, 76% 1-year prevalence, and 86% lifetime prevalence (Schmidt et al., 2007). Higher prevalences were consistently reported for high-income countries (Volinn, 1997; Hoy et al., 2012).

The mean total costs per back pain patient in Germany (including acute and chronic LBP) were estimated as approximately €1300 per year (Wenig et al., 2009) and €1000 for 6 months (Becker et al., 2010) including direct (e.g. health care utilisation) and indirect costs (e.g. production losses due to days off work). Wenig et al. extrapolated their results to the German adult population and calculated the total annual costs of LBP as €48.96 billion, which equates to 2.2% of the German gross domestic product, indicating the major impact of LBP on the German economy (Wenig et al., 2009).

The majority of LBP is benign (Henschke et al., 2009) and 74-89% of acute LBP patients recover after 3-6 months (Chou and Shekelle, 2010). However, LBP can have a severe impact on a patient‘s quality of life. For example, approximately 11% experience high intensity pain and a further 11% perceive high disability due to LBP (Schmidt et al., 2007; Walker et al., 2004). In a recent cross sectional study in the Netherlands (Soer et al., 2013), 178 patients with acute LBP rated the mean perceived quality of life using the European Quality of Life instrument (EuroQol-D5) (Centre for Health Economics, 1990) as 0.43 (standard deviation (SD) =0.29), with 0 indicating no quality of life and 1 indicating maximum imaginable quality of life.

1.2 Chronic low back pain (CLBP)

Approximately 9-28% of LBP patients develop chronic pain (Grotle et al., 2005; Gurcay et al., 2009; Henschke et al., 2008; Balague et al., 2011). This variability in rates for the transition to CLBP can be explained by inconsistencies in the definition of CLBP. The most widely used definition for CLBP is ongoing LBP for more than 3 months (Rozenberg, 2008; Bogduk, 2004; Airaksinen et al., 2006). This definition, based only on duration, has been criticised as too simplistic because it neglects the psychosocial aspects associated with CLBP (Cedraschi et al., 1999) and does not accommodate subgroups of recurrent (Dunn and Croft, 2005) or fluctuating (Tamcan et al., 2010) pain. More recent tools developed to identify patients at risk for CLBP (The Keele Start Back Screening Tool) (Hill et al., 2008) and chronic musculoskeletal pain (Örebro Musculoskeletal Pain Screening Questionnaire) (Linton and Boersma, 2003) include psychosocial aspects such as fear avoidance beliefs, depression, bothersomeness and disability. However, published prevalence rates are still based on duration of LBP. Differences in reported prevalence rates also depend on the instrument used, e.g. measuring the duration of pain results in higher prevalence rates than measuring the duration of work absenteeism (Chou and Shekelle, 2010; Ozguler et al., 2000). In a survey of approximately 5000 households in the United States, the point prevalence of CLBP has been reported as 3.9% (95% confidence interval (CI), 3.4%-4.4%) in 1992 and as 10.2% (95% CI, 9.3%-11.0%) in 2006 highlighting the rising tendency of CLBP (Freburger et al., 2009).

The mean direct and indirect costs for CLBP in Germany in 2003 / 2004 have been recorded as twice as high as the costs for acute LBP in a patient sample with 41% CLBP and 59% LBP (Becker et al., 2010) and also twice as high as the costs for age and gender matched participants without CLBP (Hong et al., 2013). In addition, CLBP has been identified as the disease with the highest overall degree of resource use in Canadians under the age of 60 (Rapoport et al., 2004). Annual costs for CLBP patients in Germany have been estimated as >€7000, mainly derived from absence from work and lost productivity data (Juniper et al., 2009).

Further to the economic impact of CLBP, patients exhibit high levels of psychological distress, including reduced quality of life (Morone et al., 2011; van Hooff et al., 2011; Frettloh et al., 2009), depression (Demyttenaere et al., 2007; Hagen et al., 2006; Rush et al., 2000; Currie and Wang, 2004), and sleep disorders (Hill et al., 2008; Hagen et al., 2006; O'Donoghue et al., 2009); and are at a high risk of musculoskeletal co-morbidities, such as arthropathies or rheumatism (Gore et al., 2012).

1.2.1 Chronic non-specific low back pain (CNSLBP)

Approximately 85-90% of LBP patients presenting to primary care have no diagnosable pathology and are referred to as non-specific low back pain (NSLBP) (Hart et al., 1995; Manek and MacGregor, 2005). NSLBP is defined as "tension, soreness and/or stiffness in the lower back region for which there is no identifiable specific cause" (Balague et al., 2011, p.482). The majority of CLBP has no defined source and is therefore generally referred to as CNSLBP (Airaksinen et al., 2006; Balague et al., 2011). The European Guidelines for the Management of CNSLBP defined the condition as "non-specific low back pain that persists for more than 12 weeks" (Airaksinen et al., 2006, p.S208). The literature does not clearly distinguish between CLBP and CNSLBP regarding prevalence, costs, burden of the disease, and management, but implies that CLBP is generally non-specific (Hong et al., 2013; Henschke et al., 2009; Juniper et al., 2009). Hence, prevalence and socio-economic burden reported in Section 1.2 also refer to CNSLBP. This lack of distinction between CLBP and CNSLBP is indicated by the inclusion criteria for CLBP trials that cover all types of ongoing LBP rather than specific pathologies (Hong et al., 2013), exclusion criteria that include patients with spinal pathologies (Moon et al., 2013), and interventions that target central nervous system processing rather than local or systemic pathologies (Henschke et al., 2010; Juniper et al., 2009).

For the purpose of this thesis and to promote a clearer distinction between CLBP caused by ongoing pathologies (e.g. rheumatoid arthritis, spondylolisthesis, or spinal

stenosis) and non-specific CLBP, the term CNSLBP will be used throughout. It is defined as pain, tension, soreness, or stiffness in the lower back region (below the costal margin and above the inferior gluteal folds, with or without referred leg pain) without identifiable cause that persists for a minimum of 12 weeks (Airaksinen et al., 2006, p.S208).

1.2.2 Pathogenesis of CNSLBP

The pathogenesis of CNSLBP is not fully understood, but multidimensional risk factors have been identified for the transition from NSLBP to CNSLBP:

- Physical factors: severe pain at onset (Fransen et al., 2002; Hilfiker et al., 2007; Valat et al., 1997) and high levels of disability (Fransen et al., 2002).

- Psychological factors: depression, psychological distress, passive coping strategies and fear-avoidance beliefs (Pincus et al., 2002; Ramond et al., 2011; Hilfiker et al., 2007; Carragee et al., 2005; Gatchel et al., 1995; Nicholas et al., 2011) as well as pessimistic thoughts about the prognosis (Campbell et al., 2013).

- Occupational factors: heavy labour, unavailability of light duties, low levels of job satisfaction and poor working conditions (Linton, 2000; Valat et al., 1997; Hilfiker et al., 2007; Fransen et al., 2002; Carragee et al., 2005; Gatchel et al., 1995).

- Social and economic factors: level of schooling, language problems, a low income, and an unfavourable family status (Abasolo et al., 2012; Valat et al., 1997).

- Acute pain itself is also a risk factor for the transition to chronic pain as the processing of repeated sensory stimuli leads to a sensitisation of the central

nervous system, and subsequently chronic pain (Apkarian et al., 2009; Campbell et al., 2013; Seifert and Maihofner, 2009).

1.2.2.1 Central nervous system processing of CNSLBP

In the absence of a peripheral pathology, central sensitisation is the main mechanism responsible for the development and maintenance of NSCLBP (Latremoliere and Woolf, 2009; Woolf, 2011). Central sensitisation is defined as the "augmented responsiveness of the central neurons to input from low-threshold mechanoreceptors" (Meyer et al., 1995, p.13-44). A cascade of events is responsible for this altered responsiveness of the central nervous system. The 2 main mechanisms are an increased release of excitatory neurotransmitters at spinal level, influencing pain perception via the spinothalamic pathway, and an altered top-down pain control system from the brain that includes facilitation of nociception and reduced pain inhibition (Apkarian et al., 2009; Zhang et al., 2005) (Figure 1.1). At the synapses of the spinal dorsal horn, substances such as cytokines, prostaglandins, glutamates, substance P, and calcitonin gene-related peptides result in a prolonged excitatory state of second order neurones (Bradley, 2008). Analgesia induced as a descending mechanism from the brain involves a network of cortical and subcortical pathways as well as the endogenous opioid system and the release of adrenergic agents (Millan, 2002).

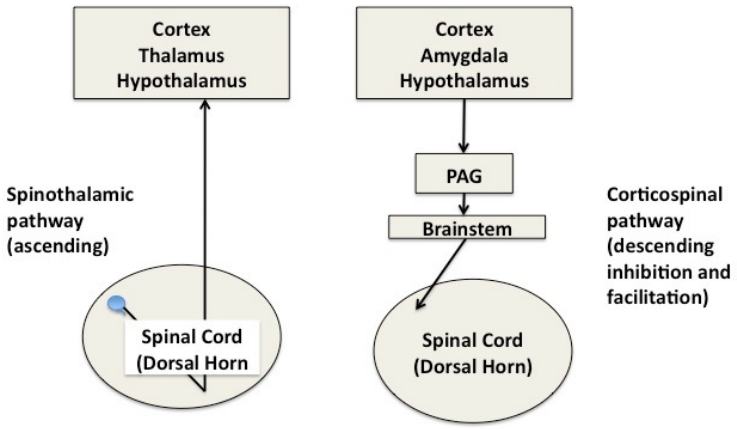


Figure 1.1 Ascending and descending pain pathways

Footnotes: PAG=periaqueductal grey

The central role of the brain in the maintenance of CNSLBP is reflected by the extent of neuroplastic changes reported. The literature distinguishes between structural changes that refer to adaptive anatomical changes in volume and location of brain regions, and functional changes that describe alterations of the activity of brain regions (Davis and Moayedi, 2012). A recent systematic review of reported structural and functional changes in chronic pain indicated that the localisation of observed changes is independent of the type of pain and that structural and functional changes occur in overlapping areas of the brain (May, 2011). Brain areas mutually affected by different types of chronic pain are illustrated in Figure 1.2. Additional areas can be affected that are specific for the localisation and type of pain. Reported structural changes include reduced grey matter in brain areas associated with pain processing (e.g. dorsolateral prefrontal cortex (DLPFC), primary motor cortex (M1), thalamus, brainstem, primary somatosensory cortex (S1), and posterior parietal cortex) (Apkarian et al., 2004; Buckalew et al., 2008; May, 2008; Schmidt-Wilcke et al., 2006; Seminowicz et al., 2011) as well as shifts of the representational areas of the lower back on S1 (Flor et al., 1997) or of areas attributed to lumbar spine stabilising muscles on M1 (Tsao et al., 2008).

Functional changes in the brain suggest that pain processing for CLBP patients is altered compared to healthy controls. Central sensitisation can be observed in

functional magnetic resonance imaging (MRI) as an increased excitability of pain processing regions (Diers et al., 2007; Flor et al., 1995; Kobayashi et al., 2009). Recent trials suggest that functional changes are reversible (Flor and Diers, 2009; Tsao et al., 2010; Seminowicz et al., 2011) and that structural losses of grey matter are not due to irreversible neuro-degeneration as previously hypothesised (Apkarian et al., 2004). It might be possible, therefore, to reverse functional changes with successful treatment (Rodriguez-Raecke et al., 2009; Seminowicz et al., 2011).

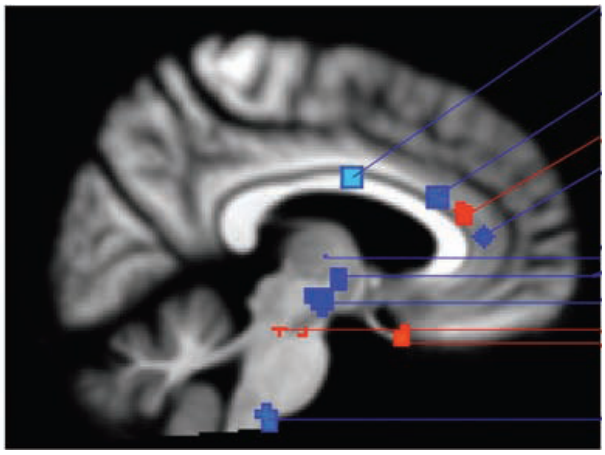


Figure 1.2 Illustration of functional (A) and structural (B) brain changes in chronic pain (May, 2011).

1.2.2.2 Management of CNSLBP

1.2.2.2.1 Multimodal pain management programmes

International guidelines for the management of CNSLBP recommend cognitive behavioural multimodal pain management programmes (CBT) (Koes et al., 2010; Airaksinen et al., 2006; Lambert, 2010; Savigny et al., 2009) combining work conditioning, behavioural therapy, relaxation techniques and general fitness training. The multimodal nature of this approach is required to target the multidimensional risk factors for NSCLBP (Section 1.2.2). Central nervous system pain processing (Section 1.2.2.1) is addressed by supporting patients' coping with pain and by influencing fear avoidance beliefs, function, and disability (Morone et al., 2011). Multimodal pain management programmes are expensive but were evaluated as cost-effective in relation to the estimated direct and indirect costs associated with CNSLBP and in comparison with (for example) surgical management (Rolli Salathe et al., 2012). A recent systematic review on physical interventions for CLBP identified moderate evidence for the short-term effectiveness of multimodal management compared to other kinds of active intervention on pain intensity and work readiness (4 randomised controlled trials) (van Middelkoop et al., 2011). However, the pooled effect size for pain reduction was low (12 mm on a 0-100 mm VAS for pain) and, at both 12 and 24 months post intervention, reduction in pain and change in work readiness were reported as not statistically significant in included RCTs. Additional approaches to influence the central nervous system, such as graded motor imagery or sensory discrimination training have been proposed, to improve effect sizes and long-term benefits of multimodal pain management programmes (Moseley and Flor, 2012; Wand and O'Connell, 2008; Wand et al., 2011).

1.2.2.2.2 Pharmaceutical pain management

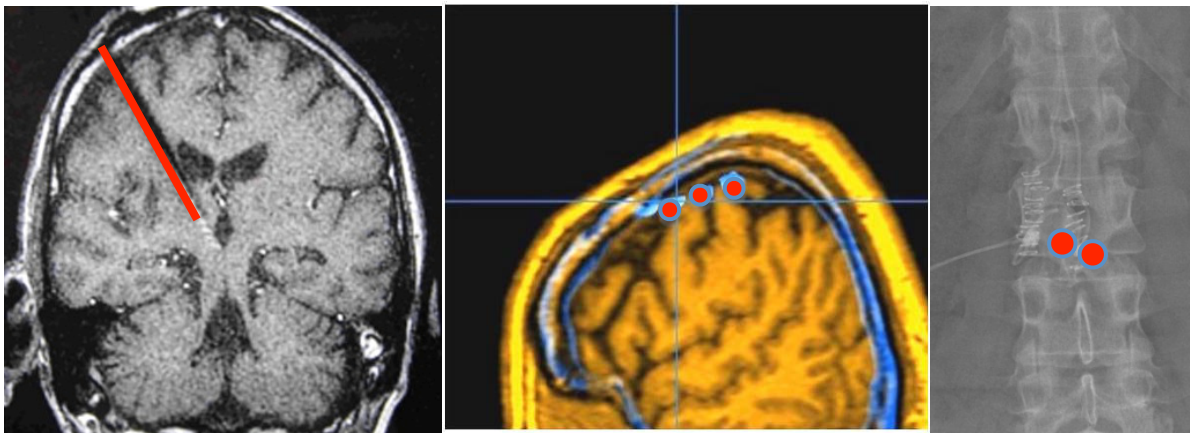
Unimodal management such as medication are insufficient to improve clinical symptoms in CNSLBP. For example, Kovacs et al. reported that usual unimodal medical management did not significantly reduce pain in 28% and disability in 37% of CNSLBP patients (n=830) (Kovacs et al., 2012). However, pharmaceutical interventions are frequently used as an adjuvant intervention in multimodal pain management programmes (Dufour et al., 2010; Paolucci et al., 2011; Morone et al., 2011; Artner et al., 2012).

Two recent overviews of recommendations from international guidelines found that guidelines agree on the use of non-steroid anti-inflammatory drugs (NSAIDs), opioids, muscle relaxants, and antidepressants for CNSLBP (Dagenais et al., 2010; Pillastrini et al., 2011). Due to the common and often severe side effects of these drugs (Benyamin et al., 2008; Mago et al., 2008; Roelofs et al., 2008; van Tulder et al., 2003), the authors highlighted that medication should be used only for short-term pain relief and be accompanied by non-pharmaceutical interventions (Pillastrini et al., 2011). Another pharmaceutical option is injection therapy, using mainly corticosteroids and local anaesthetics. A systematic review evaluating injection therapy for subacute and CLBP concluded that there was no strong evidence for or against the use of any type of injection therapy (Staal et al., 2008).

1.2.2.2.3 Neurosurgical pain management

In severe cases of chronic pain, neurosurgical pain management is an option to influence central nervous system pain processing when all other management approaches have failed. The activity of central nervous system neurones that are affected in the processing of pain can be altered by changing the electrical load of their cell membranes (Hallett, 2000). Electrical stimulators are surgically implanted into either the spinal cord or the brain. Spinal cord stimulators (Figure 1.2) have been

evaluated as effective, but this conclusion was based on 2 randomised clinical trials (RCTs) and 23 observational studies that included patients with failed back syndrome (i.e. CNSLBP that did not improve with any available types of management including back surgery) (Frey et al., 2009). Deep brain stimulation (DBS) with electrical stimulators implanted into the somatosensory thalamus and the periventricular grey matter regions (Figure 1.2) had a clinically significant effect (defined as 51% pain reduction or more) on the perceived pain intensity of 42 out of 68 CNSLBP patients (Kumar et al., 1997) and 80% of patients with failed back syndrome (Bittar et al., 2005; Rasche et al., 2006). Due to the invasive surgical procedure required for DBS, it is increasingly replaced by the less invasive motor cortex stimulation (MCS) (Figure 1.2) (Levy et al., 2010) that was developed in the 1990s (Tsubokawa et al., 1991). MCS is easier to perform, safer and potentially more effective than DBS (Nizard et al., 2012). A systematic review and meta-analysis found a pain relieving effect of MCS on various types of chronic pain with a mean responder (a patient who demonstrated a global response according to the included study's definition) rate of 64% (Lima and Fregni, 2008). Patient populations in the reviewed studies included spinal cord injuries but no patients with CNSLBP. The advantage of surgically implanted electrical stimulators is the avoidance of the systemic adverse effects from long-term drug management, but adverse effects including infections, hardware problems and seizures have been reported (Fontaine et al., 2009).



A B C

Figure 1.2 Location of stimulation electrodes for DBS (A), MCS (B), and Spinal Cord Stimulation (C)

1.2.2.2.4 Non-invasive brain stimulation

Recent research has aimed to replicate the pain reducing effect of MCS without surgical intervention, by either applying electrical currents through the skull or producing a magnetic field that results in an electrical current flow (Hallett, 2000). The use of electrical currents was based on historical documents that described how, as early as 2750 BC, ancient Egyptians took advantage of the unique characteristics of the Torpedo fish. The fish produced electrical shocks that the Egyptians used to cure pain e.g. in patients with gout. Hellwag documented, in 1802, how he cured a patient with severe headache using galvanic currents (Hellwag, 1802). In the 1950s and 1960s, investigators discovered that transcranial electrical stimulation could alter the activity of the brain of animals (Burns, 1954; Creutzfeldt et al., 1962; Goldring and O'Leary, 1951) but these studies could not be reproduced in humans, and the limited technology available at that time was unable to quantify the effects. The application of transcranial electrical stimulation was re-visited in the 1990s in animal studies (Moriwaki, 1991). It was first applied in humans in 2000 (Nitsche and Paulus, 2000), when effects of tDCS could be measured using transcranial magnetic stimulation (TMS) or functional magnetic resonance imaging (fMRI). The first trials evaluating the effect of tDCS in patients with chronic pain were published in 2006 (Fregni et al., 2006a, 2006b). These 2 trials acted as a trigger for a series of trials on tDCS for different types of pain.

A recent systematic review, published by the Cochrane collaboration, evaluated the effect of non-invasive brain stimulation techniques, including tDCS and repeated TMS (rTMS), on chronic pain (O'Connell et al., 2010). High frequency single-dose rTMS of the M1 resulted in a combined mean effect of 15% pain reduction that just reached recommended minimum relevant clinical change. tDCS over M1, similarly, resulted in a small but statistically significant reduction of chronic pain. However, the authors concluded that available evidence was either of unclear or of high risk of bias and included trials with heterogeneous features (I^2=71%). Hence, research of high methodological quality was required to evaluate the use of tDCS or rTMS as interventions for chronic pain conditions.

When directly compared, the following advantages of tDCS over rTMS have been reported in the literature:

- No serious side effects of tDCS have been reported (Poreisz et al., 2007; Nitsche et al., 2003b, 2003c). Reported minor side effects have included mild burning, tingling, itching, and stinging at the site of stimulation (Borckardt et al., 2011); headaches and tiredness (Nitsche et al., 2003c); or, infrequently, nausea or insomnia (Poreisz et al., 2007). rTMS has also been regarded as a safe intervention, however, the occurrence of seizures as a serious adverse event has been reported (Loo et al., 2008).

- The equipment is smaller, portable, less costly, and easier to handle (Priori et al., 2009). Hence, with regards to clinical practice, more clinics could afford tDCS as a treatment method and more clinicians would be able to apply the technique. Theoretically, self-application by patients would also be possible, in a manner similar to transcutaneus electrical nerve stimulation (TENS).

- A sham-paradigm has been established for tDCS that includes a brief period of stimulation that is unable to produce a clinical or neurophysiologic effect (Nitsche et al., 2003b). The sham stimulation mimics the sensations perceived by the patient during the real (verum) stimulation. This might include tingling underneath the electrodes or a mild burning sensation. Two publications have reported that sham and verum stimulation are indistinguishable (Gandiga et al., 2006; Poreisz et al., 2007). Blinding patients in TMS trials is more difficult as TMS produces a clicking noise and a typical skin sensation below the coil that produces the magnetic field (Loo et al., 2000).

1.3 tDCS

tDCS is a weak (1-2 mA) direct current produced by a small battery driven device. It is applied to the skull via sodium chloride (NaCl) solution soaked sponge electrodes. Current flows from the cathode to the anode, thereby inducing positively or negatively charged currents at the site of the stimulation (Nitsche et al., 2008). Stimulation of M1, for example, modulates the membrane resting potential of local neurones and, thereby, induces local excitability changes (Nitsche et al., 2003b). Cortical excitability increases under anodal stimulation (positive electrode positioned over M1) and decreases during cathodal stimulation (Liebetanz et al., 2002). Motor-evoked potentials (MEP) and fMRI confirmed these observations (Bergmann et al., 2009; Boros et al., 2008; Kwon et al., 2008). In a Positron Emission Tomography (PET) study, Lang et al. (2005) demonstrated that the current induced by tDCS over M1 affected the structures directly underneath the electrodes as well as neuronal activity in remote structures including the thalamic nucleus (Lang et al., 2005). Hence, stimulation of accessible superficial structures could also affect more remote structures known to be critical for pain processing.

1.3.1 Proposed neurophysiological mechanisms of tDCS over M1 for the reduction of pain

Although neurophysiological explanations for the effectiveness of tDCS over M1 are not fully understood, this target area was supported by neurophysiological evidence that anodal stimulation increased cortical excitability (Kwon et al., 2008; Liebetanz et al., 2002; Kirimoto et al., 2011), that cortical excitability was reduced in patients with chronic pain (Mhalla et al., 2010), and that surgically implanted M1 stimulators showed pain reducing effects in the past (Lima and Fregni, 2008). M1 is a superficial area of the brain positioned on the cortical convexity of the precentral gyrus and, therefore, easily accessible (Antal et al., 2011). Furthermore, based on fMRI data, M1 has been consistently associated with pain processing (Bingel et al., 2002; Singer

et al., 2004), mainly due to the strong thalamic projections found in animal models (Hirayama et al., 1990; Yamashiro et al., 1994).

Authors attributed the pain reducing effect to various mechanisms, including activation of the endogenous opioid system (DosSantos et al., 2012), influence on the emotional appraisal of pain (Garcia-Larrea and Peyron, 2007), and descending pain inhibition (Garcia-Larrea and Peyron, 2007; Medeiros et al., 2012; Knotkova et al., 2013). Evidence for an activation of the endogenous opioid system is based on evidence from an invasive MCS study using PET to indicate increased cebrebral blood flow in areas associated with high opioid receptor density, such as the periaqueductal grey (Maarrawi et al., 2007). However, only 8 patients were assessed in this trial and cerebral blood flow is an indirect measure for endogenous opioid release.

Descending pain inhibition or top-down pain control is the most discussed working mechanism and was demonstrated in an animal study on rats with experimentally induced sciatica pain (Pagano et al., 2010). It is based on the hypothesis that altered cortical excitability results in the modulation of a widespread neural network that includes the thalamic nuclei, limbic system, brainstem nuclei, and spinal cord (Holsheimer et al., 2007). Prolonged non-invasive brain stimulation has been reported to result in ongoing effects comparable to long-term depression and long-term potentiation (Nitsche and Paulus, 2000) explaining the long-lasting effects of therapeutic stimulation (Fregni et al., 2006a, 2006b; Mori et al., 2010). Long-term depression and long-term potentiation rely on the modulation of the serotonergic system (Zhong et al., 2008). The influence of tDCS on the serotonergic system has been investigated by pharmaceutically modulating the serotonergic system using Citalopram, a selective serotonin re-uptake inhibitor. Citalopram increased and prolonged the facilitatory effect of anodal stimulation and reversed the inhibitory effect of cathodal stimulation, indicating an interaction of tDCS and the serotonergic system as well as proposing an enhanced therapeutic effect when combining anodal stimulation with Citalopram (Nitsche et al., 2009).

Further neurophysiological systems have been reported to play a role in pain reduction following tDCS, such as the glutamatergic, GABAergic, dopaminergic, and cholinergic systems (Medeiros et al., 2012; Tremblay et al., 2013; Stagg et al., 2009).

The interaction between the glutamatergic system and the GABAergic system following tDCS stimulation has been investigated intensively by Stagg et al. (2009). Glutamate and GABA are the two principal neurotransmitters mediating respectively excitatory and inhibitory signals in the CNS (Ciranna, 2006). Reductions of GABA levels result in increased glutamatergic activity (Stagg et al., 2009), thereby allowing for brain plasticity to occur (Sanacora et al., 2008; dos Santos et al., 2012). Evidence from magnetic resonance spectroscopy indicates that anodal tDCS reduces GABA and increases glutamatergic neuronal activity (Stagg et al., 2009), explaining the excitatory effects of anodal stimulation. Pharmacological studies using NMDA receptor (glutamatergic) blocking medication, such as ketamine, confirm this effect of tDCS on the glutamatergic system (Nitsche et al., 2003a).

Top-down pain control ist therefore hypothesised to rely on the excitation of the pain inhibitory network through various pathways including the immediate activation of local and distant brain areas associated with pain inhibition as well as the involvement of various neurotransmitter systems that might explain the reported long-term effects of tDCS. Further details on neurophysiological working mechanisms are provided in the Discussion chapter (Section 8.8).

1.3.2 tDCS parameters (duration and frequency)

The duration and frequency of tDCS applications influence the duration of observed neurophysiological changes. Nitsche and Paulus (2001) demonstrated that 5-7 minutes stimulation of 1 mA anodal tDCS changed MEP amplitudes for up to 5 minutes. When stimulation was continued for 13 minutes, amplitude changes were maintained for up to 90 minutes with stable effects during that period of time. Effects gradually reduced, returning to baseline after 150 minutes (Nitsche and Paulus,

2001). Monte-Silva et al. (2010) postulated that repeating the stimulation could prolong M1 excitability changes. The longest effects were observed when the second stimulation was applied while excitability changes from previous stimulations were still ongoing (Monte-Silva et al., 2010). In a rat model, a lasting effect of tDCS on chronic inflammation was demonstrated for ≥24 hours after an 8-day period of stimulation (Laste et al., 2012). Trials that applied tDCS to patients with chronic pain reported that significant pain reducing effects (compared to sham stimulation) occurred after 2-3 days of daily stimulation (Antal et al., 2010; Fregni et al., 2006b) and were maintained for ≥3 weeks post stimulation (Fregni et al., 2006a, 2006b). Stimulation parameters used in trials evaluating chronic pain were commonly 20 minutes of stimulation on 5 consecutive days. However, trials investigating the clinical use of tDCS for the reduction of pain employed small sample sizes (maximum of 11 patients per group) (Fregni et al., 2006a, 2006b) and mixed parallel group and crossover-design within 1 trial (Antal et al., 2010). These trials were described as exploratory (Antal et al., 2010) or proof of principle (Fregni et al., 2006b) and their pain reducing results can be regarded as propositions for future research, but effectiveness remains to be evaluated in large scale, methodologically sound, randomised controlled trials. Furthermore, the most effective stimulation parameters remain to be investigated.

1.3.3 tDCS combined with other treatment modalities

Recent research suggests that the pain reducing effect of traditional interventions was enhanced by applying tDCS as an adjuvant intervention. For example, when used as a priming technique to an rTMS protocol, tDCS modulated pain thresholds in healthy volunteers (Moloney and Witney, 2013). The combination of tDCS and TENS resulted in a pain reducing effect in patients with chronic pain that was significantly larger than the effect of each intervention alone (Boggio et al., 2009a), and tDCS applied in combination with a multidisciplinary programme improved the perceived level of pain of patients with fibromyalgia (Riberto et al., 2011). As with the trials on tDCS alone, clinical trials showed methodological limitations such as small sample sizes and inappropriate study designs. For example, in a crossover trial, Boggio et al.

applied all conditions to participants (n=8) with only a 48-hour interval between interventions to wash out intervention effects. Since neurophysiological effects might have been ongoing (Section 1.3.2), this trial design could provide erroneous results (Boggio et al., 2009a). Riberto et al. used a sample size calculation based on the outcome measure VAS for pain but reported a secondary outcome measure (SF-36) as the main result (Riberto et al., 2011). Hence, the trial was not adequately powered to evaluate the effectiveness of tDCS as an adjuvant intervention for pain reduction.

Chapter Summary

This chapter introduced CNSLBP with its serious personal and socio-economic consequences. International guidelines recommended multimodal management. Based on the knowledge that pain processing within the central nervous system is altered in patients with CLBP, interventions that target pain processing might enhance the effect of multimodal management programmes. tDCS is a non-invasive option, with no known serious side effects. However, its effectiveness, as a single intervention or combined with multimodal management for the reduction of CNSLBP is unclear. Researchers used different stimulation parameters for different types of pain. To gain a comprehensive overview of the current available evidence, it was important to initially summarise all published reviews on tDCS for the reduction of pain.

2. CHAPTER

OVERVIEW OF PUBLISHED REVIEWS OF TDCS FOR THE REDUCTION OF PAIN

Chapter 1 introduced CNSLBP with its associated serious socio-economic consequences and significant impact on patients' quality of life. tDCS was introduced as an evolving intervention designed to target pain processing within the brain. The recent scientific interest in this intervention is illustrated by the number of publications in this field within a short period of time (16 entries in PubMed between 2006 and 2008). Germany hosted its third *International Conference on TMS and tDCS* in Goettingen in 2008 and a new scientific journal (*Brain Stimulation*, published by Elsevier) was launched in the same year. Hence, before planning new research in this area, it was important to critically appraise existing research to gain an overview of the current level of evidence and to identify gaps requiring further investigation. Consequently, a literature review was conducted to initially synthesise published reviews (and subsequently clinical trials) to evaluate the effectiveness of tDCS for the reduction of pain. This chapter describes the process followed to identify and critically appraise published reviews and discusses the findings of individual reviews as well as drawing overall conclusions from this evidence.

2.1 Introduction

At commencement of the research reported in this thesis (September 2009), tDCS for the reduction of pain was a rapidly evolving area of research. In September 2010, the Cochrane Collaboration published a systematic review and meta-analysis on different non-invasive brain stimulation techniques, including 6 trials on tDCS for the reduction of various types of chronic pain (O'Connell et al., 2010). No trial was included that evaluated the effectiveness of tDCS for CNSLBP. An initial scoping

search of the literature further identified non-systematic reviews that focussed on the neurophysiological impact of brain stimulation or its effectiveness for different clinical or experimental conditions. Reviews focussed on different aspects of the topic and reported different conclusions for similar research questions. Consequently, a comprehensive overview of the existing reviews was required to summarise key findings on a) the focus and content of existing reviews and b) the methodological quality of published reviews, to subsequently summarise the current evidence and evaluate the overall level of evidence for the effectiveness of tDCS for the reduction of pain. The objective of this overview of reviews was therefore to identify, critically appraise, and summarise existing reviews on tDCS for the reduction of pain.

2.2 Methods

The overview of reviews was prepared following the guidelines in Chapter 22 of the Cochrane Handbook on Overviews of Reviews (Becker and Oxman, 2008).

2.2.1 Eligibility criteria for review inclusion

- **Participants of trials included in reviews satisfied the following criteria:** Patients had a clinical pain condition or were healthy participants exposed to a type of experimental pain. Both clinical and experimental types of pain were included because a scoping search of the literature revealed that only a small number of trials on clinical pain conditions had been published on tDCS and no trials were available that focussed exclusively on tDCS for the reduction of LBP. Reviews identified in the scoping search typically focussed on both healthy participants and participants experiencing clinical pain (Nitsche et al., 2008; Rosen et al., 2009). Experimental pain research has the advantage of using standardised pain procedures and greater reproducibility (Cavallone et al., 2013). Results from experimental pain trials can inform trials on clinical pain and thereby contribute to the overall evidence on tDCS for pain reduction. A comprehensive overview of the current level of evidence on

tDCS for the reduction of pain therefore required the inclusion of all types of pain.

- **Interventions applied in trials included in reviews satisfied the following criteria:** tDCS was defined as an electrical stimulation using direct current, applied to the outside of the skull (Nitsche et al., 2008). Reviews were excluded if they focussed on TMS or other types of transcranial electrical stimulation that used pulsed or alternating currents.

- **Control groups in trials included in reviews satisfied the following criteria**: Included trials had to include a sham or placebo group. Hence, reviews that reported only case studies were excluded.

- **Outcome measures in trials included in reviews satisfied the following criteria**: The primary outcome of interest was pain intensity, measured on a VAS, a numerical rating scale (NRS), or using a pain evaluation questionnaire. Reviews were excluded if they primarily focussed on the neurophysiology of tDCS or on outcome measures other than pain.

- **Types of review:** An initial scoping search demonstrated that the majority of published reviews were narrative in nature. To gain a comprehensive overview of the topic, systematic and non-systematic reviews were included that focussed on effectiveness of brain stimulation for pain and included ≥1 trial on tDCS for the reduction of pain.

- **Language of publication of reviews:** Review articles had to be published in English or German language.

2.2.2 Search methods

The search for reviews evaluating the effectiveness of tDCS for the reduction of pain was conducted on 15th September 2010 to inform the design of a systematic review of clinical trials on tDCS for the reduction of pain (Chapter 3) and updated on 30th March 2012. Results reported in this chapter are based on the updated literature search. The search strategy included 3 search steps. Initially, a search was performed in databases specific to systematic reviews recommended by internationally respected resources for the conduct of systematic reviews (Cochrane Handbook (Becker and Oxman, 2008); Centre for Reviews and Dissemination (Centre for Reviews and Dissemination, 2009)):

- Cochrane Database of Systematic Reviews
- Database of Abstracts of Reviews of Effects
- National Institute for Health and Clinical Excellence
- Health Technology Assessment
- Campbell Library of Systematic Reviews
- Scottish Intercollegiate Guidelines Network.

Search terms were ("tDCS" OR "brain stimulation") AND "pain". These broad terms were used since it was anticipated that only a small number of reviews would be identified. The second search was conducted in general health related databases:

- EMBASE 2006 to 2012 Mar 30
- Ovid MEDLINE(R) Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 2006 to present
- PsycArticles Full Text 2006 to present
- CAB Abstracts 2006 to 2012 Week 13
- PsycINFO 2006 to March Week 4 2012
- PubMed 2006 to present

The search terms included a combination of MeSH terms such as *pain* and *brain*, natural language terms such as *tDCS* and *non-invasive*, and phrases such as *"transcranial direct current stimulation".* The searches were limited to review articles published later than 01.01.2006 since the first 2 trials on tDCS for pain reduction were published in 2006. The search history for Ovid is reported in Appendix 2.1.

Additionally reference lists of included articles were screened and hand searches conducted of the contents of pain and neurophysiology related journals (BMC Neuroscience, Brain, Brain Stimulation, Clinical Journal of Pain, Clinical Neurophysiology, Clinical Neuroscience Research, European Journal of Neurology, European Journal of Pain, International Journal of Neuroscience, Journal of Clinical Neurophysiology, Journal of Clinical Neuroscience, Journal of Neuroscience, Journal of Pain and Symptom Management, Neurophysiology, Neuroscience, Pain, Pain Medicine, The Journal of Pain), as well as the publication list of a tDCS related website (Transcranial Technologies, 2012).

The titles and abstracts of all reviews identified in the 3 search steps were screened using the pre-defined eligibility criteria (Section 2.2.1). Subsequently, the full text of articles meeting the eligibility criteria at the title / abstract stage were retrieved and evaluated.

2.2.3 Assessment of methodological quality

All eligible reviews were analysed using the critical appraisal tool for the assessment of the methodological quality of systematic reviews (AMSTAR, Appendix 2.2) (Shea et al., 2007b) as recommended by Smith et al. (Smith et al., 2011) and referenced in the Cochrane Handbook (Becker and Oxman, 2008). The tool comprises 11 items and has good face and content validity (Shea et al., 2007b), external validity (Shea et al., 2007a) and reliability (Shea et al., 2009) for measuring the methodological quality of systematic reviews. Each item offers the options "yes", "no", "cannot answer" or "not applicable", with a higher number of "yes" scores indicating higher

methodological quality. The methodological quality of individual trials included in the reviews was not reviewed, but the AMSTAR tool does include an item that evaluates whether trial methodological quality was assessed as part of the review process.

2.2.4 Data extraction and management

Important information on characteristics and results of included reviews were extracted and entered into a data extraction table with pre-specified headings designed to focus on the research question and to provide information in a structured and clear format (Smith et al., 2011). This information included: author(s), year of publication, brain stimulation techniques reviewed, clinical conditions of patients or experimental pain paradigms applied in included trials, authors (year) of included trials and key results from the review.

2.2.5 Data analysis

It was anticipated after the scoping search, that only 1 meta-analysis on tDCS for the reduction of pain would be identified. Hence, a statistical synthesis of meta-analysis results was not anticipated to be possible. Data were synthesised in a narrative manner, stating the contents and the results from individual reviews, along with methodological quality.

2.3 Results

2.3.1 Database and hand search results

One review was identified in review specific databases (O'Connell et al., 2010). The search in health related databases identified 104 entries, and hand searching added 4 further reviews (Arul-Anandam et al., 2009; Brunoni et al., 2012; Lima and Fregni, 2008; Zaghi et al., 2009). Of these 108 entries, 82 were excluded according to the pre-defined inclusion criteria when title and abstract were screened. Full text screening excluded 7 further articles: one was the report on the included Cochrane review (O'Connell et al., 2011) and 6 articles did not review any clinical trials on the use of tDCS for the reduction of pain (Borckardt et al., 2009; Brunoni et al., 2012; Cruciani et al., 2009; Lefaucheur, 2008; Nitsche et al., 2008; May and Jurgens, 2010). Nineteen reviews were included. The selection process was illustrated as a flowchart adapted from the PRISMA statement (Liberati et al., 2009) (Figure 2.1). Lists of included and excluded reviews are provided in Appendix 2.3.

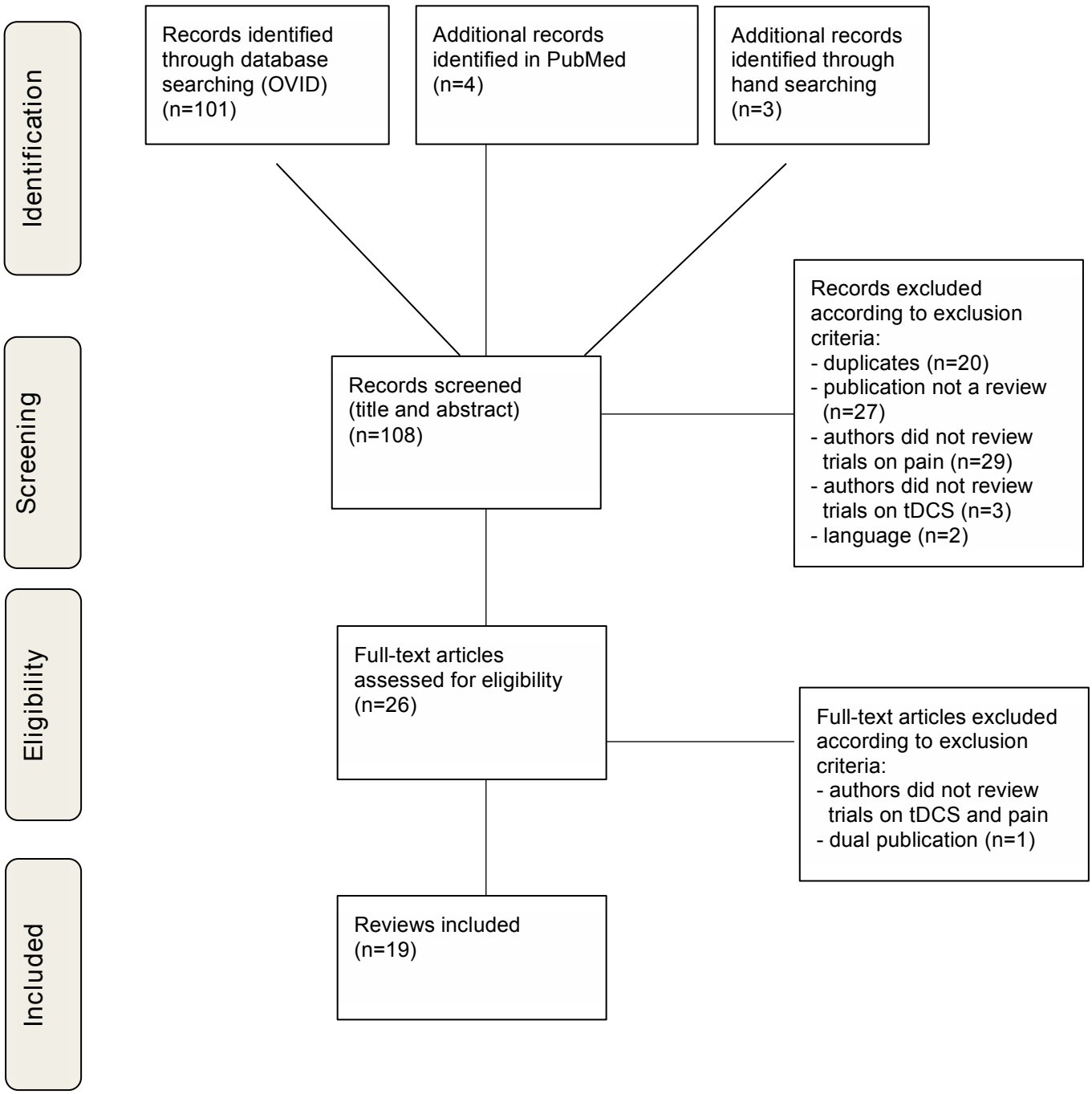


Figure 2.1 Flowchart for review selection process (Moher et al., 2009)

2.3.2 Methodological quality of included reviews

Only the Cochrane review scored "yes" on all 11 items of the AMSTAR tool (O'Connell et al., 2010) (Table 2.1) and was therefore regarded as of high methodological quality. Two further reviews reached 7 and 5 "yes" scores (Lima and Fregni, 2008; Zaghi et al., 2011). The remaining reviews ranged between 0-2 items scored as "yes". The 3 highest ranking publications were the only reviews with a systematic approach following a clearly stated research question and providing details for a comprehensive literature search as well as the characteristics of the included studies (Lima and Fregni, 2008; O'Connell et al., 2010; Zaghi et al., 2011). All other reviews adopted a non-systematic narrative style, with no a priori statement of design, a non-systematic (or not reported) literature search, no duplicate study selection / data extraction, not including a list of included and excluded trials, not using the publication status as an inclusion criteria, not assessing the likelihood of publication bias, and no assessment of the methodological quality of included trials (Table 2.1). The inclusion of these elements is strongly recommended by guidelines for the reporting of systematic reviews (Centre for Reviews and Dissemination, 2009; Green et al., 2008; Liberati et al., 2009) since only reviews of high methodological quality can provide reliable conclusions on the current level of evidence for tDCS for pain reduction (Shea et al., 2009).

Table 2.1 Quality of included reviews

Author; Year	1	2	3	4	5	6	7	8	9	10	11	No of Yes
Antal & Paulus 2007	No	No	No	No	No	No	No	No	N/A	No	No	0
Antal & Paulus 2010	No	No	No	No	No	No	No	No	N/A	No	Yes	1
Arul-Anandam et al. 2009	No	No	No	No	No	No	No	No	N/A	No	No	0
Been et al. 2007	No	No	No	No	No	No	No	No	N/A	No	No	0

Table 2.1 continued

Fregni et al. 2007	No	No	Yes	No	No	Yes	No	No	N/A	No	No	2
Fregni & Pascual-Leone 2007	No	No	Yes	No	No	Yes, online	No	No	N/A	No	Yes, online	2(4)
Jensen 2008	No	No	No	No	No	No	No	No	N/A	No	No	0
Jensen 2009	No	No	No	No	No	Yes	No	No	No	No	No	1
Knotkova & Cruciani 2010	No	No	No	No	No	No	No	No	No	No	No	0
Lefaucheur 2008	No	No	No	No	No	No	No	No	No	No	No	0
Lefaucheur 2009	No	No	No	No	No	No	No	No	No	No	No	0
Lima & Fregni 2008	No	No	Yes	Yes	Yes	Yes	No	No	Yes	Yes	No	7
Nitsche & Paulus 2011	No	No	No	No	No	Yes	No	No	N/A	No	No	1
O'Connell et al. 2010	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	11
Rosen et al. 2009	No	No	No	No	No	No	No	No	No	No	No	0
Short et al. 2009	No	No	No	No	No	No	No	No	No	No	Yes	1
Williams et al. 2009	No	No	No	No	No	No	No	No	No	No	Yes	1
Zaghi et al. 2009	No	No	No	No	No	No	No	No	Yes	No	No	2
Zaghi et al. 2011	No	No	Yes	Yes	No	Yes	No	No	Yes	Yes	No	5

Footnotes: **1**=Was an 'a priori' design provided?; **2**=Was there duplicate study selection and data extraction?; **3**=Was a comprehensive literature search performed?; **4**=Was the status of publication (i.e. grey literature) used as an inclusion criterion?; **5**=Was a list of studies (included and excluded) provided?; **6**=Were the characteristics of the included studies provided?; **7**=Was the scientific quality of the included studies assessed and documented?; **8**=Was the scientific quality of the included studies used appropriately in formulating conclusions?; **9**=Were the methods used to combine the findings of studies appropriate?; **10**=Was the likelihood of publication bias assessed?; **11**=Was the conflict of interest stated?; **N/A**=not applicable.

2.3.3 Analysis of the characteristics of included reviews

Of the 19 included reviews, 2 were published in German and 17 in English. Four were published in 2007, 3 in 2008, 7 in 2009, 3 in 2010, and 2 in 2011, indicating an ongoing scientific interest in tDCS as a treatment option for pain reduction. Three reviews focused on tDCS alone (Arul-Anandam et al., 2009; Knotkova and Cruciani, 2010; Nitsche and Paulus, 2011), while most reviews included other invasive or non-invasive brain stimulation techniques (Table 2.2). Six reviews included trials on chronic pain as well as experimental pain (Antal and Paulus, 2007, 2010; Been et al., 2007; Lefaucheur, 2009; Nitsche and Paulus, 2011; Rosen et al., 2009). Some reviews evaluated the effect of tDCS on pain as well as other clinical conditions such as Parkinson's disease (Been et al., 2007; Williams et al., 2009), stroke (Arul-Anandam et al., 2009; Been et al., 2007; Jensen et al., 2008; Williams et al., 2009), depression (Arul-Anandam et al., 2009; Been et al., 2007), and tinnitus (Jensen et al., 2008), or focussed exclusively on specific chronic pain conditions such as neuropathic pain (Knotkova and Cruciani, 2010), central pain (Zaghi et al., 2009) or fibromyalgia (Short et al., 2009). Twelve reviews included only the same 2 trials (Fregni et al., 2006a, 2006b) on tDCS for the reduction of chronic clinical pain, both published in 2006 (Arul-Anandam et al., 2009; Antal and Paulus, 2010; Lefaucheur, 2009; Fregni et al., 2007; Fregni and Pascual-Leone, 2007; Jensen et al., 2008; Lima and Fregni, 2008; Williams et al., 2009; Short et al., 2009; Antal and Paulus, 2007; Been et al., 2007; Jensen et al., 2009). The Cochrane review included 6 trials (O'Connell et al., 2010) and an additional trial was identified by one of the 2 most current reviews (Nitsche and Paulus, 2011). The most current reviews (Nitsche and Paulus, 2011; Zaghi et al., 2011) included chronic pain trials published between 2006 and 2010 and experimental pain trials published between 2008 and 2010. The 3 reviews with the highest methodological quality also included trials up to 2010 (Lima and Fregni, 2008; O'Connell et al., 2010; Zaghi et al., 2011).

2.3.4 Analysis of the results of included reviews

The review of the highest methodological quality by O'Connell et al. (2010) was a systematic review and meta-analysis of randomised controlled and crossover trials on different non-invasive brain stimulation techniques including tDCS for the reduction of chronic clinical pain, conducted within the framework of the Cochrane Collaboration (O'Connell et al., 2010). The results demonstrated that the combined effect of trials on tDCS applied over M1 showed a small pain reduction compared to sham tDCS (standardised mean difference -0.59, 95% CI -1.10 to -0.08). The authors further concluded that there was significant heterogeneity of included trials and that the existing evidence was insufficient to draw valid conclusions regarding the effect of tDCS for the reduction of pain. Only 1 of the 5 trials included in the meta-analysis was assessed as low risk of bias. All other trials showed substantial methodological weaknesses due to unclear allocation concealment, unclear carry-over effects, potential for selective outcome-reporting and unclear strategies for the management of missing data. Hence, results from the systematic review were based on the limited evidence available at the time and conclusions might change depending on future research.

A second systematic review and meta-analysis by Lima et al. (2008) evaluated the effects of invasive (surgically implanted stimulators) and non-invasive (rTMS and tDCS) electrical stimulation methods that targeted M1 for the relief of chronic pain (Lima and Fregni, 2008). The results showed that both approaches (invasive and non-invasive) reduced pain but that invasive stimulation of M1 induced a larger pain reduction compared to non-invasive stimulation (rTMS and tDCS) (responder rate: 64% for invasive stimulation with 95% CI 58.7 to 69.2 and 40% for non-invasive stimulation with 95% CI, 33.9 to 46.0). The evaluation of tDCS studies only, showed an improved mean responder rate of 74% (95% CI, 52.1 to 90.7). However, this result was based on 2 tDCS trials, only (Fregni et al., 2006a, 2006b). The update of this review (Zaghi et al., 2011) included 3 further tDCS trials and resulted in a combined pooled effect size of -0.86 cm (95% CI -1.54 to -0.19 cm on a 0 to 10 cm VAS for pain for tDCS and rTMS. Clinically minimum relevant change

recommendations for pain in chronic pain populations range from 1.5 to 4 cm on a 0-10 cm VAS (Maughan and Lewis, 2010; Ostelo et al., 2008), hence pain reduction cannot be regarded as clinically meaningful. The remaining narrative reviews on chronic pain agreed that tDCS was an effective future method for the treatment of chronic clinical pain (Arul-Anandam et al., 2009; Fregni et al., 2007; Antal and Paulus, 2007, 2010; Lefaucheur, 2008, 2009; Short et al., 2009; Jensen et al., 2008; Fregni and Pascual-Leone, 2007; Been et al., 2007; Rosen et al., 2009; Williams et al., 2009; Knotkova and Cruciani, 2010; Nitsche and Paulus, 2011; Jensen et al., 2009).

Reviews that included trials on experimental pain concluded that cathodal tDCS reduced the perceived intensity of experimentally induced pain in healthy participants (Lefaucheur et al., 2008; Rosen et al., 2009) and altered neurophysiological measures for pain such as laser-evoked (Rosen et al., 2009; Antal and Paulus, 2007, 2010; Lefaucheur et al., 2008; Nitsche and Paulus, 2011) and somatosensory-evoked potentials (Been et al., 2007). Five reviews concluded that tDCS was a safe technique with few side effects (Antal and Paulus, 2007; Been et al., 2007; Knotkova and Cruciani, 2010; Lefaucheur, 2009; Nitsche and Paulus, 2011). Further advantages identified for tDCS were that it is inexpensive (Arul-Anandam et al., 2009; Jensen et al., 2008; Knotkova and Cruciani, 2010; Zaghi et al., 2009), easy to apply (Jensen et al., 2008), mobile (Arul-Anandam et al., 2009; Knotkova and Cruciani, 2010) and had a reliable placebo condition (Antal et al., 2010; Jensen et al., 2008) supporting it as a future pain management and research tool.

Table 2.2 Contents and characteristics of included reviews

Author / year	Stimulation techniques	Clinical conditions	Experi-mental pain	tDCS+pain trials included	Key results on tDCS and pain
Antal & Paulus 2007	tDCS rTMS	chronic pain, migraine	LEPs	(Fregni et al., 2006a; Csifcsak et al., 2006)	- tDCS potential future therapy - no safety risks
Antal & Paulus 2010	rTMS tDCS	chronic pain	LEPs	(Antal et al., 2008; Fregni et al., 2006a; Fregni et al., 2006b; Terney et al., 2008)	- tDCS seemed capable to reduce chronic pain and experimental pain perception - reliable placebo condition for tDCS at 1 mA
Arul-Anandam et al.2009	tDCS	chronic pain, depression, stroke	none	(Fregni et al., 2006a; Fregni et al., 2006b)	- tDCS inexpensive, mobile, may have long-lasting effects - tDCS may emerge as a therapeutic modality, particularly for major depressive disorders - evidence base small, more studies needed
Been et al. 2007	tDCS CVS	stroke, chronic pain, Parkinson's disease, depression, migraine	SEPs	(Fregni et al., 2006a; Fregni et al., 2006b;)	- tDCS safe method - tDCS implied neurophysiological effects on M1 and S1 - tDCS reduced chronic pain
Fregni et al. 2007	rTMS tDCS	chronic pain	none	(Fregni et al., 2006a)	- reviewed one trial on tDCS and introduced tDCS as a new method for the treatment of chronic pain
Fregni & Pascual-Leone 2007	rTMS tDCS	chronic pain	none	(Fregni et al., 2006a)	-tDCS reduced pain in one clinical trial -indicated therapeutic potential
Jensen 2008	rTMS tDCS	chronic pain, stroke, tinnitus	none	(Fregni et al., 2006a; Fregni et al., 2006b)	-tDCS altered cortical activity -tDCS reduced chronic pain

Table 2.2 - continued 1

Jensen 2009	DBS, MCS rTMS, tDCS	chronic pain	none	(Fregni et al., 2006a; Fregni et al., 2006b)	- tDCS held promise for treating chronic refractory spinal cord injury pain - advantages: not invasive, easy to apply, inexpensive, reliable placebo condition, modulatory effects may be stronger than rTMS
Knotkova & Cruciani 2010	tDCS	neuropathic pain	none	(Fregni et al., 2006a; Fregni et al., 2006b; Fenton et al., 2009; Roizenblatt et al., 2007)	- analgesic effect of tDCS on neuropathic pain - evidence justified clinical use - easy to apply, portable, not expensive, safe
Lefaucheur 2008	rTMS tDCS	chronic pain	LEPs	(Antal et al., 2008; Boggio et al., 2008; Csifcsak et al., 2006; Fregni et al., 2006a; Fregni et al., 2006b; Silva et al., 2007; Terney et al., 2008)	-tDCS altered LEP response -tDCS reduced experimental pain perception -experimental pain reduction was increased by additional medication -tDCS reduced chronic pain, but experience limited to 2 studies
Lefaucheur 2009	rTMS,TECS tDCS, ECS	chronic pain	none	(Fregni et al., 2006a)	-explained neurophysiological mechanisms of action -tDCS was safe within published safety limits
Lima& Fregni 2008	MCS rTMS tDCS	chronic pain	none	(Fregni et al., 2006a; Fregni et al., 2006b)	-meta-analysis shows good responder rates for invasive and non-invasive techniques -weighted responder rate was 45.3% (95% CI, 39.2–51.4) for tDCS+rTMS
Nitsche& Paulus 2011	tDCS	chronic pain	LEPs	(Antal et al., 2010; Mori et al., 2010; Fenton et al., 2009; Boggio et al., 2009a; Bachmann et al., 2010; Csifcsak et al., 2009; Fregni et al., 2006a; Fregni et al., 2006b)	- further research should focus on stimulation protocols - tDCS is safe technique

Table 2.2 - continued 2

O'Connell et al. 2010	rTMS tDCS CES	chronic pain	none	(Fregni et al., 2006a; Fregni et al., 2006b; Boggio et al., 2009; Fenton et al., 2009; Mori et al., 2009; Valle et al., 2009)	-meta-analysis of trials of active stimulation over M1 superior to sham stimulation (SMD -0.59, 95% CI -1.10 to -0.08) -heterogeneity does not allow an estimation of the effect size -no firm conclusions regarding effectiveness for pain reduction
Rosen et al. 2009	rTMS tDCS	chronic pain	LEPs	(Antal et al., 2008; Fregni et al., 2006a; Fregni et al., 2006b; Roizenblatt et al., 2007; Terney et al., 2008)	-tDCS altered LEP response -tDCS reduced chronic clinical pain -tDCS reduced experimentally induced pain
Short et al. 2009	rTMS tDCS ECT	fibromyalgia	none	(Fregni et al., 2006b; Roizenblatt et al., 2007)	-tDCS may be effective to reduce fibromyalgia pain - further research needed - combination of different stimulation techniques as a future option
Williams et al. 2009	rTMS tDCS	chronic pain, stroke Parkinson's disease	none	(Fregni et al., 2006a; Fregni et al., 2006b)	-tDCS reduced pain in 2 clinical trials
Zaghi et al. 2009	MCS, rTMS tDCS	central pain	none	(Fregni et al., 2006a; Fregni et al., 2006b; Cecilio et al., 2008)	-all treatment modalities appeared to induce clinical gains -tDCS most cost-effective
Zaghi et al. 2011	rTMS tDCS	chronic pain	none	(Fregni et al., 2006a; Fregni et al., 2006b; Boggio et al., 2009; Fenton et al., 2009; Mori et al., 2009)	-update of the SR and meta-analysis by Lima & Fregni 2008, -combined pooled effect for rTMS and tDCS -0.86 (95%CI -1.54,-0.19) - yearly cost of tDCS approx $11,740

Footnotes: CES= cranial electrotherapy stimulation; ECS=epidural cortical stimulation; ECT= electroconvulsive therapy; LEPs=laser evoked potentials; M1=primary motor cortex; MCS=motor cortex stimulation; rTMS=repetitive transcranial magnetic stimulation; SEP=somatosensory-evoked potential; SR=systematic review; SMD=standard mean difference; TECS=transcranial electrical stimulation using pulsed currents; tDCS=transcranial direct current stimulation

2.4 Discussion

Nineteen reviews were included in this overview of reviews. Three of these used a systematic approach (Lima and Fregni, 2008; Zaghi et al., 2011; O'Connell et al., 2010), but only 1 was assessed as high methodological quality (O'Connell et al., 2010). However, the results of Connell et al. (2010) were based on 6 clinical trials, only, and did not include trials on experimental pain although results from experimental pain research might provide valuable information about the effectiveness of tDCS in a more standardised setting. The cut-off date for the literature search of the Cochrane review was between November 2009 (for MEDLINE) and January 2010 (for CINAHL). As tDCS is a new technique for the reduction of pain with high scientific interest, new trials might have been published since these cut-off dates that might change the results from the meta-analysis.

The results of the 2 further systematic reviews were based on the same trials as the Cochrane review but the authors had not conducted an assessment of the methodological quality of the included trials (Lima and Fregni, 2008; Zaghi et al., 2011). Both reviews reported a meta-analysis but Lima & Fregni only included 2 trials (Zaghi et al., 2011; Lima and Fregni, 2008) and Zaghi et al. (2011) stated the effect size for a combination of rTMS trials with tDCS trials and provided no information on the effect of tDCS alone (Lima and Fregni, 2008). A combination of the results of the 3 meta-analyses was therefore not feasible. All other reviews were of narrative nature and scored low in the methodological quality assessment. These narrative reviews contributed 1 RCT additional to those included in the systematic reviews (Zaghi et al., 2011) and 2 case studies on chronic clinical pain (Antal et al., 2010). The RCT was published after the cut-off date of the Cochrane review and had not been formally evaluated for risk of bias. All authors concluded that tDCS was a promising future treatment approach for the reduction of chronic pain and underlined the advantages of tDCS such as its low cost, portability and safety as well as the option for a reliable placebo condition for research purposes.

Six reviews included a total of 4 trials on experimentally induced pain or pain-representing neurophysiological measurements and concluded that tDCS was effective in the reduction of experimental pain as well as in altering the responses to laser-evoked and somatosensory-evoked potentials (Antal and Paulus, 2007, 2010; Been et al., 2007; Lefaucheur et al., 2008; Nitsche and Paulus, 2011; Rosen et al., 2009). Different stimulation sites and parameters affected different types of experimentally induced pain with M1 emerging as the most widely used target. However, none of the trials on experimental pain were assessed for risk of bias. Hence, the risk that reported effects over- or underestimated the true effect has not been evaluated.

None of the included reviews had evaluated the overall level of current evidence by, for example, using GRADE (Grading of Recommendations Assessment, Development and Evaluation (Schunemann et al., 2008). Despite the agreement on the potential efficacy and safety of tDCS, the available evidence from systematic and non-systematic reviews was therefore insufficient to recommend tDCS as a tool for the reduction of chronic pain or experimentally induced pain. Only 1 available review had conducted a risk of bias assessment of the included trials that indicated methodological shortcomings in all but 1 of the included trials. The authors considered this risk of bias and the heterogeneity of included trials as so severe that they did not recommend the use of tDCS for the reduction of chronic pain despite the pain reducing effect of tDCS over M1 found from their meta-analysis (O'Connell et al., 2010).

Narrative reviews indicated ongoing scientific interest in the topic with 1 further RCT published after the cut-off date of the Cochrane review. This RCT, as well as all trials on experimental pain, still require formal assessment of methodological quality. Trials included in the Cochrane review focussed on patients experiencing pain due to fibromyalgia, spinal cord injury, chronic pelvic pain, and multiple sclerosis. Two case studies included in the narrative reviews stated an effect on cancer pain and on vulvodynia. Trials on experimental pain included pain paradigms induced by laser-evoked potentials and somatosensory-evoked potentials. It remained unclear

whether tDCS had been applied to other clinical conditions or different pain paradigms in the meantime. The reviews further showed that different stimulation locations, durations and intensities had been used in published trials, but they did not recommend any stimulation paradigm that was used most frequently or had been shown to be most effective. It remained unclear whether different types of chronic pain required different stimulation paradigms and whether experimental pain responded to the same stimulation paradigms as chronic pain.

This overview of reviews had 2 limitations. For time and resource reasons, only 1 researcher had conducted the search, quality assessment, and data extraction. This potential risk of bias was addressed by the *à priori* definition of a standardised procedure, with clear inclusion / exclusion criteria and a pre-designed data extraction process following international guidelines (Becker and Oxman, 2008; Centre for Reviews and Dissemination, 2009). The second limitation was the exclusion of reviews published in a language other than German or English. Two reviews were identified from the literature search with an English abstract but a French full text. Both focussed on invasive MCS only and were published by the research group of Lefaucheur et al. (Lefaucheur et al., 2009; Nguyen et al., 2009).

This overview of reviews therefore strongly supports the need for a high quality and up-to-date systematic review, that focuses on the effectiveness of tDCS for the reduction of pain, includes all currently available publications on different types of clinical and experimental pain, evaluates the methodological quality or risk of bias of included trials, evaluates the stimulation paradigm that is most effective, and uses GRADE to evaluate the overall level of evidence.

Chapter summary:

A comprehensive search and evaluation of published reviews on the effectiveness of tDCS for the reduction of pain was conducted. Assessment of the methodological quality of 19 included reviews indicated that a systematic review and meta-analysis conducted by the Cochrane Collaboration showed the highest methodological quality and 2 further reviews met the requirements of a systematic review. Results from the Cochrane review indicated a small effect for tDCS on clinical pain reduction but did not include trials on experimental pain. Experimental pain trials were included in 6 reviews but trials were not evaluated for methodological quality. Reviews did not report the most effective or most frequently used stimulation paradigm. Reported advantages of tDCS over other brain stimulation techniques included low cost, safety, portability, and a reliable placebo condition for research purposes.

3. CHAPTER

TRANSCRANIAL DIRECT CURRENT STIMULATION FOR THE REDUCTION OF CLINICAL AND EXPERIMENTALLY INDUCED PAIN - A SYSTEMATIC REVIEW AND META-ANALYSIS

Chapter 2 provided an overview of existing reviews on the use of tDCS for the reduction of pain. Critical appraisal of the reviews identified 3 reviews that had used a systematic approach and only 1 that had conducted a risk of bias assessment of included trials. None of the reviews had evaluated the overall level of evidence. The 3 systematic reviews included only a small number of trials, and trials on experimental pain were not formally assessed for methodological quality. Furthermore, the included reviews had not provided information on the most frequently used or most effective tDCS paradigm for the reduction of pain to inform the design of a clinical trial. The overview of reviews therefore identified a need to conduct an up-to-date systematic review of the literature on tDCS for the reduction of pain, including clinical and experimentally induced pain, to inform the design and protocol for a randomised controlled trial. Hence, a systematic review was conducted. This chapter describes the process of the systematic review and discusses the findings regarding tDCS for the reduction of clinical pain and experimentally induced pain.

3.1 Introduction

The overview of published reviews on tDCS for the reduction of pain demonstrated that the first clinical trials were conducted in 2006. Twenty-six review articles (of which 19 were included in the overview of reviews) were published between 2006 and 2012 (Section 2.3.1). This comparably large number of reviews, based on 4 trials evaluating experimental pain and 7 trials evaluating clinical pain, illustrated the scientific interest in the topic. Reviews focused on the neurophysiological pain reducing mechanisms of tDCS, on tDCS amongst other stimulation techniques such as surgically implanted stimulators, or repetitive magnetic stimulation (rTMS). None of the reviews exclusively evaluated the effectiveness of tDCS for the reduction of pain (Section 2.3.4).

Three of the included review articles used a systematic approach, but only 1 was assessed as high methodological quality (O'Connell et al., 2010). It focused on various non-invasive brain stimulation techniques and included 6 trials on tDCS for the reduction of clinical pain published prior to 11th of January 2010. The authors conducted a meta-analysis on the results of 5 trials on tDCS over M1 for the short-term (immediately post intervention) reduction of clinical pain resulting in a small combined standardised mean effect of -0.59 (95% CI -1.10,-0.08) on a 0-10 cm VAS for pain (compared to sham stimulation). Despite the thorough methodological approach, the systematic review had some shortcomings:

- Evaluation of the level of evidence according to the GRADE approach (Guyatt et al., 2008) as recommended by the Cochrane Handbook (Schünemann et al., 2008), was not conducted. Consequently the overall level of evidence from the systematic review remained unclear.

- Trials using tDCS for the reduction of experimental pain were excluded. Experimental pain plays an important role in the understanding of pain and for the development of pain reducing interventions (Petersen-Felix and

Arendt-Nielsen, 2002). It has some advantages over clinical pain for research purposes as it can be standardised regarding its duration, intensity, frequency, and location, and applied to healthy volunteers who are less susceptible to confounding factors (Cavallone et al., 2013; Petersen-Felix and Arendt-Nielsen, 2002). Hence, it was important to evaluate whether tDCS had a pain reducing effect on experimental pain and whether this could be achieved using the same stimulation parameters as trials on chronic pain to inform future research on tDCS.

- The cut-off date for the literature search was January 2010.

In summary, the evaluation of evidence from published reviews was not up-to-date, the methodological quality of the majority of reviews was low, and there was insufficient evidence to either support the effectiveness of tDCS for the reduction of clinical pain, or to indicate whether tDCS reduced experimentally induced pain in a research setting. Additionally, it remained unclear whether any specific stimulation approach regarding mode of stimulation (anodal / cathodal), site of stimulation (e.g. M1, S1), duration, intensity or frequency of stimulation was most effective for either type of pain.

Hence, the objective of this review was to provide up-to-date evidence on the effectiveness of tDCS on both clinical and experimentally induced pain, based on sound methodology. A secondary objective was to identify the most effective stimulation parameters regarding stimulation site, mode, intensity, duration and frequency for the reduction of both types of pain. Addressing both objectives will inform the design of a clinical trial on tDCS for the reduction of CNSLBP.

3.2 Methods

A protocol was developed prior to conducting the review to minimise the potential for introducing bias (Appendix 3.2). Structure and contents of the protocol were adapted from Chapter 4 of the Cochrane Handbook for Systematic Reviews of Interventions (Higgins and Green, 2008), the handbook "Systematic Reviews" published by York University (Centre for Reviews and Dissemination, 2009), and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement (Liberati et al., 2009) as internationally recognised guidelines for the conduct and reporting of systematic reviews. The systematic review and meta-analysis adhered to the protocol throughout, and no amendments were required.

3.2.1 Eligibility criteria for trial inclusion

- **Types of articles:**

  The review included RCTs, controlled trials, and other designs such as crossover trials, defined as trials that allocate participants to a sequence of interventions in a randomised order (Higgins and Deeks, 2008). These other designs were included because, from the existing reviews, it was not anticipated that many RCTs would be available and the systematic review was designed to provide a comprehensive overview of existing trials on tDCS for pain reduction. Non-controlled trials and case studies were excluded. No language or publication status restrictions were imposed.

- **Types of participants:**

  Trial participants were adults (≥18 years), since there were no publications on the neurophysiological effect of tDCS on the juvenile brain. Trials included participants with clinical pain or healthy participants, who were experimentally exposed to a pain paradigm. Trials on patients with primary symptoms other than pain, such as depression, stroke, or Parkinson's disease were excluded.

Animal trials were not included because the transferability of brain stimulation results to humans is not fully understood (Brunoni et al., 2011b).

- **Types of interventions:**

  tDCS defined as an electrical stimulation applied to the outside of the skull using direct currents (Nitsche et al., 2008). Furthermore, identified reviews used terms such as "motor cortex stimulation" and specified them later as non-invasive and electrical (Lima and Fregni, 2008), or mentioned "non-invasive brain stimulation" to subsequently distinguish between magnetic and electrical techniques (Rosen et al., 2009; Williams et al., 2009). These terms were therefore included in the search strategy. Trials on invasive brain stimulation methods, on magnetic stimulation (e.g. rTMS) and on electrical stimulation that used pulsed or alternating currents were excluded.

- **Types of comparisons:**

  Acceptable comparator interventions were sham-stimulation (placebo) or a control group, so that conclusions could be drawn about the effectiveness of tDCS.

- **Types of outcome measures:**

  The outcome of interest was pain severity immediately post intervention as a primary or secondary outcome measure. The time-point immediately post intervention was chosen to allow comparability with the results of the overview of reviews. The type of pain measurement tool was not pre-determined (e.g. VAS for pain, NRS for pain). If a self-report tool (e.g. questionnaire) was used, pain had to be a main focus of the questionnaire to enable comparison with the results of other trials (e.g. Roland-Morris Disability Questionnaire (Roland and Morris, 1983) or Oswestry Disability Questionnaire (Fairbank et al., 1980), Brief Pain Inventory (Serlin, 1995), McGill Pain Questionnaire (Melzack, 1975)).

3.2.2 Search methods

3.2.2.1 Information Sources

Two researchers independently conducted a systematic search of electronic databases relevant for the medical and allied health professions literature. The cut-off date for the literature search was 30th Sept 2010. OVID was used to search the databases: MEDLINE, EMBASE, CAB Abstracts (Centre for Agricultural Bioscience International), and PsychINFO. Searches were performed in the Cochrane Register of Controlled Trials (CENTRAL), CINAHL, and PeDRO.

To identify non-published trials and, thereby reduce publication bias, trials in progress were searched in the Clinical trial register of the U.S. National Institute of Health (www.clinicaltrials.gov), the Current Controlled Trials Register, U.K. (www.controlled-trials.com), the NHS National Research Register (https://portal.nihr.ac.uk/Pages/NRRArchive.aspx), the European Trial Register Eudract (https://eudract.emea.europa.eu), and key authors were contacted by email.

Conference proceedings of relevant events known to the researchers and detailed on the ZETOC website (http://zetoc.mimas.ac.uk) were screened. Reference lists of previously identified reviews and of the newly acquired trial publications were hand searched. The contents of all journals in which identified trials were published (Arthritis and Rheumatism, Brain Stimulation, Clinical Journal of Pain, European Journal of Neurology, Journal of Pain and Symptom Management, Neuropsychologia, Pain, Pain Medicine, The Journal of Pain) as well as key journals for neurophysiology and neuroscience (BMC Neuroscience, Brain, Clinical Neurophysiology, Clinical Neuroscience Research, International Journal of Neuroscience, Journal of Clinical Neurophysiology, Journal of Clinical Neuroscience, Journal of Neuroscience, Neurophysiology, Neuroscience) were searched.

3.2.2.2 Literature Search

Medical subject heading (MeSH) terms and natural language terms were combined in the search strategy. The search strategy included terms referring to the population studied, the intervention this review was focussed on, the control intervention and the outcome studied. The following search terms were combined:

Population:
adult AND (pain OR healthy)

Intervention:
(transcranial direct current stimulation OR tDCS OR electric(al) OR direct current) AND (brain OR motor cortex OR M1 OR somatosensory cortex OR S1 OR prefrontal cortex OR DLPFC) AND stimulation AND non-invasive

Comparison:
sham OR placebo OR control

Outcome:
pain OR numerical rating scale OR visual analogue scale

Search filter or limitations were set to "humans". The search was limited to the timeframe of 2006 to current (30th Sept 2010) (according to the existing reviews the first clinical trials on tDCS were published in 2006). An example for the search strategy in Medline (Ovid format) is shown in Table 3.1.

Table 3.1 Search history Medline (Ovid)

	Searches	Results	Search Type
1	(tDCS or direct current).mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, tx, ct, bt, nm, an, hn, ui, tc, id]	14666	Advanced
2	(brain or cortex or M1 or S1).mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, tx, ct, bt, nm, an, hn, ui, tc, id]	3344001	Advanced
3	stimulation.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, tx, ct, bt, nm, an, hn, ui, tc, id]	1619454	Advanced
4	(non-invasive or non invasive or noninvasive).mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, tx, ct, bt, nm, an, hn, ui, tc, id]	318937	Advanced
5	(sham or placebo or control).mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, tx, ct, bt, nm, an, hn, ui, tc, id]	6692365	Advanced
6	(pain or numerical rating scale or verbal rating scale or visual analogue scale or VAS or NRS).mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, tx, ct, bt, nm, an, hn, ui, tc, id]	1575621	Advanced
7	1 and 2 and 3 and 4 and 5 and 6	155	Advanced
8	limit 7 to humans [Limit not valid in HMIC,Journals@Ovid,CAB Abstracts, Your Journals@Ovid,PsycINFO; records were retained]	154	Advanced
9	(RCT or randomised or randomized).mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, tx, ct, bt, nm, an, hn, ui, tc, id]	1433110	Advanced
10	8 and 9	109	Advanced
11	remove duplicates from 10	79	Advanced

3.2.2.3 Study Selection

Articles identified in the search were selected independently by 2 reviewers (Higgins and Deeks, 2008) to minimise bias. Both reviewers had subject as well as methodological knowledge. In the first stage of study selection, the eligibility criteria (Section 3.2.1) were applied to the title and abstract of identified articles. In the second stage, the full text publications of potentially eligible articles were obtained and criteria reapplied.

Strength of inter-reviewer agreement regarding study eligibility was expressed using Cohen's Kappa coefficient, a statistical test that determines the statistical agreement of 2 raters on nominal / categorical data (Cohen, 1960). In the case of disagreement between the 2 reviewers that was not resolved by discussion, a third reviewer with expertise in systematic review methodology was approached. The third reviewer decided whether the article was included (Higgins and Deeks, 2008).

3.2.3 Data extraction and management

Data from included trials were collected by 2 independent reviewers and entered into a table with pre-specified headings (Higgins and Deeks, 2008) designed to meet the research objectives. The data extraction table comprised the following data items:

- Author, date and country of the trial study population
- Study population (healthy volunteers or pain patients, type of pain condition / experimental pain paradigm, number of participants, age range)
- Stimulation parameters (site of stimulation, duration, intensity, mode, frequency)
- Control paradigm used (placebo / sham / no intervention)
- Type of pain related outcome measures, mean effects, and statistical procedures
- Observed side effects.

To facilitate the combination of results in meta-analyses, it was required that pain measurements (means and standard deviations post intervention, change over time and standard errors, or confidence intervals for mean values or for change over time) were reported. Trial authors were contacted via email when important data were missing (Higgins and Deeks, 2008).

3.2.4 Assessment of risk of bias in included trials

Included trials were critically appraised for potential risk of bias by 2 independent researchers using the Cochrane risk of bias assessment tool (Higgins et al., 2008), as recommended by the PRISMA statement (Liberati et al., 2009). The risk of bias assessment was important for the evaluation of the internal validity of trial results and to estimate the overall level of evidence for tDCS for pain reduction (Higgins et al., 2008). The tool comprised the domains: Sequence generation, allocation concealment, blinding of participants, blinding of therapist, incomplete outcome data, selective outcome reporting, and other sources of bias. Each domain can be rated as high, low, or unclear risk of bias. When a domain was rated as "unclear" due to inadequate reporting, the trial authors were contacted via email and asked to clarify research procedures. Strength of inter-rater agreement was expressed using Cohen's Kappa coefficient (Cohen, 1960). In the case of continuing disagreement after discussion, a third researcher decided the risk of bias for the domain. Each risk of bias component was considered with regard to the key outcome measures (Higgins et al., 2008; Juni et al., 1999). If blinding of the therapist was impossible for technical reasons and therefore rated as of high risk of bias, but patient blinding was maintained, the trial was included in the meta-analysis. The domain "incomplete outcome data" was considered to induce a risk of bias if data were statistically analysed per-protocol and losses to follow-up were 20% or higher (Fewtrell et al., 2008), or if participant withdrawal patterns indicated the risk of a systematic bias.

To support the decision to include or exclude trials from the main meta-analysis, a summary risk of bias rating was conducted: Trials with a rating of “high risk of bias”

in one or more domains were assessed as of overall high risk of bias, trials with a rating of “unclear risk of bias” in one or more domains were assessed as of overall unclear risk of bias. The justification for inclusion or exclusion in the main meta-analysis was detailed in an additional column of the risk of bias table specifying high risk of bias and external validity issues.

3.2.5 Summary Measures

Summary measures were means and standard deviations post intervention, change over time and standard errors, or confidence intervals for mean values or for change over time for any type of pain intensity measurement, including NRS, VAS, verbal rating scales or questionnaires.

3.2.6 Synthesis of results

All trials were included in the descriptive analysis. Meta-analyses across trials that had comparable outcome measures and comparable interventions in terms of nature, stimulation sites, mode, and duration were conducted using a random effects model allowing for population and intervention parameters (e.g. type of clinical pain, stimulation paradigm to vary between trials (Schmidt et al., 2009). Studies with high risk of bias domains can lead to invalid conclusions (Higgins et al., 2008). Trials with a high risk of bias in a minimum of 1 domain were therefore excluded from the meta-analysis.

The software used for the meta-analyses was Review Manager Version 5.0. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2008. The meta-analyses were performed by entering the mean pain intensity and standard deviations post-intervention for the tDCS and the sham group into the Review Manager Software. Where standard deviations were not reported, they were estimated from reported confidence intervals (Higgins and Deeks, 2008). When numerical data were unavailable, data were extracted from published graphs.

3.2.7 Risk of bias across trials

Results from the risk of bias assessment across trials were summarised narratively. Heterogeneity defined as inconsistency across studies was explored by I^2. "I^2 describes the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance)" (Deeks, 2008, p.276).

3.2.8 Additional analyses (sensitivity analysis)

A second meta-analysis including all trials independent of the results from the risk of bias assessment was conducted to evaluate whether risk of bias judgements for individual trials would influence the combined effect of tDCS on pain (Deeks, 2008; Higgins et al., 2008).

3.2.9 Overall level of evidence

The overall level of evidence for tDCS for the reduction of pain was evaluated using GRADE (Schunemann et al., 2008). The GRADE approach is used to formulate an overall conclusion on the level of evidence based on the methodological quality of included trials (Schünemann et al., 2008). Evidence based on RCTs with a low risk of bias is regarded as high while evidence from observational studies is regarded as low (Guyatt et al., 2008). Following specific criteria (e.g. imprecision of results indicated by wide confidence intervals), the level of evidence from low risk of bias RCTS can be downgraded by 1 or 2 levels. Accordingly, the level of evidence from observational studies can be upgraded when specific criteria are fulfilled (Guyatt et al., 2008).

3.3 Results

3.3.1 Study Selection

A total of 88 studies were identified during the electronic and hand search process. After screening titles / abstracts, 15 studies were retrieved as full text articles (Figure 3.1). Full text screening excluded 1 study (Roizenblatt et al., 2007), because it investigated the same study population as Fregni et al. (Fregni et al., 2006b), resulting in a total number of 14 included trials. The inter-rater agreement of studies to be included in the systematic review during title / abstract and full text screening was kappa 0.946 ($p<0.0005$). Disagreement (following discussion) was on 1 article out of 88.

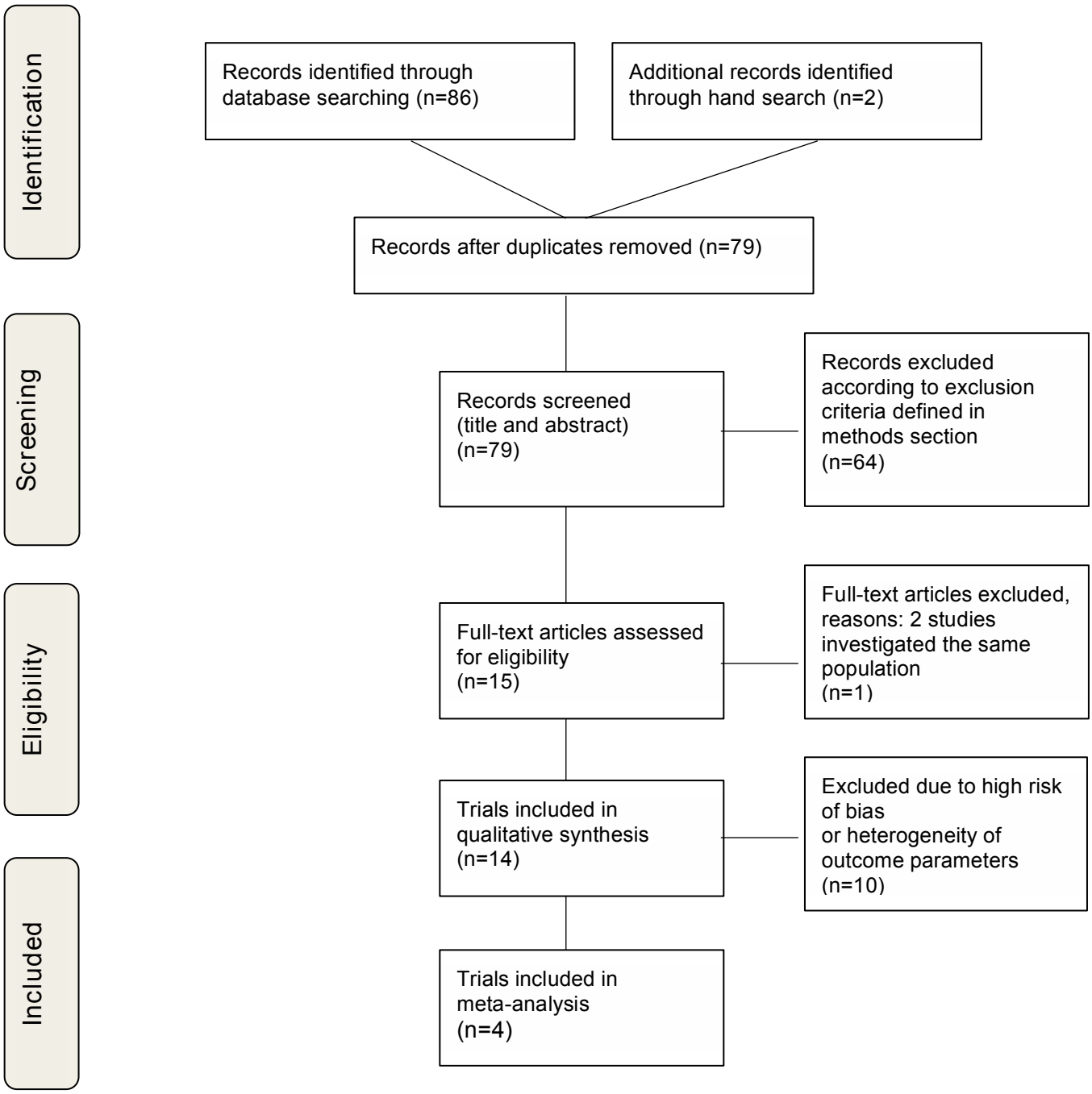


Figure 3.1 Flowchart for study selection process (Moher et al., 2009)

3.3.2 Risk of bias within studies

The risk of bias assessment resulted in a considerable number of "unclear" ratings. Most ratings of "unclear" were due to inadequate reporting (Table 3.2). Four authors were contacted to request clarification on details from 8 trials. Three authors responded and provided additional information and data. The risk of bias domains that most frequently received the ratings 'high' or 'unclear' referred to insufficiently described allocation concealment (all trials), unclear or invalid randomisation procedures (Antal et al., 2008, 2010; Bachmann et al., 2010; Csifcsak et al., 2009; Fenton et al., 2009; Terney et al., 2008; Valle et al., 2009) and not reporting missing data strategies (Antal et al., 2010; Boggio et al., 2009a, 2009b; Terney et al., 2008). Since only 1 trial had an accessible trial protocol (Fenton et al., 2009), selective outcome reporting for all other trials was rated as unclear. The key domain "other sources of bias" included methodological aspects such as differences between groups at baseline, parametrical statistical tests that were conducted on small sample sizes (Antal et al., 2010; Bachmann et al., 2010; Boggio et al., 2009a; Fenton et al., 2009; Valle et al., 2009) and further statistical issues (Antal et al., 2010). The inter-rater agreement for the risk of bias assessment was kappa 0.950 ($p<0.0005$). The third rater was approached to decide on 3 out of 98 conflicting evaluations that could not be resolved by discussion.

Table 3.2 Risk of bias assessment of included trials

		1	2	3 a	3 b	4	5	6	Sum-mary RoB	RoB and external validity justification for inclusion in main meta-analysis
Antal et al. 2008	1st reviewer 2nd reviewer	U U	U U	L L	U U	L L	U U	L L	U	No high risk component.
Antal et al. 2010	1st reviewer 2nd reviewer 3rd reviewer	H H	U U	L L	L L	U U	U U	H U H	H	High risk of bias: No adequate randomization procedure. Numbers in each group too small. Data from crossover and sham-controlled study groups entered into the same data analysis.
Bachmann et al. 2010	1st reviewer 2nd reviewer	H H	U U	L L	H H	U U	U U	H H	H	High risk of bias due to small sample size and invalid sequence generation (pseudo randomised).
Boggio et al. 2008	1st reviewer 2nd reviewer	L L	U U	L L	U U	H H	U U	U U	H	High risk due to 4 drop-outs (20%) not accounted for.
Boggio et al. 2009a	1st reviewer 2nd reviewer	L L	U U	L L	H H	L L	U U	U U	U	Only high risk component refers to therapist blinding.
Boggio et al. 2009b	1st reviewer 2nd reviewer	L L	U U	L L	H H	U U	U U	H H	H	Small sample size, preliminary study. Two drop-outs (25%), reasons (scheduling issues) provided.
Cfiszak et al. 2009	1st reviewer 2nd reviewer 3rd reviewer	U U	U U	L L	L L	L L	U U	U L H	H	No randomization procedures reported. Small sample size for NAS as outcome measure.
Fenton et al. 2009	1st reviewer 2nd reviewer	U U	U U	L L	L L	L L	H H	H H	H	Small sample size, pilot study. Randomization procedure unclear. Raw data spreadsheet indicates 2 drop-outs (22%) that were not reported (originally 9 patients participated in study). Protocol available, planned primary outcome "patient global assessment" not reported.
Fregni et al. 2006a	1st reviewer 2nd review 3rd reviewer	L L	U U	L L	U U	L U L	U U	U U	U	No high risk component. Allocation concealment clarified by author. Sample size calculation based on very large effect size.
Fregni et al. 2006b	1st reviewer 2nd reviewer	L L	U U	L L	H H	L L	U U	L L	U	Only high risk component refers to therapist blinding (not possible). Allocation concealment clarified by author. Baseline pain scores higher in treatment group but not statistically significant.

Table 3.2 - continued 1

Mori et al. 2009	1st reviewer	L	U	L	U	L	U	L	L	No high risk component. Allocation concealment clarified by author. Sample size calculation based on very large effect size.
	2nd reviewer	L	U	L	U	L	U	L		
Soler et al. 2010	1st reviewer	L	U	L	U	U	U	L	U	No high risk component.
	2nd reviewer	L	U	L	U	U	U	L		
Terney et al. 2008	1st reviewer	U	U	L	U	H	U	H	H	Questionable intervention effect for group tDCS+placebo (pain reduction at time-point A2 only)
	2nd reviewer	U	U	L	U	H	U	H		
Valle et al. 2009	1st reviewer	H	U	L	U	L	U	H	H	Inappropriate randomisation procedure and small sample size.
	2nd reviewer	H	U	L	U	L	U	H		

Footnotes: 1 Sequence generation; 2 Allocation concealment; 3a Blinding of participants; 3b Blinding of therapist; 4 Incomplete outcome data; 5 selective outcome reporting; 6 Other sources of bias. H= high risk of bias; U=unclear risk of bias; L= low risk of bias. Summary: high risk of bias = 1 or more of the key domains were rated as *high*; unclear =1 or more of the key domains were rated as *unclear*.

3.3.3 Data extraction

Methods: Of the 14 included trials, n=6 investigated the effect of tDCS on experimental pain and n=8 focused on clinical pain. The reported experimental pain paradigms were laser-evoked pain, mechanical and thermal pain, images of human pain and electrical pain stimuli.

Participants: Clinical pain syndromes included a variety of chronic conditions such as chronic pelvic pain, fibromyalgia, and neuropathic pain due to spinal cord injury or multiple sclerosis (total number of participants n=167). Experimental pain trials only included healthy participants (n=89).

Interventions: All trials investigating clinical pain employed anodal (positively charged electrode over the target area) stimulation over M1 (2 trials additionally applied tDCS to the DLPFC) with a duration of 20-30 minutes, and intervention repetitions from a single session to ten sessions on consecutive working days. Experimental pain trials varied greatly regarding the stimulation site and parameters. Two trials focused on anodal stimulation, 1 trial on cathodal stimulation and 3 trials applied both modes of stimulation. The M1 was stimulated in 5 of the trials, 2 of which also stimulated the visual cortex (V1) and the DLPFC. One trial investigated the stimulation of the S1 only. Duration of stimulation ranged from 5-15 minutes.

Outcomes: Outcome measures in all clinical pain trials included a NRS or VAS, while outcomes in all experimental pain trials were reported through numerical scales as well as pain thresholds and emotional discomfort (Tables 3.3 and 3.4).

Table 3.3 Characteristics of trials on experimental pain

Authors, date (country)	Type of pain	Number of partici-pants	Age (mean or range)	Stimulation mode	Control	Site	Intensity (mA)	Duration (min)	Side effects	Pain related outcome measures
Antal et al. 2008 (Germany, Hungary)	laser-evoked pain	10	18-30	anodal cathodal	sham	S1	1	15	not reported	NRS
Bachmann et al. 2010 (Germany)	thermal + mechanical pain threshold	8	25-41	anodal cathodal	sham	M1	1	15	not reported	heat pain threshold, cold pain threshold, mechanical pain Threshold, wind-up
Boggio et al. 2008 (USA, Brazil)	electrical stimulation	20	21	anodal	sham	M1 DLPFC V1	2	5	headache tingling	perception threshold, pain threshold
Boggio et al. 2009a (USA, Brazil)	images of human pain	23	21	anodal	sham	M1 DLPFC V1	2	5	headache dizziness tingling	emotional discomfort
Csifcsak et al. 2009 (Germany, Hungary, Denmark)	laser-evoked pain	16	20-30	anodal cathodal	sham	M1	1	10	not reported	NRS
Terney et al. 2008 (Germany, Hungary)	laser-evoked pain	12	20-31	cathodal + pergolide	placebo medication	M1	1	15	not reported	NRS

Footnotes: DLPFC= dorsolateral prefrontal cortex; LEPs= laser-evoked potentials; M1= primary motor cortex; NRS= Numerical Analogue Scale; S1= somatosensory cortex

Table 3.4 Characteristics of trials on clinical pain

Author, year (country)	Type of pain	No. of patients	Age (mean or range)	Mode	Control	Site	Intensity (mA)	Duration	Side effects	Pain outcome measures
Antal et al. 2010 (Germany)	fibromyalgiapost-stroke, LBP, trigeminal neural.	23	28-70 yrs	anodal	sham	M1	1	20 min, 5 days	no adverse	VAS, SICI (paired-pulse TMS)
Boggio et al. 2009 (USA, Brazil, Australia)	chronic pain	8	63.3	anodal + TENS	sham, sham TENS	M1	2	30 min	headache	VAS
Fenton et al. 2009 (USA, Brazil)	chronic pelvic pain	7	38	anodal	sham	M1	1	20 min, 2 days	headache, neck pain, burning sensation, redness	VAS Regional Pain Scale for FMS
Fregni et al. 2006 (USA, Brazil, Germany)	fibromyalgia	32	53.4	anodal	sham	M1 DLPFC	2	20 min, 5 days	sleepiness, headache, local redness, itching	VAS, analgesics use, tender points
Fregni et al. 2006 (USA, Brazil, Spain, Germany)	spinal cord injury	17	35.7	anodal	sham	M1	2	20 min, 5 days	headache, itching under electrodes	VAS
Mori et al. 2009 (Italy)	multiple sclerosis	19	44.8	anodal	sham	M1	2	20 min, 5 days	no adverse effects	VAS, SF-MPQ
Valle et al. 2009 (Brazil)	fibromyalgia	41	54.8	anodal	sham	M1 DLPFC	2	20mins, 10 days	minor skin redness and tingling	VAS, Fibromyalgia questionnaire
Soler et al. 2010 (Spain, USA)	spinal cord injury	20	45	anodal +visual illusion	sham sham illusion	M1	2	20 min, 10 days	mild headache, tiredness	NRS, NPSI, BPI

Footnotes: BPI= br
neuropathic pain sy
stimulation; VAS= vis

3.3.4 Synthesis of the results

3.3.4.1 Descriptive analysis of trials on experimental pain

The overall high risk of bias in 4 out of 6 trials on tDCS for the reduction of experimental pain was mainly due to inadequate randomisation procedures, insufficient allocation concealment, and selective outcome reporting (Table 3.2). None of the trials on experimental pain had published a trial protocol. Trial reports did not define primary outcome measures but reported altered pain or sensory thresholds as main results, depending on statistical significance.

Experimental pain was induced by different methods (Table 3.3) but always to the dorsal surface of the hand. Both anodal and cathodal stimulation demonstrated pain-relieving effects compared to sham stimulation. Sham stimulation in all trials was a brief period of stimulation that mimicked the typical initial burning sensation underneath the electrodes but had in previous research not resulted in neurophysiological change (Nitsche et al., 2003b). All trials reported some pain reduction with the stimulation paradigm chosen. Cathodal stimulation resulted in a statistically significant pain reduction when applied over S1 (Antal et al., 2008) and significantly reduced the laser intensities required to induce a mild pain sensation (Csifcsak et al., 2009), as well as the mechanical pain threshold (Bachmann et al., 2010) when applied over M1. Small, but statistically significant effect sizes in pain reduction were achieved by Terney et al. (2008) after sham and cathodal stimulation of M1, measured 40 minutes post stimulation. Anodal stimulation of M1 demonstrated significantly increased perception thresholds and increased pain thresholds in 1 trial (Boggio et al., 2008) that was not observed by other authors (Bachmann et al., 2010) and demonstrated no effect on pain reduction when applied over S1 (Antal et al., 2008). Anodal stimulation further reduced emotional discomfort when applied over DLPFC (Boggio et al., 2009b). Additionally, trials on experimental pain showed significantly altered neurophysiological measures such as the P2 and N2 components of evoked potentials as surrogate markers for pain perception

(Antal et al., 2008; Csifcsak et al., 2009; Terney et al., 2008). Owing to the variety of stimulation sites and parameters as well as outcome measures (e.g. pain thresholds, emotional discomfort, pain intensity) it was not feasible to combine data from the experimental pain trials.

3.3.4.2 Descriptive analysis and meta-analyses of trials on clinical pain

Although trial populations included various clinical pain conditions, all trials applied anodal stimulation and used M1 as the site of stimulation. A numerical or visual rating scale was the primary or secondary outcome measure of all trials, thereby allowing synthesis of data in a meta-analysis.

All 8 trials demonstrated a pain relieving effect. Six trials were conducted by the same research group (Boggio et al., 2009a; Fenton et al., 2009; Fregni et al., 2006a, 2006b; Soler et al., 2010; Valle et al., 2009) inducing a risk for reporting bias. Four trials (Antal et al., 2010; Boggio et al., 2009a; Fenton et al., 2009; Valle et al., 2009) were excluded from the meta-analysis owing to a high risk of bias in 1 or more domains. In 2 cases, this referred to a very small sample size (n=7 (Boggio et al., 2009a)) and (n=8 (Fenton et al., 2009)) and methodological issues, such as insufficient allocation concealment and losses to follow-up (>20%) that were either not reported or not accounted for. Two trials (Antal et al., 2010; Valle et al., 2009) used a non-random sequence generation (order of entrance) and 1 trial entered data from 2 different trial designs (crossover trial and sham-controlled trial) into the same data analysis (Antal et al., 2010). Hence, 4 trials with a total of 107 patients were included in the meta-analysis. The pooled effect size (mean difference; random effects model) was -2.29 with a 95% confidence interval of -3.5 to -1.08, p=0.0002 (Figure 3.2).

Table 3.5 Reported outcomes of trials on experimental pain

Author, year (country)	Pain related outcome measures	Neurophysiological outcome measures
Antal et al. 2008 (Germany, Hungary)	Laser-induced pain pre and post tDCS over S1. Percentage change from baseline **mean (SD)** **cathodal** - 12.5% (2.14) **sham** + 3.0% (3.57) **anodal** + 1.0% (3.93)	LEPs pre and post stimulation over S1. Percentage change from baseline. **LEP N2 mean (SD)** **LEP P2 mean (SD)** **cathodal** -32% (7.58) -13% (9.18) **sham** -17% (7.58) + 7% (9.18) **anodal** -11% (7.58) -11% (9.18)
Bachmann et al. 2010 (Germany)	Cold pain threshold (F-value 0.42) and heat pain threshold (F-value 0.21) not significantly different after anodal, cathodal, or sham tDCS over M1.	
Boggio et al. 2008 (USA, Brazil)	Electrical pain threshold pre and post tDCS. Percentage change from baseline after anodal stimulation. **mean** **M1** +8% **DLPFC** +13% **sham** 0%	
Boggio et al. 2009b (USA, Brazil)	Emotional discomfort / pain associated with images of human pain at baseline and post anodal stimulation. **mean NRS (SD)** **Baseline** 4.8 (0.84) **M1** 5.8 (1.09) **V1** 5.75 (1.09) **DLPFC** 4.45 (0.93) **sham** 5.05 (1.09)	
Csifcsak et al. 2009 (Germany, Hungary, Denmark)	Mean laser intensities to induce mild pain before and after stimulation over M1. **cathodal** **mean (mJ)** *before* 523 *after* 556 **anodal** *before* 510 *after* 495 **sham** *before* 510 *after* 508	LEPs before and after tDCS over M1. **LEP N2 mean µV (SD)** **LEP P2 mean µV (SD)** **cathodal** *before* -13.9 (7.2) 20.04 (9.25) *after* -8.2 (6.2) 15.56 (7.55) **anodal** *before* -13.3 (6.8) 19.38 (8.11) *after* -10.6 (6.4) 15.87 (6.82) **sham** *before* -12.24 (8.7) 16.03 (6.44) *after* -9.1 (6.2) 15.23 (5.80)
Terney et al. 2008 (Germany, Hungary)	Laser-induced NRS values before and after tDCS over M1. **cathodal** **mean NRS (SD)** *before* 4.39 (1.39) *after* 3.98 (1.66) **sham** *before* 3.28 (1.15) *after* 3.19 (1.32)	LEPs before and after tDCS over M1. **LEP N2 mean µV (SD)** **LEP P2 mean µV (SD)** **cathodal** *before* -11.04 (5.82) 15.14 (6.96) *after* -9.36 (6.59) 12.27 (7.11) **sham** *before* -13.12 (7.52) 12.94 (3.51) *after* -11.83 (7.92) 10.06 (3.21)

Footnotes: LEP= laser evoked potentials; M1= primary motor cortex; NRS= numerical rating scale; S1= primary sensory cortex; SD= standard deviation; tDCS= transcranial direct current stimulation; V1= visual cortex.

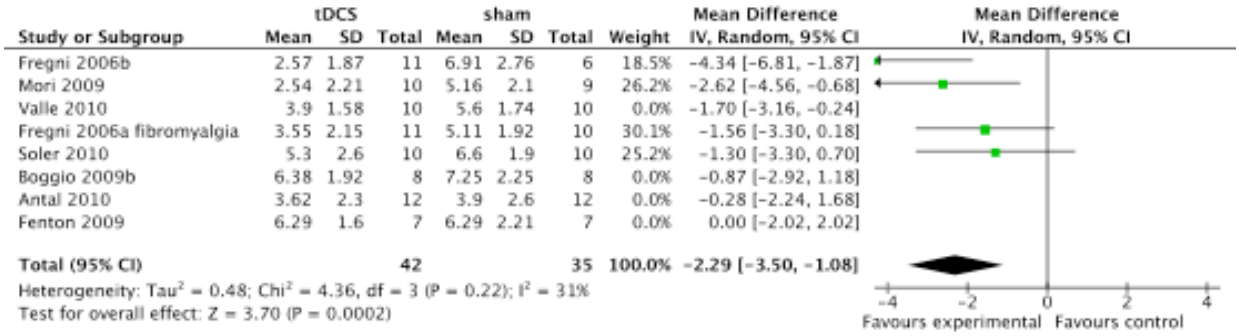


Figure 3.2 Meta-analysis of 4 trials with a low or unclear risk of bias

3.3.4.3 Heterogeneity

Although 3 of the 4 trials included in the meta-analysis adopted homogeneous methodological approaches (same research group), the diversity of clinical pain syndromes could introduce heterogeneity of intervention effects. However, the estimated heterogeneity across studies was I^2=31%, P= 0.22 and χ^2= 4.36 (Figure 3.2). According to the Cochrane Handbook this level of heterogeneity (0-40%) is interpreted as "might not be important" (Deeks, 2008, p.278). It has been recommended that at least 10 trials should be included to distinguish chance from potential publication bias in the case of funnel plot asymmetry (Sterne, 2008), hence an exploration of publication bias in a funnel plot was not conducted.

3.3.4.4 Additional analyses (sensitivity analysis)

A second meta-analysis was conducted to explore whether exclusion of the 4 trials with a high risk of bias had influenced the findings of the first meta-analysis. A meta-analysis of all 8 trials resulted in an effect estimate (mean difference; random effects model) of -1.51 with a 95% confidence interval from -2.34 to -0.68, p=0.0004 (Figure 3.3). The level of heterogeneity was not changed when considering all trials (independent of associated risks of bias) in the meta-analysis (Figure 3.3).

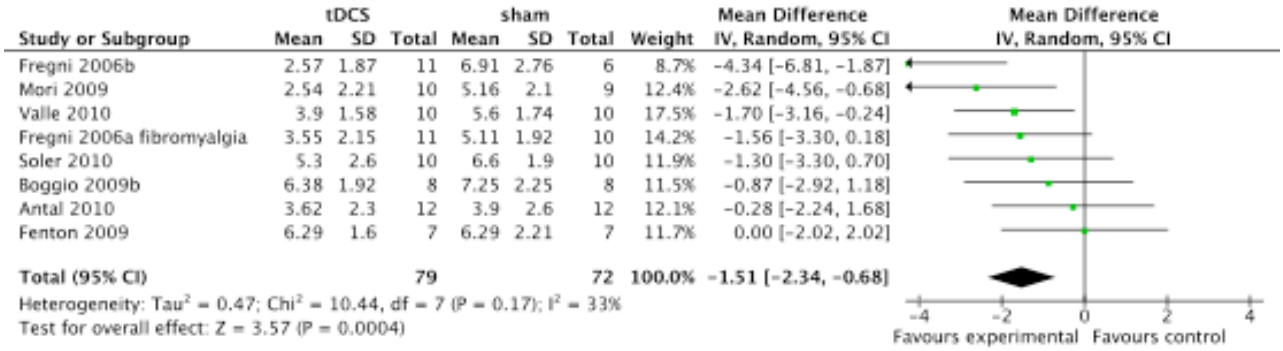


Figure 3.3 Meta-analysis of all 8 trials

3.4 Discussion

3.4.1 Discussion of results for tDCS for the reduction of experimental pain

The evidence for tDCS for pain reduction is currently based on 6 trials investigating experimental pain and 8 trials investigating chronic pain. Only 1 trial was assessed as showing an overall low risk of bias. Reporting did not follow current guidelines for the reporting of clinical trials, although the revised CONSORT statement was published in 2001 (Moher et al., 2001), e.g. procedures for allocation concealment were not described for any trial, randomisation procedures were not clearly stated in 4 cases, and only 1 trial had a published trial protocol that detailed planned trial procedures and, thereby, minimised the risk of selective outcome reporting.

Experimental pain trials applied a wide variety of tDCS parameters (stimulation sites, mode, duration) and the diversity of outcome measures as well as a high overall risk of bias in 4 out of 6 trials made it impossible to combine the data in a meta-analysis. Although all authors reported either significant pain reduction or reduced pain related outcomes, no consistent pattern for the most effective stimulation approach emerged. Whilst cathodal stimulation consistently altered the N2 and P2 components of laser evoked potentials (Antal et al., 2008; Csifcsak et al., 2009; Terney et al., 2008), it only reduced perceived pain in 1 trial (Antal et al., 2008). Anodal stimulation introduced small changes in emotional discomfort (Boggio

et al., 2009b) and increased the threshold to electrical pain in 1 trial (Boggio et al., 2008). This finding was reproduced for mechanical but not for thermal pain thresholds by other authors (Bachmann et al., 2010). Further research is required to establish the most effective stimulation paradigm to reduce different types of experimental pain. Furthermore, future research should focus on the most responsive outcome measure for experimental pain reduction following tDCS, e.g. pain intensity measured on a numerical rating scale, laser-intensity (in μV) or hot/cold temperature (in C°) to induce the sensation of pain.

It is unclear whether results from experimental pain trials can be translated to clinical pain reduction. Experimental pain has some advantages over clinical pain for research purposes as it can be standardised with regards to duration, intensity, frequency, and location, and applied to healthy volunteers who are less susceptible to confounding factors such as psychological disorders that frequently accompany chronic disease (Staahl and Drewes, 2004). Recently, authors confirmed the importance of experimental pain research for above mentioned reasons, but acknowledged that findings might not be relevant to clinical and, especially, chronic pain populations, since experimental pain cannot reproduce the psychological, cognitive and social aspects of the condition (Reddy et al., 2012). The current systematic review indicated that anodal stimulation, the stimulation mode used in all trials on clinical pain, had neither a positive nor negative effect in 3 experimental pain trials (Antal et al., 2008; Csifcsak et al., 2009; Terney et al., 2008), suggesting that healthy volunteers responded differently from clinical pain patients to anodal stimulation. Hence, while research applying experimental pain paradigms is helpful to further understand the neurophysiological mechanisms underlying the effect of tDCS, results from tDCS on experimentally induced pain might not be transferable to clinical pain patients.

3.4.2 Discussion of results for tDCS for the reduction of clinical pain

The evidence for the reduction of clinical pain was more consistent than the evidence from trials on experimental pain: all trials employed anodal stimulation of M1 with intensities of either 1 or 2 mA, with 2 mA delivered for 20 minutes, on 5 consecutive days, as the most frequently used combination of stimulation parameters. A pooling of the effect sizes was feasible since all trials used a numerical scale to measure pain. However, only 4 trials met the minimum methodological requirements to be included into the meta-analysis and data of different patient populations with different types of clinical pain (fibromyalgia, pain due to spinal cord injury and pain due to multiple sclerosis) were combined. All pain conditions represented chronic pain populations and similar reductions in pain were reported across all trials, supporting the potential transferability of systematic review results to further chronic pain populations.

Although effects for pain were reported as statistically significant across all trials, the pooled effect of -2.29 with a 95% confidence interval of -3.5 to -1.08 just reach clinical importance. Minimal clinically important pain reduction was reported as 15 mm on a 0-100 mm VAS, equivalent to 1.5 cm on a 0-10 cm NRS (Ostelo et al., 2008) and more recently as 2.4 cm on a 0-10 cm NRS (Maughan and Lewis, 2010). The results from the sensitivity analysis that included trials with a high risk of bias showed an effect size of -1.51 (95% confidence interval -2.34 to -0.68). Sensitivity analysis results were just within limits of the lowest minimum clinically relevant change recommendation (Ostelo et al., 2008). Comparing the results of both meta-analyses showed that the high risk of bias trials did not result in larger effect sizes for pain reduction than trials that only had a low or unclear risk of bias. The width of the confidence interval was comparable for both analyses, hence, methodological quality of trials did not appear to influence precision of the results.

3.4.3 Discussion of systematic review results based on current evidence

The findings of this systematic review were comparable with the conclusions from the systematic review and meta-analysis published by the Cochrane Collaboration (O'Connell et al., 2010) that reported a low level of methodological quality of available trials. The meta-analysis from O'Connell et al. (2010) resulted in a standardised mean difference of -0.59 with a 95% CI from -1.10 to -0.08 with p=0.02 (tDCS short-term follow-up, M1 stimulation). In the current review, when using standardised mean differences instead of the reported mean differences, the effect was estimated as -0.97 (95% CI -1.49 to -0.45). This small difference was introduced by 1 recent trial that was included in this current meta-analysis (Soler et al., 2010) and 2 trials that were excluded owing to a high risk of bias (Boggio et al., 2009a; Fenton et al., 2009).

The small, but statistically significant, combined mean effect for pain reduction only referred to immediate results after the final stimulation. Further research, of high methodological quality is required that investigates longer-term effects of tDCS on pain reduction.

Using GRADE, the quality of the evidence for tDCS as a method to reduce pain, based on the 4 trials included in the meta-analysis, was low. This estimate is interpreted as "further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate" (Guyatt et al., 2008, p.926). This interpretation was the result of downgrading the level of evidence by 2 levels due to limitations in the design of the included trials (3 trials with an unclear risk of bias) (Fregni et al., 2006a; Fregni et al., 2006b; Soler et al., 2010) and overall imprecision of results (wide confidence intervals in trials with small sample sizes) in all trials.

To upgrade the level of evidence for tDCS for the reduction of clinical pain and to allow recommendations for the future use of tDCS, a well-designed, low risk of bias randomised controlled trial with an adequate sample size is required that assesses

the effect of tDCS on pain and includes follow-up time-points for the evaluation of longer-term effects of the intervention.

3.4.4 Limitations of the systematic review

- When data were unavailable from the trial reports and after unsuccessful contact of trial authors, values for mean pain intensity and standard deviations were retrieved from graphs. This procedure might have introduced some inaccuracy in the data but allowed the inclusion of trials that would have otherwise been excluded.

- Systematic review results only refer to short-term pain reduction immediately after the final stimulation. For the clinical use of tDCS it would be essential to evaluate longer-term results.

Chapter summary

This chapter has detailed the process and the results of a systematic review including a meta-analysis on tDCS for the reduction of experimental and clinical pain. The systematic review was published in the Clinical Journal of Pain (Journal Impact Factor 2.552) in 2012 (Luedtke et al., 2012b) (Appendix 3.1).

Fourteen trials, 6 on experimental pain and 8 on clinical pain, were included in this review. Only 1 trial on clinical pain was assessed as having an overall low risk of bias. Seven trials had methodological shortcomings. Trials on experimental pain investigated different stimulation approaches and used a wide variety of outcome measures. Future research is required to establish an effective stimulation paradigm and to identify reliable and responsive outcome measures. A meta-analysis of all trials on clinical pain indicated that pain reduction just reached a minimal clinically important difference. The stimulation paradigm applied in the majority of trials was 2 mA for 20 minutes, on 5 consecutive days. The transferability from experimental trial

results to clinical pain has still to be established. Hence, to promote a recommendation for the clinical effectiveness of tDCS for the reduction of pain, future research should focus on clinical pain conditions.

The overall level of evidence was rated as "low". Based on the current level of tDCS no recommendation can be made for its use in clinical practice. In conclusion, there was a need for a well designed randomised controlled trial, with an adequate sample size, to assess the effectiveness of tDCS for the reduction of clinical pain.

4. CHAPTER

EFFECTIVENESS OF ANODAL TRANSCRANIAL DIRECT CURRENT STIMULATION IN PATIENTS WITH NON-SPECIFIC CHRONIC LOW BACK PAIN: DESIGN AND METHODS FOR A RANDOMISED CONTROLLED TRIAL

Previous chapters have presented the theoretical background and the current evidence on tDCS for the reduction of pain. The systematic review and meta-analysis of the available evidence concluded that there was a low level of evidence for tDCS as an intervention for pain reduction. Experimental pain trials did not demonstrate conclusive results regarding optimum stimulation parameters and outcome, and the transferability of results to clinical pain was questioned. To assess the effectiveness of tDCS for the reduction of clinical pain, methodologically sound RCTs, with adequate power were required. This chapter details the design and methods for an RCT investigating the effect of tDCS alone and in combination with CBT on NSCLBP.

4.1 Trial objectives

The main objectives of this trial were:

- To investigate the immediate effectiveness of tDCS on NSCLBP.
- To investigate whether tDCS as an adjunct further improved the immediate effectiveness of a CBT in patients with NSCLBP.

A secondary objective was:

- To assess after how many days of stimulation a pain reducing effect occurred.

4.2 Trial design

A single-centre, double blind, sham-controlled, stratified parallel group RCT, with 2 study arms, was designed and conducted in Germany. The trial design and its reporting followed the internationally recognised recommendations published by the CONSORT group (Schulz et al., 2010), the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH, 1996), the World Medical Association's Declaration of Helsinki (WMA, 2008) and the Cochrane Collaboration (Sterne, 2008). A well-conducted RCT is considered to be the gold standard for evaluating the effect of an intervention (Barton, 2000; Grossman and Mackenzie, 2005; Kaptchuk, 2001; Manchikanti et al., 2003) and was therefore the design of choice to investigate the effectiveness of tDCS in NSCLBP. Randomisation of participants to sham (Section 4.5.2) and verum tDCS (Section 4.5.1) was required to ensure that the measured effects were the result of the stimulation mode and not influenced by selection or sampling bias (selection of participants likely to respond to tDCS) (Altman and Bland, 1999b). The sham arm of the trial controlled for the potential placebo (e.g. montage of electrodes, attention of researcher) (Manchikanti et al., 2003). Participants and researcher were blind to the group allocation throughout the data collection period and during the analysis of the data, to avoid reporting and observer bias (Hrobjartsson and Boutron, 2011; Psaty and Prentice, 2010).

All participants received 5 consecutive days of tDCS (verum or sham) (Section 4.5), followed by a 4-week CBT programme, which was the standard care for NSCLBP patients at the study centre. International guidelines recommended CBT as the most effective available management for NSCLBP (Section 1.1.3.3.1). It was neither feasible nor ethical to deprive patients of their recommended management. Hence, tDCS was applied as an adjunct to CBT to investigate whether tDCS further improved the effectiveness of the CBT. Outcomes were measured prior to the first stimulation, 24 hours after the final stimulation, at the end of the CBT and at 4, 12, and 24 weeks follow-up (Section 4.8.2). This study design (Figure 4.1) was developed to enable testing of the immediate effect of tDCS alone, and the

immediate and longer-term effect (final follow-up at 24 weeks post intervention) of tDCS as an adjuvant prior to a CBT.

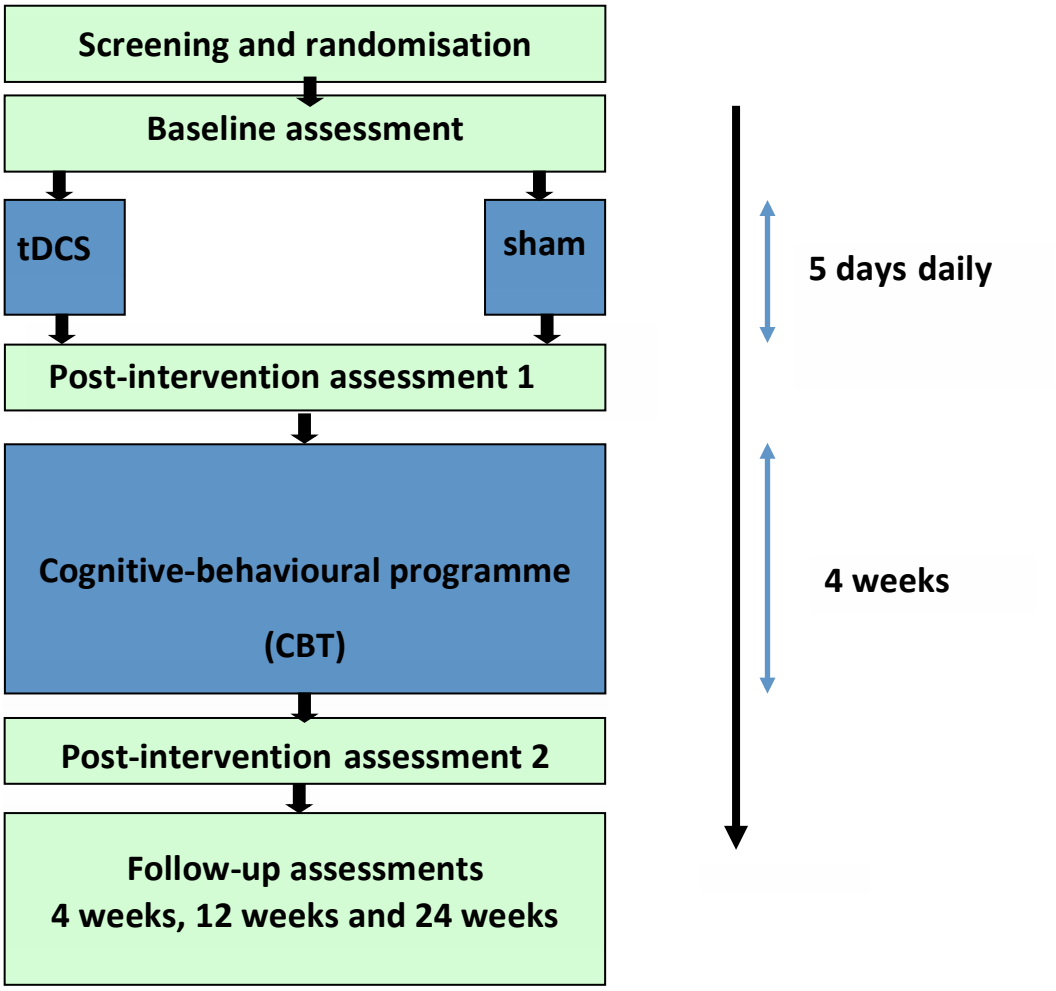


Figure 4.1 Trial design flowchart

4.3 Eligibility criteria for participants

4.3.1 Inclusion criteria

Eligible participants were adults aged 18-65 years, with NSCLBP (as defined in Section 1.3), who met the eligibility criteria for a CBT at a back pain clinic in Germany. Although back pain occurs in patients younger than 18 years (McBeth and Jones, 2007), its prevalence increases with age until it gradually declines from the age of 60-65 (Hoy et al., 2010). The upper age limit of 65 years was selected because it was the legal age for retirement in Germany and health insurances do not pay for pain management programmes beyond that age since they target the patient's capacity to return to work. Hence, this age restriction was important because all patients were required to commence a CBT programme after the stimulation period. The lower age limit of 18 years was required because at commencement of the study, there was no prior evidence that tDCS was safe in under 18 year olds. The first research study on the tolerability of tDCS in children and adolescents was published after commencement of the trial and considered only children and adolescents with psychiatric disorders (Mattai et al., 2011). A computational model, developed during the data collection period, confirmed the decision to exclude children. The model indicated that tDCS induced higher electrical fields when applied to the brain of a child. Studies on paediatric populations, therefore, would require different stimulation parameters (Minhas et al., 2012).

Eligibility for the CBT programme required the patient to understand and speak German so that they could benefit from the cognitive elements within it. The patient had to be a member of a participating health insurance company that covered the costs of the CBT. Health insurance is compulsory in Germany. Private and public health insurance companies participated in the CBT scheme covering a wide range of patients of different socio-economic background. Bias due to health insurance membership was therefore not expected. Patients had to be motivated to return to

work after the programme (a health insurance requirement) and had to be physically fit (e.g. without severe cardiorespiratory disease) to tolerate a 4-week physical training programme. Eligibility for the CBT was confirmed by agreement of an orthopaedic consultant, a psychologist, and a physiotherapist following a standard screening procedure (standard procedure of back pain clinic).

4.3.2 Exclusion criteria

Participants who fulfilled the inclusion criteria were excluded if they had any of the following:

- Other chronic pain syndromes: in particular other musculoskeletal pain syndromes (e.g. chronic neck pain), since no research was identified that reported whether or how 2 or more chronic pain syndromes interact within the central nervous system.

- Spinal surgery in the past 6 months: patients were excluded if they were recovering from surgery because any effect of the stimulation would be confounded with the natural course of healing. After 6 months the majority of spinal surgery patients returned to work and sports, and were regarded as fully recovered (Oestergaard et al., 2012; Reinhold et al., 2010; Watkins et al., 2012).

- Neurological disease: any neurological disease that might have an impact on the brain cortex of the participant, such as Parkinson's disease (Brown et al., 2008; Pasquereau and Turner, 2011; Vardy et al., 2011), multiple sclerosis (Ceccarelli et al., 2010; Filippi et al., 2002; Valsasina et al., 2011), or epilepsy (O'Muircheartaigh et al., 2011; Vollmar et al., 2011). These were excluded because it was unknown whether central nervous system diseases affected the cortical response to tDCS.

- Psychiatric disease: especially severe depression that could reduce the chances to gain any benefit from either the tDCS intervention or the CBT. It was shown that severe depression strongly influenced the transition from acute to chronic pain (Epping-Jordan et al., 1998) and that highly distressed patients benefited less from therapy interventions (McCracken and Turk, 2002). Although tDCS had been applied to reduce depression in the past, those trials used a different stimulation approach by targeting the DLPFC (Boggio et al., 2007; Dell'Osso et al., 2012, 2011).

- Pregnant or trying to become pregnant: no published research had investigated whether (or how) tDCS affects the foetus.

- Alcohol, drug, or medication abuse: no published research had evaluated the interaction of substance abuse with the response to tDCS or CBT. It was known that centrally effective medication influenced the effect of tDCS (Terney et al., 2008), therefore, substances such as alcohol that affect the central nervous system should not be consumed immediately prior to or after the stimulation.

The eligibility criteria were similar to those used in recent large trials on patients with non-specific CLBP who were treated in pain management programmes with cognitive-behavioural elements (Dufour et al., 2010; Lamb et al., 2010). Additional exclusion criteria were applied based on those used in published tDCS trials (Antal et al., 2010; Fregni et al., 2006a, 2006b). Although medication intake was not specified as an exclusion criterion, type and dosage of preventive and acute medication was recorded and any change in medication was documented to allow distinction between stimulation and medication effects.

4.4 Settings and location for data collection

Patients were recruited and treated at a back pain clinic in North Germany, starting from January 2011. The clinic was established in 2001 and specialises in the management of patients with ongoing spinal pain. The CBT programme is led by orthopaedic specialists, physiotherapists, sports scientists, and psychologists with expertise in chronic pain management. Based on initial feasibility work, 100 to 150 eligible non-specific CLBP patients per year are treated at the clinic. Patients were referred by their health insurance company when they had been off work for more than 6 weeks, or, repeatedly during the past 12 months, due to NSCLBP.

4.5 Interventions

4.5.1 Verum tDCS (intervention group)

4.5.1.1 Stimulation paradigm

Participants in the verum group received 20 minutes of anodal stimulation over the left M1 with an intensity of 2 mA, on 5 consecutive days, administered by the researcher. Selection of this stimulation paradigm was based on results from the systematic review of the current available evidence (Section 3.4.2). The review indicated that all trials on chronic pain had stated a positive effect from anodal stimulation over M1, with some variation in intensity, duration, and number of stimulations (Luedtke et al., 2012b). The most frequently applied paradigm in trials with the lowest risk of bias was 2 mA on 5 days for 20 minutes per session (Fregni et al., 2006a, 2006b; Mori et al., 2009). The application of tDCS on consecutive days was supported by trials that resulted in a greater cumulative effect on cortical excitability or a greater pain reducing response than single session tDCS (Alonzo et al., 2013; Fregni et al., 2006a, 2006b; Reis et al., 2009).

4.5.1.2 Localisation of the stimulation site

Single-pulse TMS was used to accurately determine the position of M1 and, therefore, the 'hotspot' for the tDCS stimulation in an individual participant: A figure of 8 coil with an outer diameter of 70 mm was placed over the left side of the skull near the anticipated area of M1 (Figure 4.2). The single-pulse TMS was produced with an initial intensity of 50% by a Magstim 200 magnetic stimulator (The Magstim Company, Dyfed, UK). The position of the coil was adjusted and intensity of the magnetic pulse increased (as necessary) until an isolated twitch of the right abductor digiti minimi muscle was observed by the researcher. This procedure had been reported as a reliable technique for the localisation of the M1 in a trial that investigated the reliability of motor mapping on 6 healthy volunteers on 2 separate days (Mortifee et al., 1994). The procedure had been used in previous trials on tDCS (Fregni et al., 2006a; Jurgens et al., 2012; Luedtke et al., 2012a; Nitsche et al., 2007).

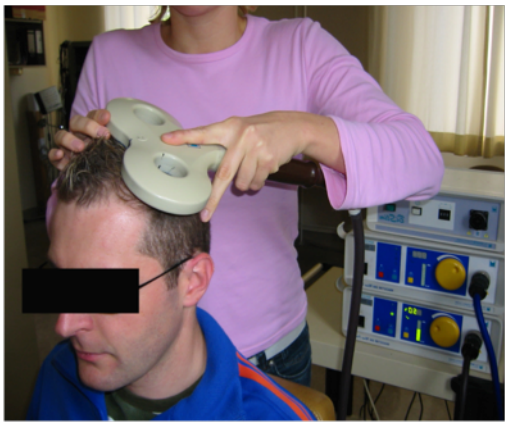


Figure 4.2 Position of the TMS coil to identify M1

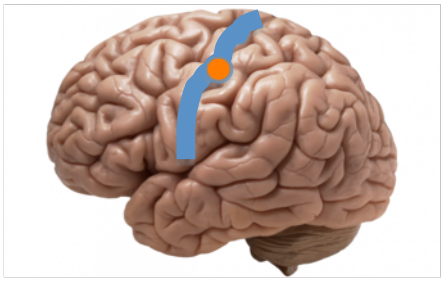


Figure 4.3 Localisation of left M1 (blue) and approximate position of the abductor digiti minimi muscle (red)

tDCS was produced by a battery driven small stimulator device and applied to the skull via sponge electrodes (Figure 4.4). Large size (7x5 cm = 35 cm^2) sponge electrodes, comparable to those used in all previous trials on tDCS in patients with

chronic pain, were soaked in a saline solution (0.9%), then placed over the stimulation sites, and held in place by elastic bandages (Figure 4.5). The anode (positively charged electrode) was placed over the left M1, while the cathode (negatively charged electrode) was placed supraorbitally on the opposite side (above the right eyebrow). The electricity was slowly increased to 2 mA at the beginning of the stimulation and slowly decreased at the end of the stimulation, to reduce skin sensations, such as itching or burning, underneath the electrodes (Ambrus et al., 2012). When the electrodes were securely attached, the participants chose a comfortable position (in most cases supine with legs elevated) for the duration of the stimulation.

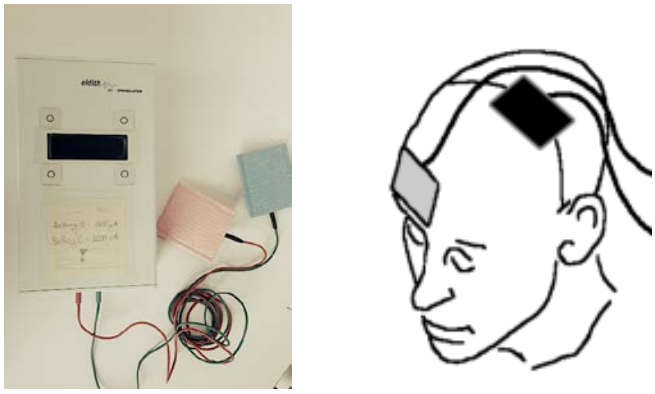


Figure 4.4 tDCS machine (NeuroConn) and stimulation sites

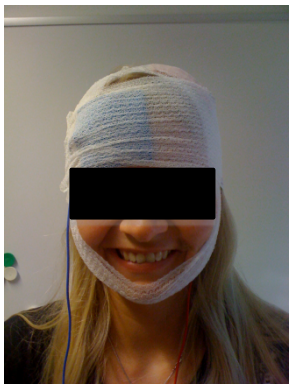


Figure 4.5 Attachment of the electrodes with elastic bandages

4.5.2 Sham Intervention (comparator group)

The sham procedure was identical to the verum stimulation procedure (Section 4.5.1) except that the DC stimulator automatically switched off after 30 seconds (after slowly reducing the stimulation intensity). The machine display continued to indicate the time and the impedance in the same manner as during the verum stimulation. During the initial 30-second stimulation period, participants perceived skin sensations identical to those perceived during the real stimulation. This short stimulation did not result in any measurable neurophysiological changes as identified by motor evoked

potentials and somato-sensory evoked potentials (Kirimoto et al., 2011; Nitsche and Paulus, 2001) and had been used as a placebo condition in all previous trials on tDCS for the reduction of chronic pain (Antal et al., 2010; Boggio et al., 2009a; Fenton et al., 2009; Fregni et al., 2006a, 2006b; Mori et al., 2009; Soler et al., 2010; Valle et al., 2009). Due to the initial brief stimulation period and the associated skin sensation as well as the identical machine display, this method is regarded as a reliable placebo condition for double blind trial designs (Gandiga et al., 2006; Loo et al., 2010; Priori et al., 2009) (further detail on blinding is given in Section 4.12).

4.6 Standard Care: CBT programme

A maximum of 8 patients per group received physically challenging sessions, including cardiovascular exercises, machine assisted muscle strength training, specific muscle stabilisation exercises for the trunk muscles, work hardening sessions, as well as information sessions on the neurophysiology of pain, pain coping strategies, and relaxation classes. Individual physiotherapy sessions were added in the case of specific needs, such as acute pain limiting the capacity for exercise. Patients attended 5 hours daily (Monday to Friday) for 4 weeks as outpatients. The CBT programme was delivered by an interdisciplinary team of orthopaedic consultants, physiotherapists, psychologists, and sports scientists.

CBT programmes have been reported internationally as effective for the reduction of pain and the improvement of function and disability in patients with CLBP (Bendix et al., 1996; Dufour et al., 2010; Lamb et al., 2010). However, the addition of techniques directly influencing central nervous system pain processing, such as tDCS, might further contribute to the reduction of pain and associated symptoms in NSCLBP (Section 1.1.3.3.1). The effectiveness of this CBT programme was later evaluated by Heinrich et al. (2011), who found a significant reduction in pain ($F=96.61$; $df=2.65$; $p\leq0.001$), disability ($F=210.79$; $df=1.48$; $p\leq0.001$), and function ($F=139.3$; $df=2.28$; $p\leq0.001$) immediately after the programme. The effects remained stable at a 12 months follow-up (Heinrich et al., 2011).

4.7 Primary and secondary outcome measures

NSCLBP is a condition that is influenced by a variety of contributing physical and psychosocial factors (Alschuler et al., 2011). Hence, it has been recommended in the research literature that a range of outcome measures should be used (dependent on the research question and the study design) to capture the influence of the intervention (Chapman et al., 2011; Turk et al., 2003). The Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) defined the following outcome domains as important for chronic pain trials: pain, physical functioning, emotional functioning, participant ratings of improvement and satisfaction, symptoms and adverse events, as well as participant disposition (e.g. adherence to the treatment regimen and reasons for premature withdrawal from the trial) (Turk et al., 2003). This recommendation is supported by the World Health Organisation's International Classification of Functioning, Disability and Health (ICF) that highlights that a disease or impairment does not only result in impaired physical structures and functions but also in reduced activities and participation. It further stresses the importance of environmental factors (World Health Organisation, 2014). Hence, a range of outcome measures is required to cover all aspects of chronic pain.

4.7.1 Primary outcome measures

tDCS and CBT have different roles within the management of NSCLBP. tDCS directly targets pain-processing areas within the brain, aiming to reduce pain intensity. Pain intensity was therefore required as a primary outcome measure for the effectiveness of tDCS. It covers the first domain of the IMMPACT recommendations (Turk et al., 2003) and the domain "physical structures" of the ICF core set for LBP (Cieza et al., 2004). CBT targets disability, cognitions and beliefs associated with chronic pain and other psychosocial aspects of the pain experience and might not necessarily result in a reduction of pain intensity (McCracken and Turk, 2002; Scascighini et al., 2008; Turk, 2002). Hence, to answer the research question on the combined effect of tDCS and CBT, a second primary outcome measure was required

that reflected the effects of the CBT. Recent trials on the effectiveness of CBT were identified and screened for primary endpoints (Brox et al., 2009; Dufour et al., 2010; Fairbank et al., 2005; Johnsen et al., 2013; Kääpä, 2008; Lamb et al., 2010; Smeets et al., 2006b). The only outcome measure included in all trials was disability. Disability covers the domain "physical functioning" of the IMMPACT recommendations and the domain "activities and participation" of the ICF core set for LBP (Cieza et al., 2004). High levels of disability were consistently reported in patients with LBP / CLBP (Sections 1.1 and 1.2) and correlated with reduced quality of life (Guclu et al., 2012; Kovacs et al., 2004). Disability was, therefore, an important second primary outcome measure. The statistical implications associated with 2 primary outcome measures are discussed in the section on data analysis (Sections 4.3 and 4.13).

4.7.1.1 Visual analogue scale for pain (VAS)

Pain intensity was chosen as a primary outcome measure, to reflect the neurophysiological mechanisms of tDCS and to allow the comparison of trial results with previously published research. All published tDCS trials measured pain intensity on NRS or VAS for pain (Antal et al., 2010; Boggio et al., 2009a; Fenton et al., 2009; Fregni et al., 2006a, 2006b; Mori et al., 2009; Soler et al., 2010; Valle et al., 2009).

In the current trial, pain intensity was measured on a VAS (0-100 mm), where 0 mm indicated no pain and 100 mm indicated the worst imaginable pain (Appendix 4.2). VAS for pain is an internationally validated (Gramling and Elliott, 1992; Jensen et al., 1986) and reliable (Lundeberg et al., 2001) tool, easy to use and understood by patients (McCormack et al., 1988). The recommended minimum clinically important change for visual and numerical pain scales in chronic pain patients ranged from 15 mm (Ostelo et al., 2008) to 24 mm (Maughan and Lewis, 2010). Back pain might vary in intensity throughout the day and, consequently, can be difficult to quantify (De Souza and Frank, 2000). Hence, for the purpose of this trial, participants were instructed to indicate the average pain level during the past 24 hours. Average pain ratings had been used as a primary outcome measure in all previous tDCS trials and

were reported to be more consistent than recalled minimum or maximum levels of pain, when compared to momentary pain ratings recorded throughout the day (Stone et al., 2010).

4.7.1.2 Disability

The 2 most frequently used and internationally validated tools to measure disability in previously published trials were the Roland Morris Disability Questionnaire (RMDQ) (Roland and Morris, 1983) and the Oswestry Disability Index (ODI) (Fairbank et al., 1980). Both questionnaires were recommended for research use in LBP populations (Chapman et al., 2011; Deyo et al., 1998), and both tools have previously been shown to discriminate accurately between LBP patients with high and low levels of disability (Leclaire et al., 1997). Table 4.1 details the test properties of the ODI and RMDQ. Findings differed across studies. Since 1 publication evaluated the ODI as more sensitive to change than the RMDQ (Davidson and Keating, 2002), and other authors reported RMDQ to be the more sensitive to change (Beurskens et al., 1996), a small preliminary study was conducted to evaluate sensitivity to change of both outcome measures in the proposed study population.

Table 4.1 Test properties of ODI and RMD

	ODI	RMDQ	References
Authors / Date **Range** **Instructions for patients**	Fairbank / 1980 0-24 Points "Please answer every section and mark in each one only the one box which applies to you."	Roland & Morris / 1983 0-50 Points "Check the box before each sentence that describes you today. Leave the box blank if the sentence does not describe you."	(Roland and Morris, 1983; Fairbank et al., 1980)
Validated in German	yes	yes	(Exner and Keel, 2000; Mannion et al., 2006; Osthus et al., 2006)
Test-Retest Reliability	Same day: ICC = 0.99 4 days: ICC = 0.91 1 week: ICC = 0.83 (excellent to adequate)	Same day: ICC = 0.91 1 to 14 days: ICC = 0.93 3 to 6 weeks: ICC = 0.86 (excellent to adequate)	(Davidson and Keating, 2002; Fairbank et al., 1980; Fairbank, 2000; Gronblad et al., 1993; Kopec et al., 1996; Osthus et al., 2006; Vianin, 2008)
Internal consistency	Cronbach's alpha ranged from 0.71 to 0.87 (acceptable)	Cronbach's alpha = 0.83 (acceptable)	(Fairbank and Pynsent, 2000; Fischer et al., 2001; Kopec et al., 1996; Mousavi et al., 2006; Strong et al., 1994; Vianin, 2008)
Sensitivity to change / responsiveness	High responsiveness (Vianin, 2008) Might not be sensitive to change at lower levels of disability (Dawson et al., 2010; Beurskens et al., 1996). ODI more responsive to change than RMDQ (Davidson and Keating, 2002). Directly compared to RMDQ: equal properties in the detection of improvement or worsening of patient symptoms (Stratford et al., 1996).	Might not detect improvements in patients with an initial score above 20 or decreases in patients with an initial score below 4. Directly compared to ODI: equal properties in the detection of improvement or worsening of patient symptoms (Stratford et al., 1996).	(Beurskens et al., 1996; Davidson and Keating, 2002; Dawson et al., 2010; Fairbank, 2000; Stratford et al., 1996; Vianin, 2008)
MCRC	0% 6-17 points	30% 2-5 points	(Bombardier et al., 2001; Jordan et al., 2006; Kovacs et al., 2007; Maughan and Lewis, 2010; Ostelo et al., 2008)

Footnotes: ICC=intraclass coefficient; MCRC=minimum clinically relevant change; ODI=Oswestry Disability Index; RMDQ=Roland Morris Disability Questionnaire

4.7.1.2.1 Evaluation of ODI and RMDQ

Both outcome measures were evaluated during a 3-month preliminary study prior to commencement of the trial, to determine which tool was easiest to use and most responsive to change in a sample taken from the anticipated study population. The validated German versions of the ODI (Mannion et al., 2006) and the RMDQ (Exner and Keel, 2000) were completed pre- and post-intervention, by 27 consecutive NSCLBP patients who were participating in a CBT programme during the 3-month preliminary phase. Responsiveness to change was analysed by calculating standardised response mean (mean change divided by standard deviation of change scores) for each outcome measure (Beurskens et al., 1996; Davidson and Keating, 2002; Monticone et al., 2011; Stratford et al., 1996). The results (Table 4.2) indicated that both tools had comparable standardised response mean values of 1.29 and 1.17 for RMDQ and ODI, respectively. However, the RMDQ was rated as 0 in 7 out of 27 post-CBT-patients (floor-effect), indicating that these patients were fully recovered after the CBT. Only 2 of these patients also scored 0 on the ODI post-CBT, while the remaining 5 still showed some disability according to the ODI (Figures 4.6 and 4.7) (Appendix 4.1). This result is in line with the publication by Davidson & Keating (2002), which indicated that the ODI was more sensitive to identify lower levels of disability.

Furthermore, the written patient instructions provided by the ODI questionnaire were more easily understood by patients, as identified by comparing the number of “?” that patients wrote on the questionnaires (3 "?" on RMDQ compared to 0 "?" on ODI). The RMDQ required patients to tick the sentences that described their “pain today”. Sentences that patients felt did not describe their back pain had to be left blank. This made it difficult to distinguish between patients who were completely free of disability and those who did not fill out the questionnaire, since the submitted questionnaires showed only un-ticked sentences in both situations. Hence, the ODI was chosen as the second primary outcome measure to assess changes due to the CBT.

The ODI (Appendix 4.2) is a self-rating scale that evaluates the degree of disability in a number of areas of activities of daily living. It also evaluates how the level of pain interferes with 10 categories of physical activity. Patients tick the statement they find most suitable within each category. The sum score of all categories is multiplied by 2 to indicate a percentage level of disability (Fairbank et al., 1980). Percentages can be interpreted as: 0-20%=minimal disability, 21-40%=moderate disability, 41-60% severe disability, 61%-100% crippled / bedbound / exaggerated symptoms (Fairbank et al., 1980). The ODI has been widely used and validated internationally in chronic low back pain populations (Beurskens et al., 1996; Holm et al., 2003; Leclaire et al., 1997).

Table 4.2: 3-month evaluation of RMDQ and ODI

	RMDQ_pre	RMDQ_post	Difference pre-post	ODI_pre	ODI_post	Difference pre-post
mean	8.37	3.59	4.78	14.07	8.07	6
SD	4.02	3.92	3.69	5.48	4.61	5.12
SRM			1.29			1.17

Footnotes: ODI=Oswestry Disability Index; RMDQ=Roland Morris Disability Questionnaire; SD= standard deviation; SRM=standardised response mean.

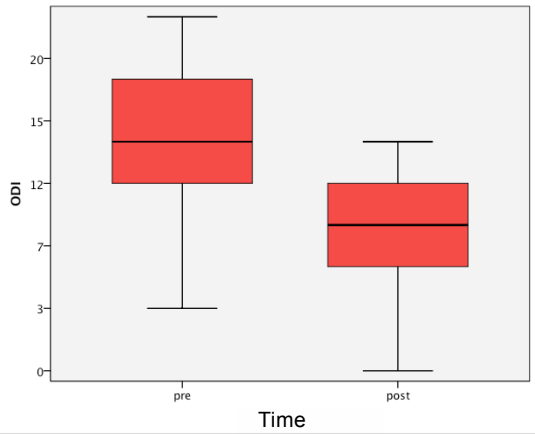


Figure 4.6 Boxplots of values for ODI pre and post CBT

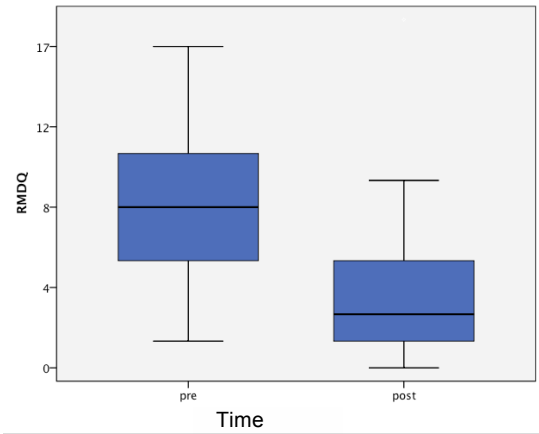


Figure 4.7 Boxplots of values for RMDQ pre and post CBT

Footnotes: CBT=cognitive-behavioural therapy; ODI=Oswestry disability index; RMDQ=Roland-Morris disability questionnaire

4.7.2 Secondary outcome measures

To explore the effects of tDCS and CBT on all aspects of NSCLBP, secondary outcome measures were selected according to their evidence base for evaluating NSCLBP and their measurement properties. Secondary outcome measures were further selected to cover the remaining recommended outcome domains for chronic pain trials (emotional functioning, improvement and satisfaction) (Turk et al., 2003) and ICF core set for LBP recommendations (Cieza et al., 2004). A search of the literature on tDCS and CBT trials was conducted to identify established and clinically relevant secondary outcome measures that were subsequently evaluated for measurement properties. tDCS trials mainly reported on the aspects of quality of life (Fregni et al., 2006a; Mori et al., 2009; Valle et al., 2009), global improvement (Fregni et al., 2006a, 2006b; Soler et al., 2010), depression (Fregni et al., 2006b; Mori et al., 2009) and disease specific outcome measures as secondary endpoints. Published CBT trials, additionally to pain and disability, typically measured fear avoidance beliefs (Brox et al., 2009; Lamb et al., 2010), quality of life (Dufour et al., 2010; Huge et al., 2006; Lamb et al., 2010), and depression and anxiety (Kääpä, 2008; Smeets et al., 2006a). These identified outcome measures are in line with recent recommendations on outcome measures for CLBP based on a systematic review of the literature (Chapman et al., 2011). Authors recommended VAS for pain, ODI or RMDQ for function and SF-36 for quality of life supported by additional psychological outcome measures, such as fear avoidance beliefs and depression. Based on previously used outcome measures, published recommendations, ICF domains, and measurement properties, the following secondary outcome measures were chosen for this trial (Table 4.3) (Appendix 4.3):

- ICF domain of physical functioning:
  - Funktionsfragebogen Hannover (FFBH)
  (Hannover Functional Ability Questionnaire)
  - Bothersomeness
  - RAND 36-Item Health Survey subscales
    Physical functioning
    Role limitations due to physical health

- ICF domain of emotional functioning:
  - RAND 36-Item Health Survey subscales
    Energy / fatigue,
    Emotional well-being
    Role limitations due to emotional problems
  - Fear Avoidance Beliefs Questionnaire (FABQ)
  - Hospital Anxiety and Depression score (HADS)

- ICF domains of improvement and satisfaction:
  - Patient Perceived Satisfactory Improvement (PPSI)

Table 4.3 Psychometric properties of secondary outcome measures

	FfBH	Bothersomeness	RAND36	FABQ	HADS	PPSI
Authors / Date	(Kohlmann and Raspe, 1996)	(Dunn and Croft, 2005)	(Hays et al., 1993; Ware and Sherbourne, 1992)	(Waddell et al., 1993)	(Zigmond and Snaith, 1983)	(ten Klooster et al., 2006)
Description	12 items on the patient's capacity to perform daily life activities. Responses rated on a 3-point scale: - no can't perform activity - yes, with difficulties - yes	Single question: "How bothersome is your pain today?" 5 response options: - not at all - slightly - moderately - very much - extremely	36 item scale on general health. Subscales on Physical Functioning, Role limitations due to physical health and emotional problems, Energy / fatigue, Emotional well-being, Pain, and General health Public domain version of SF-36. In contrast to SF-36, no sum-score is evaluated.	Fear-avoidance beliefs in patients with low back pain. Two subscales: physical activity and work	14 item scale with subscales on anxiety and depression in patients with health problems	5-point Likert-type scale ranging from "much worse" to "much better"
Validated in German	Originally developed in German	no	SF-36 (Bullinger, 1995)	(Pfingsten et al., 2000; Staerkle et al., 2004)	(Herrmann and Buss, 1994)	no

Table 4.3 - continued 1

	FfBH	Bothersomeness	RAND36	FABQ	HADS	PPSI
Construct Validity **Internal consistency**	Cronbach's alpha 0.87-0.90 (Magnussen et al., 2010; Roese et al., 1996)	Correlation with VAS on pain and disability (Dunn and Croft, 2005)	Cronbach's alpha overall: 0.791 Each subscale: >0.70-0.75 except social function dimension: 0.55-0.631 (Alonso et al., 1998; Zhang et al., 2012) All numbers refer to SF-36	Cronbach's alpha 0.882 to 0.783 (Matsudaira et al., 2013; Monticone et al., 2011) Correlation with RMDQ and Tampa Scale of Kinesio-phobia (Crombez et al., 1999; Kovacs et al., 2004)	Cronbach's alpha for subscale HADS-Anxiety: .68 to .93 HADS-Depression: .67 to .90 (Bjelland et al., 2002)	Correlation with VAS on pain (ten Klooster et al., 2006)
Test-retest reliability	ICC 0.84 (Kohlmann and Raspe, 1996; Magnussen et al., 2010)	N/A	ICC for individual subscales ranged from 0.60-0.80 >0.80 for all subscales except social functioning (Brazier et al., 1992; Steffen and Seney, 2008) All numbers refer to SF-36	Test-retest reliability ICC ranges from 0.72 to 0.97) (Chaory et al., 2004; Holm et al., 2003; Kovacs et al., 2006; Pfingsten et al., 2000; Staerkle et al., 2004)	Pearson product-moment correlation coefficient of 0.89 (anxiety), 0.86 (depression) and 0.91 (total scale) ($P < 0.001$) over 3 weeks (Spinhoven et al., 1997)	N/A

Table 4.3 - continued 2

	FfBH	Bothersomeness	RAND 36	FABQ	HADS	PPSI
Sensitivity to change	High responsiveness assessed as correlation with change in VAS and global change (Magnussen et al., 2010)	80% sensitivity (61% specificity) to detect people in the highest category of pain and disability (Dunn and Croft, 2005)	High sensitivity to change evaluated in comparison with Dartmouth CO-OP charts; Ceiling effects in physical and emotional role subscales and social functioning. Floor effect in physical and emotional role subscales. (Jenkinson et al., 1995; Koh et al., 2006) All numbers refer to SF-36	Satisfactorily as evaluated by minimum clinically relevant change (Monticone et al., 2011)	Good sensitivity to change over time as measured by a change reliability coefficients of 0.70 (Hinz et al., 2009)	Not evaluated

Footnotes: Dartmouth CO-OP= Dartmouth Primary Care Cooperative Information Project**;** FABQ=fear avoidance beliefs questionnaire; FfBH=Funktionsfragebogen Hannover; HADS=hospital anxiety and depression scale; ICC=intra-class coefficient; PPSI=patient perceived satisfactory improvement; RMDQ=Roland-Morris disability questionnaire; SF-36=quality of life questionnaire with 36 items; VAS=visual analogue scale

4.8 Timing of assessments

4.8.1 Primary endpoints

The trial was designed to investigate the effectiveness of tDCS alone and in combination with CBT. Two primary endpoints were defined to meet these objectives: 24 hours after the final tDCS (post stimulation) and immediately after the CBT (post CBT). The implications of 2 primary endpoints for the trial sample size are discussed in Sections 4.3 and 4.13.

4.8.2 Follow-up assessments

Participants were assessed immediately prior to the first tDCS (baseline), 24 hours after the final stimulation (immediate effect of tDCS), and on the last day of the CBT (immediate effect of tDCS & CBT). Follow-up assessments took place 4 weeks, 12 weeks, and 24 weeks after the final day of the CBT to observe longer-term treatment effects. Follow-up time-points were chosen according to published research on tDCS and CBT for NSCLBP. tDCS trials generally used shorter follow-up periods ranging from 2 weeks (Fenton et al., 2009; Fregni et al., 2006b; Soler et al., 2010) to 60 days (Soler et al., 2010). Pain reduction following tDCS was statistically significant at all reported follow-up time-points. No research was published that indicated whether and after how many weeks the intervention effect would recede. CBT trials generally included longer-term follow-ups e.g. after 3 months (Dufour et al., 2010), 6 months (Dufour et al., 2010), 12 months (Dufour et al., 2010; Lamb et al., 2010), or 24 months (Dufour et al., 2010). Follow-ups of more than 6 months post intervention were not feasible within the time-frame of a PhD, therefore, follow-up time-points were chosen that were comparable with tDCS trials and allowed comparison with results of published CBT trials.

Additionally, average pain intensity over the past 24 hours was assessed daily during the stimulation period to evaluate the number of stimulation sessions required to observe an effect. This was important since pain is a variable parameter (de Souza et al., 2008) and previous researchers had reported pain reductions after 1 (Boggio et al., 2009a), 2 (Fenton et al., 2009) or 5 (Antal et al., 2010; Fregni et al., 2006a, 2006b; Mori et al., 2009) consecutive days of stimulation.

All measurement tools were questionnaires that participants were required to complete independently. The baseline questionnaires were completed at the clinic to allow participants to ask the researcher questions should they not understand the written instructions. All follow-up assessments were sent to the participant's home address and returned by post. If questionnaires were not returned within 5 working days, participants were contacted by telephone. This was repeated after 5 more days in those cases for which the questionnaires were still not returned.

While postal questionnaires (compared to interviews or supervised questionnaires) might result in a higher number of non-responders (Hébert et al., 1996) and missing data (Addington-Hall et al., 1998), and might further introduce bias since it is not certain that questionnaires are filled-out by the participant himself, it is generally viewed as a reliable (Wilson et al., 2002) and cost-effective (Wolffsohn et al., 2000) method for data collection.

4.9 Determination of the required sample size

Based on the 2 primary outcome measures (VAS and ODI), n=135 participants were required (calculated using G*Power, Version 3.1.2). The sample size estimation was based on minimum clinically relevant change recommendations of 15 mm on a 0-100 mm VAS (Ostelo et al., 2008) and 8 points on the ODI (Maughan and Lewis, 2010). Values for the standard deviations were taken from the baseline data from a previous trial (Kääpä, 2008) with a comparable study population, intervention and timing schedule for the measurements of the outcomes. The reported standard deviations

were 19 mm for VAS and 10.6 points for ODI. The sample size calculation was based on α= 0.0125 and 90% power (2-tailed). The α-value was determined by dividing the commonly accepted α= 0.05 by the number of primary endpoints (post stimulation and post CBT) and the number of primary outcome measures (VAS and ODI) (Bonferroni correction for multiple testing) (Cleophas and Zwinderman, 2006; Neuhäuser, 2006). The calculated effect sizes were 0.79 for VAS and 0.75 for ODI and were regarded as medium to large (Cohen, 1992). This resulted in a required sample size of n=96 for VAS and n=104 for ODI. Allowing for a loss to follow-up of 12% up to the first primary endpoint (after the stimulation) as observed in a previous tDCS trial on spinal pain patients (Fregni et al., 2006a), and a further loss of 16% to the second primary endpoint (after the CBT) as observed in a recent large scale trial on CBT for CLBP patients (Lamb et al., 2010), the required sample size was n=125 and n=135 for VAS and ODI, respectively, resulting in a trial sample size of n=135.

4.10 Interim analyses and stopping guidelines

No interim analyses were planned during the data collection period. However, in the case of a serious adverse event or a serious side effect (defined as a participant requiring medical attention), the researcher would have been unblinded and the trial discontinued. This decision was made by the researcher. It was independent of the group allocation of the affected participant. Although safety studies had not identified any serious side effects (Kessler et al., 2012; Nitsche et al., 2003c; Poreisz et al., 2007), participants were required to complete a safety questionnaire after each stimulation session. This comprised a range of potential side effects and allowed the participant to add any unpleasant effect they had perceived (Appendix 4.4). The questionnaire was used to compare published side effects with those observed in the trial population.

4.11 Randomisation

4.11.1 Sequence generation

The sequence was generated by an independent researcher using a computer randomisation of a list of 160 (80 programmed to trigger a verum stimulation and 80 to trigger a sham stimulation) 5-digit stimulation codes that were used to set-off either the verum or the sham stimulation paradigm. More codes were produced than required according to the sample size calculation to allow for a block randomisation of 20 (Section 4.11.2). A 1:1 ratio was used to allocate equal numbers of participants to verum stimulation and sham stimulation.

4.11.2 Type of randomisation

Stratification based on pain intensity was required to achieve a minimum level of homogeneity in the verum and the sham stimulation group (Altman and Bland, 1999a; Roberts and Torgerson, 1998). During the 3-months preliminary phase, baseline pain ratings ranged between 5 and 90 mm on a 0-100 mm VAS (Appendix 4.1). ODI levels were more homogeneous with scores ranging between 3 and 25 points on a 0 to 50 point scale. Higher pain levels allowed for a greater range of improvement and were, therefore, an important confounding factor that needed to be distributed evenly to both groups (Altman and Bland, 1999a). Stratification was achieved by randomising the 160 stimulation codes into 2 lists: one for participants with a VAS baseline score of 0-50 mm and 1 for participants with a VAS baseline score of 51-100 mm (Zelman et al., 2003). This resulted in 2 randomised lists, each comprising 40 verum codes, and 40 sham codes.

During the computer randomisation procedure, block randomisation was conducted to ensure equal numbers of sham and verum stimulation at several time-points, e.g. if the trial had to be discontinued at any given time-point due to the stopping guidelines (Doig and Simpson, 2005). Permuted blocks of 20 were chosen to allow for adequate

allocation concealment despite the block randomisation (Altman and Bland, 1999a; Herbert, 2005; Meinert, 1986; Schulz and Grimes, 2002).

4.11.3 Allocation sequence concealment

The sequence generation and randomisation procedures described in Sections 4.11.1 and 4.11.2 and the nature of the stimulation codes ensured an unbiased intervention allocation since neither the participant, nor the researcher who conducted the recruitment and intervention, was able to predict to which group the participant was allocated.

4.11.4 Implementation

The randomisation list was generated by an independent researcher and the list that identified number codes for verum and sham stimulation was kept in a locked cabinet until data analysis was completed. Participants were enrolled by telephone by the researcher as soon as they had been recommended (by the back pain clinic team) to participate in the CBT. If patients were willing to participate in the trial, an appointment for an informed consent meeting was made, during which patients received all information regarding the trial and had the opportunity to ask questions. Those who agreed to participate signed the informed consent form and completed the baseline set of questionnaires - including pain measurement on a 0-100 mm VAS. The level of pain indicated what code list (high or low pain intensity) was accessed for the stimulation code for this participant (Section 4.11.2 for details).

4.12. Blinding

The pre-programmed stimulation paradigms (corresponding with the 5 digit number codes) allowed blinding of both, the participant and researcher, applying the stimulation. As described in Section 4.5.2, the sham intervention was designed to mimic cutaneous perception of the verum condition by producing an initial 30 second stimulation phase identical to that of the verum condition but too short to result in neurophysiological changes. The success of blinding was assessed by asking the participant (after each stimulation) which mode of stimulation they believed they had received (Fergusson et al., 2004).

Blinding of the researcher who provided the intervention was achieved by pre-programming the stimulator to either deliver a verum or a sham stimulation according to a 5 digit number code. One code per participant was used according to a list of 160 randomised codes (Section 4.11.2). The machine display was identical during verum and sham stimulation to further support successful participant and researcher blinding.

Blinding during the statistical evaluation of the collected data was achieved by labelling participants as "Group A" and "Group B" after the data collection was completed. For this purpose, an independent researcher received the list of stimulation codes that triggered the sham or the verum procedure. The independent researcher identified the stimulation code for each participant and exchanged it for the labels "A" and "B". The researcher remained blinded until the final analyses had been conducted.

4.13 Statistical methods

4.13.1 Participant flow

Following the recommendations of the CONSORT statement, participant flow was documented as a flow diagram, indicating the numbers of potential participants who were assessed for eligibility, the numbers randomised and the numbers of participants analysed at each pre-specified time-point (Schulz et al., 2010).

4.13.2 Intention-to-treat (ITT) principle

Intention-to-treat analysis is important to evaluate the clinical effectiveness of an intervention because it a) maintains the random allocation to intervention groups; and b) allows for deviations from the protocol that might be typical for a clinical setting (Hollis and Campbell, 1999). Full ITT analyses can only be conducted when outcomes for all randomised participants (including those who withdrew from the trial) are available (Higgins et al., 2011a). Since this is rarely the case in clinical trials, following ITT principles were identified for the purpose of the planned RCT:

- As recommended by the CONSORT 2010 statement (Schulz et al., 2010) as much information as possible was obtained on reasons for withdrawing from the trial.
- The double-blinded trial design did not allow participants to switch intervention groups, fulfilling a main criterion of the ITT principle.
- Statistical analysis was conducted on all available data from all participants.

4.13.3 Missing data

To keep missing data to a minimum, participants were contacted twice if they did not return a set of questionnaires (Section 4.8.2). Following the ITT principle (Section 4.13.2) participants who discontinued the trial were asked to provide follow-up data at the same time-points as participants who completed the trial.

Data were considered to be missing at random if baseline data on primary outcome measures (VAS pain and ODI) were not significantly different (using 5% level of significance) between participants who continued the trial and participants who discontinued before the second primary endpoint (post CBT) was reached. A further criterion was that missing data on primary outcome measures had to be balanced across intervention groups (Herman et al., 2009; Hollis and Campbell, 1999; Polit and Gillespie, 2009). The number of missing data on primary outcome measures was compared with the drop-out allowance rate from the sample size calculation. If data were missing at random and did not exceed the drop-out allowance, a complete case analysis was conducted to avoid additional variance induced by missing data imputation (Groenwold et al., 2012; Wood et al., 2004). In the situation that one of these assumptions was not met, a worst-best-case-scenario was anticipated followed by a sensitivity analysis of both results (Lachin, 1999).

4.13.4 Analysis of baseline and demographic data

Number of participants, gender, medication taken within the past 24 hours, duration of back pain, first onset of back pain and baseline values for primary and secondary outcome measures were computed and presented as a table to allow comparison of the groups at baseline. Continuous data were calculated as group mean values with standard deviations and minimum / maximum values provided as an indicator for variability within the data (Howell, 2002, p.41-56). For the outcome measure bothersomeness, the median was calculated and upper / lower quartiles as well as minimum / maximum values were provided (Howell, 2002, p.41-56). Following the

CONSORT recommendations, baseline differences between the 2 groups (verum and sham stimulation) were not analysed statistically (Schulz et al., 2010).

4.13.5 Primary analyses

The main analyses were conducted at an alpha level of $p<0.0125$ (calculation reported in Section 4.9), to adjust for the 2 primary outcome measures (VAS and ODI) and the 2 endpoints of primary interest (post stimulation and post CBT) (Section 4.8) (Turk et al., 2008). The outcome of the trial was regarded statistically significant if one of the primary outcome measures had a statistically significant result at one of the 2 primary endpoints. To assess the effectiveness of tDCS after the stimulation period and after the CBT, a general linear model was fitted for each of the 2 primary outcome measures (VAS and ODI) at each of the 2 primary endpoints (post stimulation and post CBT), using post intervention values as the dependent variable and pre-intervention values as covariates (ANCOVA) (Twisk and Proper, 2004; Vickers and Altman, 2001). Based on a recent systematic review of high methodological quality on prognostic factors for CLBP (Verkerk et al., 2012), no additional covariates were added to the statistical model. The authors identified a wide range of prognostic factors for pain and disability (and return to work as well as quality of life) in the literature but the methodological quality of the available evidence was low. No single factor showed consistent evidence that justified its inclusion into the statistical model (Adams et al., 1985; Verkerk et al., 2012).

Normality, homogeneity, and Levene's test of equality of error variances were conducted to assess whether assumptions for ANCOVA testing were met (Hollis and Campbell, 1999, p.397). If the assumption of sphericity was violated (Mauchly's Test), Greenhouse-Geisser corrected values were reported (Field, 2009, p.476). It was pre-determined that multilevel models (Section 4.13.6.3) would be used as primary analyses for any outcome measures that did not satisfy the assumptions for ANCOVA testing. Results from ANCOVA analyses were reported as F-values (degrees of freedom) and p-values as well as 99% CI for between group differences with Sidak adjustment for multiple comparisons (Field, 2009, p.402 and 417).

4.13.6 Secondary analyses

Secondary analyses were conducted at an exploratory level and did not require further adjustment of the alpha level for multiple testing (Turk et al., 2008). Any statistically significant and clinically meaningful results of ancillary analyses were presented and discussed as exploratory to inform future trial designs.

4.13.6.1 Effect of tDCS on secondary outcome measures at primary endpoints

To explore the effect of tDCS compared to sham stimulation on each of the secondary outcome measures, ANCOVA analyses were conducted using baseline values as covariates (Section 4.13.5). Despite the categorical nature of outcome measures (questionnaires with categories that participants were required to tick or 5-point Likert scales) parametrical analyses were conducted. This approach had been justified based on the Central Limit Theorem, and by re-analysing data using various analysis approaches that indicated the robustness of parametric testing (Norman, 2010).

4.13.6.2 VAS pain on each day of the stimulation

Following reported pain reducing effects after varying numbers of stimulation days (ranging from a single stimulation (Boggio et al., 2009a) to 10 days of stimulation (Soler et al., 2010; Valle et al., 2009)), mean values of VAS and standard deviations were calculated for each day of the stimulation. Between group differences were calculated for each stimulation day using t-tests (independent groups, 2-sided) to evaluate whether an effect can be observed after 1, 2 or more days of the stimulation.

4.13.6.3 Effect of tDCS on VAS pain and ODI over time

To evaluate the intervention effect on the primary outcome measures over time, a separate, multilevel model was fitted for VAS and for ODI, including all assessment time-points. All secondary outcome measures (that were reported as prognostic factors for pain and disability in CLBP (Verkerk et al., 2012)) were entered into the statistical model in a stepwise manner (forward approach) and removed if not statistically significant (Draper and Smith, 1981). The order of the entry was based on a high quality systematic review of prognostic factors for CLBP (Verkerk et al., 2012). Factors that were identified by systematic review authors as consistently reported by 2 or more trials were entered into the model first, followed by factors reported by 1 high quality trial and, subsequently, factors reported by 1 low quality trial. These factors as well as group (verum / sham) were added to the model as fixed effect factors while time, time^2 and time^3 were entered as random factors to model a non-linear trend over time (Twisk et al., 2013). Bonferroni corrected post-hoc t-tests were conducted if a significant interaction of group by time was identified for VAS or ODI (Field, 2009, p.372-374).

4.13.6.4 Effect of tDCS on secondary outcome measures over time

The secondary outcome measures FfBH, the 2 domains of FABQ, RAND 36 subscales, HADS (anxiety, depression), bothersomeness and PPSI were evaluated by building a multilevel model with time, time^2 and time^3 as random factors and group (verum / sham) as a fixed effect factor. No additional factors were entered into the model since no consistent evidence supported any specific covariate to strongly influence FfBH, FABQ, RAND 36, HADS, bothersomeness, and PPSI. Although a range of outcome measures had been used in the same trials, a correlation between factors was rarely conducted and causative influences of one outcome measure on another have not been reported (Bean et al., 2013; Kovacs et al., 2007b; Lang et al., 2003). Bonferroni corrected post-hoc t-tests were conducted if a significant interaction of group by time was identified for any secondary outcome measure

(Field, 2009, p.372-374). All analyses were performed using SPSS 18 for Apple Macintosh (SPSS, Inc., Chicago, IL).

4.13.7 Evaluation of side effects

To document any observed side effects, participants were required to complete a standardised questionnaire, routinely used for tDCS trials (Jurgens et al., 2012; Luedtke et al., 2012a), after each stimulation session. Answers were entered into a table. Observed side effects together with their intensities were presented as total numbers of observed side effects and percentages of observations in relation to the total number of available responses.

4.14 Ethical Considerations

Ethical approval was obtained from both the University of Birmingham (application number ERN_10-0863) and the Aerztekammer Hamburg (the local authority for medical trials in Hamburg, project number PV 3297). The trial was conducted according to the recommendations from the declaration of Helsinki 2008 (WMA, 2008) and following the ICH good clinical practice guideline (ICH, 1996). Ethical approval documents are attached as an appendix (Appendix 4.5).

4.14.1 Participant information and consent

Eligible patients were given an information brochure designed according to the ICH GCP Chapter 7 (ICH, 1996) on the proposed study and contacted via telephone prior to the initial appointment. Patients who were willing to participate in the study were given an initial appointment. At the initial appointment, study procedures were explained and the patient received the Participant Information Sheet. The patient was given the opportunity to clarify any issues arising from the study before signing a consent form. A copy of the Participant Information Sheet and consent form is

attached as an appendix (Appendix 4.6). No information regarding the trial was concealed from the participants before or during the study period apart from the participant's group allocation (verum or sham tDCS). After the final follow-up assessment, participants were offered to be informed of their group allocation. Trial results were sent to participants following statistical analysis of the data.

4.14.2 Participant withdrawal

The consent form contained a section explaining that the participant could withdraw from the study at any given time, without having to give any reasons and without any consequences for their ongoing management. Participants who withdrew from the study continued their ongoing management and had the option that their personal data be removed from the project. Any data that had already been collected for research purposes was used for the statistical analysis only with the participant's consent (ICH, 1996).

4.14.3 Compensation

Participants were compensated for additional travel costs during the stimulation phase (funded by the Institute of Systems Neurosciences, Hamburg). Participants who withdrew from the trial were compensated for travel expenses that had arisen prior to the date of withdrawal.

4.14.4 Confidentiality

Participant data were pseudonymised by assigning an individual study number. The list that matched participant names and study numbers was kept in a locked cabinet in a locked research room. Only the researcher had access to these data.

4.14.5 Storage access and disposal of data

Questionnaires and paper copies of assessment sheets were kept in a file in a locked cabinet in a locked research room to which only the researcher had access. Electronic data were kept on the password secured personal laptop of the researcher, regular backups were made and kept password secured. According to the ICH Good Clinical Practice Guidelines (ICH, 1996) and University of Birmingham requirements, essential data will be kept in the secure University Hospital storage facilities (in Germany) for 10 years after the publication of the trial results.

4.15 Trial protocol

To ensure complete transparency of trial procedures, a trial protocol was developed prior to the commencement of the data collection and published in an open access journal (Luedtke et al., 2011) (Appendix 4.7). The trial was registered with the current controlled trial register (ISRCTN8987487). This allowed a comparison between the proposed study protocol and the published results as the only reliable measure of a risk of bias induced by selective outcome reporting (DeAngelis et al., 2004).

Chapter summary

This chapter detailed the trial methods and procedures as they were planned and published in the trial protocol. These included the trial design, eligibility criteria for participants, settings, location and standard care at the back pain clinic, intervention and sham intervention, the selection process of the primary and secondary outcome measures, type and implementation of randomisation, methods of blinding of participants and researcher, planned statistical analyses and ethical considerations.

5. CHAPTER

FEASIBILITY STUDY TO EVALUATE PRACTICAL ASPECTS OF TRIAL PROCEDURES AND ACCEPTABILITY OF THE TDCS INTERVENTION

The previous chapter detailed the methods and procedures for a RCT. A feasibility study was conducted as a precursor to the main trial to ensure that all procedures could be implemented as planned and to investigate how patients perceived tDCS as an intervention for pain. This chapter details the feasibility study and concludes by justifying any changes required to trial procedures.

5.1 Introduction and objectives

Electrotherapy including direct current stimulation is traditionally used by physiotherapists internationally. However, the motor cortex as a target tissue is not a standard physiotherapy approach. tDCS has only recently been introduced as a physiotherapy intervention in a pilot study of 8 participants (O'Connell et al., 2013). The authors did not report how participants perceived and whether they accepted tDCS as a physiotherapy intervention for NSCLP. To identify recruitment barriers and to assess the potential of tDCS as a future intervention for NSCLBP, it was important to evaluate patients' views on this new management approach before the commencement of the main trial. Additionally, trial design and procedures (detailed in Chapter 4 and published in BMC Musculoskeletal (Luedtke et al., 2011)) required evaluation to ensure that it was feasible to conduct the main trial as planned within the available time frame.

Although the terms pilot study and feasibility study are often used interchangeably (Thabane et al., 2010), the objectives listed below reflect common aims for feasibility studies (Lancaster et al., 2004; National Institute for Health Research, 2014). Pilot studies focus more on the evaluation of outcome measures to determine the required sample size or to test new treatment approaches for safety and effect, whilst feasibility studies focus on the practicability of procedures, the willingness of potential participants to be in the trial, the recruitment and retention rates and do not include a statistical analysis of outcome measures (Arain et al., 2010; Lancaster et al., 2004; www.netscc.ac.uk/glossary). A preliminary pilot study was not required as sufficient data from trials with similar interventions and trial populations (Fregni et al., 2006a; Kääpä, 2008), as well as minimum clinically relevant change recommendations for the primary outcome measures (Lauridsen et al., 2006) were available to calculate required sample size. Also, large safety trials and systematic reviews demonstrated that no side effects were likely to occur (Borckardt et al., 2011; Brunoni et al., 2011a; O'Connell et al., 2010; Poreisz et al., 2007).

This feasibility study, therefore, focussed exclusively on the practicability of procedures for the main trial to ensure that data collection could be carried out as planned. It included patient interviews to evaluate how patients perceived and whether they accepted trial procedures and tDCS as a physiotherapy intervention. The following key objectives were identified for the feasibility study:

Objective 1:
To evaluate the practicability of trial procedures.

Objective 1 encompasses the following more specific objectives:

a. Determine the number of patients meeting the inclusion / exclusion criteria.
b. Assess the recruitment rate and thereby estimate the duration of the data collection period for the main trial.
c. Evaluate whether allocation was successfully concealed and whether randomisation procedures were practicable.

d. Identify recruitment barriers for potential trial participants.
e. Assess the patient information sheet and consent form for comprehensibility by potential trial participants.
f. Assess the retention rate of trial participants up to the second primary endpoint of the main trial (after the CBT programme).

Objective 2:
Assess the participants' views on the trial procedures and the intervention (tDCS) to determine acceptability.

5.2 Design of the Feasibility Study

The feasibility study was conducted using the methods for the planned RCT (Chapter 4), including the use of defined inclusion / exclusion criteria, randomisation to verum or sham intervention, and blinded assessment of outcomes at 2 primary endpoints (post tDCS and post CBT). The realistic time frame for the feasibility study did not allow collection of long-term follow-up data. Consequently, drop-out rates for the long-term assessments were not estimated. This limitation was deemed acceptable since the feasibility study objectives focused exclusively on the practicability of trial procedures that were identical for the post CBT assessment and the longer-term follow-up time-points. Losses of longer-term follow-up data were anticipated to reflect those from published trials on CBT for CLBP that included trial populations and data collection methods comparable to those of the main trial (Kääpä, 2008; Lamb et al., 2010).

5.2.1 Methods used to evaluate the practicability of trial procedures (objective 1)

Although a minimum sample size of 12 per group has been recommended for pilot studies that aim to estimate effect sizes or standard deviations (Julious, 2005), no clear recommendations for feasibility studies were found in the literature. The objective of this feasibility study was to evaluate the practicality of the proposed

procedures. Hence, a realistic duration of 10 weeks was chosen – with 6 weeks being allocated to participant recruitment and a further 4 weeks added to allow the completion of the CBT programme following the tDCS intervention. All recruited participants were randomised and treated according to the planned procedures for the main data collection phase (Sections 4.5; 4.6; 4.11). To meet the objectives defined in Section 5.1 pre-specified data were recorded (Table 5.1).

Table 5.1 Data recorded to meet objective 1

Specific objectives	Data recorded
a.	Number of contacted patients who fulfilled the eligibility criteria during the 6 weeks recruitment period.
b.	Number of patients who consented to participate in the study.
c.	The stimulation type that each individual participant believed they had received on each day.
d.	Questions asked and any concerns stated by patients during telephone recruitment and reasons provided by patients during telephone recruitment for not consenting to participate in the trial.
e.	Questions asked about the information brochure and the consent form.
f.	The number of participants who discontinued the study, the time-points at drop-out, and the reasons for withdrawing.

5.2.2 Methods used to assess participants' views on trial procedures and intervention (tDCS) to determine acceptability (objective 2)

Semi-structured interviews (n=4) were conducted to gain detailed information regarding patients' views on tDCS and to evaluate their acceptance of the proposed trial procedures and of tDCS as an intervention for CNSLBP. This interview style was chosen to pre-specify questions on procedure and intervention acceptability while still allowing interviewees to determine the type and amount of information provided for each topic (Green et al., 2008).

No literature was identified that indicated the number of interviews required for the evaluation of the acceptability of an intervention. Four interviews were considered adequate to provide this information due to the depth and richness of data generated through the open ended interview questions (Ogden and Cornwell, 2010). The 4 participants (2 male / 2 female) were selected according to purposeful stratified sampling (Patton, 1990, p.168): Participants were selected who were evaluated as "good communicators" during recruitment and intervention. A 'good communicator' was defined as a person who asked questions and provided detailed information. Stratified sampling ensured that 2 participants had received verum stimulation and 2 sham stimulation to include experiences of both stimulation types.

The interview questions were designed after a literature search on acceptability of interventions (Ayala and Elder, 2011; Barnes et al., 2012; Cowley and Houston, 2003) and according to the study objectives. The interviews followed a pre-designed interview guide (Appendix 5.2) specifying the topics of interests and with a series of prompts to encourage elaboration of any given answer. For convenience, interviews were conducted by the researcher immediately after a participant's final day of the CBT within the CBT setting. Since this might reduce the credibility of the information provided (Al-Busaidi, 2008), participants were reminded that information from the interviews was exclusively used for this study and did not influence their future management.

Interviews were conducted and transcribed verbatim in German. They were recorded on a digital voice recorder, downloaded onto a personal computer, transcribed, and analysed by the researcher. A semantic level of transcription was chosen, since for the feasibility purpose of this study only the factual contents of the interviews and not the verbal expression and body language were analysed (Gibbs, 2008, p.14).

5.2.3 Data analysis

5.2.3.1 Evaluation of practicability of trial procedures

Recorded data were analysed to meet the objectives defined in Section 5.1 (Table 5.2).

Table 5.2 Methods of data analyses to meet objective 1

Specific objective	Method used to address objective
a. and b.	The recorded number of eligible patients and the number of patients contacted during the 6 weeks recruitment period for the feasibility study were used to calculate the anticipated recruitment rate. This information was used to estimate the duration of the main trial that required a total sample size of 135 patients.
c.	Allocation concealment and blinding were assessed through the Kappa coefficient, after the researcher was unblinded following completion of the feasibility study (Landis and Koch, 1977; O'Connell et al., 2013).
d.	Questions asked and concerns stated during telephone recruitment, as well as reasons provided for not participating in the study, were used to adapt the wording and the aspects covered during telephone recruitment (Appendix 5.1.1).
e.	Questions asked about the information brochure and consent form were used to adapt the topics covered during the informed consent meeting (Appendix 5.1.2).
f.	The number of participants who discontinued the study was used to estimate the anticipated drop-out rate for the main trial. Reasons provided for discontinuing the study were documented and evaluated for possibilities to meet special requirements such as extended treatment hours and funding to cover travel costs.

5.2.3.2 Evaluation of the data on acceptability of tDCS

Transcribed interviews were analysed thematically by coding the text line by line (Gibbs, 2008, p.52). An open coding approach was chosen to allow themes to develop from the data without fitting them into preset coding frames (Green and Thorogood, 2009, p.203). Consequently, the dominantly descriptive codes were transformed into more analytic concepts and collated across interviews. Each group of concepts was provided with a global title, and regarded as a key theme. Anonymous translated examples from the texts were provided for each theme to illustrate and compare patients' views (Gibbs, 2008). All relevant data were included in this process to avoid selective reporting (Gibbs, 2008).

5.2.4 Ethical considerations and quality of qualitative research

All participants were informed of the procedures to be used in the feasibility study, had the opportunity to clarify questions with the researcher in an informed consent meeting, and signed an informed consent form if wishing to participate in the study. Privacy, confidentiality, and identity of participants were protected throughout the study.

Quality of the data collection and analysis regarding validity, reliability, and generalisability (Gibbs, 2008, p.97-104) was supported by the following strategies:

- Audio recordings and transcribed data were compared repeatedly to ensure that transcription did not introduce erroneous data.
- Participant statements selected to support concepts and themes were interpreted in relation to the previous and following sentences to avoid misinterpretation of statements separated from the context.
- To support the reliability of the data, variations of and opposing statements on the same topics were actively sought.
- Although a sample size of n=4 is too small to allow a representativeness of findings, the sampling strategy of 2 male and 2 female participants as well as

2 participants from the sham and 2 participants from the verum group allowed for some variety of experiences and perceptions.

- Participants were selected from the same population of NSCLBP patients as the participants from the main trial.

5.3 Results

5.3.1 Practicability of trial procedures (objective 1)

Six to 8 eligible patients attended the back pain clinic per fortnight. If all eligible patients were to participate in the main trial, the sample size of 135 could be reached within 34-45 weeks. Twenty participants were contacted, however only 8 patients agreed to participate in the feasibility study during the 6 week recruitment period. Hence, the data collection period for the main trial was estimated as 102 weeks. Whilst fulfilling all defined inclusion criteria, some participants scored very low on the 2 primary outcomes at baseline, with 4 participants having pain scores below 15/100 and 3 participants scoring below 8/50 for disability. Such low baseline scores allowed little room for improvement (Table 5.3). Hence minimum scores for pain and disability at baseline were required as inclusion criteria for the main trial.

Using 5-digit number codes for the randomisation procedure achieved both allocation concealment and blinding in the feasibility study. The effectiveness of participant blinding was expressed as a Kappa value of agreement. The resultant Kappa= 0.19 (with SE=0.16; and 95% CI -0.122 to 0.500) showed poor agreement between perceived group allocation and intervention received (Cohen, 1960), indicating effective participant blinding (Table 5.4).

Recruitment barriers for potential participants were expressed by the questions asked during telephone recruitment. These included:

- Are there any known side-effects of tDCS? (n=11)
- How flexible are the available intervention times? (n=9)
- Does the intervention hurt? (n=6)
- How likely is it that I will perceive a positive effect? (n=5)

Further barriers and reasons stated for not participating were:

- time (n=7)
- travel costs (n=2)
- distance to the study location (n=1)
- fear of electrical currents (n=1)
- no interest in research (n=1)

Based on the reasons provided (during telephone recruitment) for not participating in the trial, time seemed to be the most important factor for not participating (n=7): Some patients had arranged appointments with their own doctor, work meetings or other commitments for the week during which they should have been receiving tDCS. The costs for train tickets or fuel for the 5 additional tDCS days deterred 2 patients from participating. A further patient lived in a different city and was planning to stay in a hotel for the duration of the CBT and could not afford to arrive 5 days earlier for the tDCS.

The information brochure and consent form prompted patients to ask questions such as:

- Why do some participants receive sham stimulation?
- Will you tell me afterwards whether I had the real stimulation?
- Can I have the overall trial results once the trial is completed?

The retention rate at the second primary endpoint after the CBT was 7 out of 8 participants. The 1 withdrawal occurred after the first stimulation and was due to

conflicting appointments. If 1 in 8 participants were to drop-out in the main trial, this would result in 16.9 out of 135 drop-outs after the CBT or a 12.5% drop-out rate.

Table 5.3 Participant data at baseline

Participant number	Male/ Female	Age (years) at study entry	Duration of back pain (months)	Oswestry Disability Index (0-50 points)	Pain intensity (0-100 mm)
P01	f	38	156	22	21
P02	m	38	7	14	10
P03	f	51	6	4	3
P04	m	37	24	0	0
P05	m	44	120	7	75
P06	f	45	6	9	12
P07	f	63	240	20	77
P08	f	32	6	21	52

Footnotes: f=female; m=male

Table 5.4 Assessment of the success of blinding. Table for kappa statistics.

	Number of verum stimulations	Number of sham stimulations
Number of verum ratings	18	8
Number of sham ratings	7	7

5.3.2 Patient acceptability of trial procedures and tDCS (objective 2)

All 4 selected participants agreed to be interviewed. Baseline characteristics of the interviewees are presented in Table 5.5.

Table 5.5 Interview participants' data at baseline

Participant number	Male/ Female	Age (years) at study entry	Duration of back pain (months)	Oswestry Disability Index (0-50 points)	Pain intensity (0-100 mm)
I01	f	44	24	25	80
I02	m	48	6	11	55
I03	f	28	42	7	35
I04	m	54	10	9	38

Footnotes: f=female; m=male.

Two key themes were identified from the interview data (Table 5.6):

- Attitudes towards tDCS (positive, neutral, negative) as a therapy for NSCLBP.
- Feedback on information received during telephone recruitment and informed consent meeting.

Participants used different concepts to illustrate their attitudes towards tDCS. These included hope, curiosity, trust, open-mindedness, acknowledgement of the importance of research and acceptance of side effects. When asked whether there was anything else that they would like to communicate regarding trial procedures, a second theme emerged as participant feedback on the information received during telephone recruitment and at the informed consent meeting. Concepts included perceived intelligibility, comprehensiveness, and volume of information.

Overall participants showed mainly positive attitudes towards tDCS as an intervention for pain reduction and were willing to accept mild side effects, such as a sensation of burning under the electrodes. The information provided was perceived as comprehensive and intelligible, however, the volume of information was regarded as overwhelming by 2 participants. Participants were satisfied with the therapy setting despite some discomfort associated either with the stimulation itself (e.g. itching or sensation of burning under the electrode) or with the position during the stimulation (e.g. back pain increased in lying position) (Table 5.6).

Table 5.6 Findings from participant interviews

Key themes	Concepts	Examples from text
Positive attitude towards tDCS	Hope	"....a new chance" (I01)
		"I was glad that I was asked to participate. It is an additional module to my therapy that may have a positive effect on my complaints" (I03)
	curiosity	"....one can always try, can't I" (I02)
		"I was curious..., excited by what you told me on the phone" (I03)
		"I wanted to find out whether it would show a result" (I04)
	trust	"I think you wouldn't do anything that would harm my back...therefore...I totally trust you" (I02)
	acknowledging importance of health research	"Research is important for all of us, I want to make new therapies public, want to make therapy accessible for everybody" (I01)
	pleasantness of stimulation and therapy setting	"In the beginning there was always a prickly itchy sensation that stopped after a few seconds, at least that is what I felt. After that it was simply relaxing" (I04)
		"...no, that was perfect, couldn't have been any better" (I02)
		"good atmosphere, totally ok" (I03)
Neutral attitudes towards tDCS	open-mindedness	"I was completely laid-back and without any expectations because I find it important to approach things without any reservations" (I01)
		"I would honestly try anything that is not dangerous and that my back may benefit from" (I03)
		"It doesn’t hurt to try something new" (I04)

Table 5.6 - continued 1

Key themes	Concepts	Examples from text
Negative aspects of tDCS	acceptance of uncomfortable aspects	"It wasn't pleasant, not really unpleasant, it didn't hurt, but it wasn't nice. But as you said in the beginning, the unpleasantness got less and less over time, this itching, tingling, pricking.....somehow...but it wasn't a problem" (I03)
		"yes, lying hurts, sitting hurts, too, but somehow we had to find a position, it was ok, you couldn't do anything else than those blankets and pillows to make me more comfortable, it's me...nobody can influence that" (I01)
Comments on verbal and written information received		"... knew in advance what would happen after what you told me on the phone" (I01)
		"clearly written" (I01)
		"that was comprehensible, no problems with that"(I02)
		"had to read some passages a bit more slowly, somehow, but that was ok" (I03)
	comprehensiveness	"Maybe, if I could have wished for anything, I would have liked to hear some experiences from other patients who had tried the intervention, whether it worked for them or not" (I04)
		"...it didn't say whether 5 interventions can do anything at all" (I04)
		"Before the procedure when you tried to find the right spot on my head, I would have liked to know more, like, what is going to happen..it would make some people more relaxed about what you are doing" (I04)
	volume	"too much paper....read it all...just got on with filling out the forms" (I01)
		"I didn't think it was too much with the questionnaires at all. It was just ticking boxes, more than reasonable for something that might help me in the end" (I03)
		"well, I didn't go into depths with reading all the information....I know where I put the documents and...I scanned them on Sunday" (I04)

Footnotes: The number in brackets under “Example” refers to the number of the individual participant: I01=interviewee 1; I02=interviewee 2; I03=interviewee 3; I04=interviewee 4.

5.4 Discussion of the results and consequences for the main trial

5.4.1 Practicability of trial procedures (objective 1)

The results of this feasibility study indicated that minor changes were required to the planned procedures for the main trial. Low levels of pain and / or disability at baseline in some participants required the introduction of minimum levels of pain and disability as inclusion criteria. Setting the minimum levels for participant inclusion in the trial as 15 mm on the 0-100 mm VAS pain scale and 8 points on the 0-50 points ODI scale would provide the potential to detect change that was clinically relevant in all participants (Maughan and Lewis, 2010; Ostelo et al., 2008).

With 6-8 eligible patients every fortnight and a recruitment rate of approximately 35%, the required total sample size of 135 patients for the main trial would be recruited within 96-128 weeks. The final follow-up would be at 24 weeks after the 4-week group programme, resulting in a total data collection period of 125-157 weeks.

Allocation concealment and blinding could not be differentiated in this study and were expressed as 1 kappa value for all intervention days, to gain an overall impression of the success of blinding. Individual kappa values for each day showed that agreement varied (day 1 kappa=-0.429; day 2 kappa=0.25; day 3 kappa=0.467; day 4 kappa=0.75; day 5 kappa=-0.429) without indicating a systematic pattern; most importantly participants did not learn to distinguish sham and verum stimulation over time. However, daily agreement rates were based on 8 ratings per stimulation day. Larger sample sizes might provide different results.

Funding was obtained for participant travel costs to cover the 5 days of stimulation, to reduce recruitment barriers for potential trial participants. Furthermore, a research assistant was employed to increase available intervention hours. Wording on known side-effects of tDCS, flexibility of available intervention times and research results on

the effect of tDCS for pain reduction were adapted to meet participant questions in the standard operating procedures (SOP) for the telephone recruitment (Appendix 5.1.1). Explanations about the necessity of a sham stimulation group were added to the SOPs for the informed consent meeting (Appendix 5.1.2), as well as the option for participants to provide an email address to be informed of their group allocation and the overall trial results upon completion of the trial. The drop-out rate of 12.5% across groups after the CBT was lower than the drop-out rate used for the sample size calculation (Section 4.9) for the main trial. The longer duration of the main trial is likely to result in more drop-outs and missing data than the brief feasibility phase. A systematic review of drug trials reported that the drop-out rate increased with the duration of the trial (Wahlbeck et al., 2001). To ensure sufficient statistical power for the effectiveness of tDCS on pain and disability reduction in NSCLBP, the original sample size calculation based on large trials with long-term follow-ups was maintained.

5.4.2 Acceptability of trial procedures and tDCS (objective 2)

None of the trials on tDCS had evaluated participant acceptability of the intervention (Antal et al., 2010; Boggio et al., 2009a; Fenton et al., 2009; Fregni et al., 2006a, 2006b; Mori et al., 2009; Soler et al., 2010; Valle et al., 2009). However, the low rate of reported side effects and the low drop-out rates reported in tDCS trials provided an indicator that participants generally accepted tDCS as an intervention for the reduction of pain (Boggio et al., 2009a; Fenton et al., 2009; Fregni et al., 2006a, 2006b; Mori et al., 2009; Soler et al., 2010; Valle et al., 2009). However, for the feasibility of the planned main trial it was important to evaluate how participants perceived trial procedures and tDCS as an intervention. Overall, participants stated a positive attitude towards all study procedures and tDCS as a intervention for NSCLBP within a physiotherapy setting. The concepts of hope, curiosity, and trust, and the more neutral concept of open-mindedness, emerged from participants' statements. Hence, results indicated that attitudes towards tDCS as an intervention for NSCLBP will not limit the recruitment of participants for the main trial.

5.4.3 Limitations of the feasibility study

The small sample size, use of a single centre, and 1 interviewer limited the transferability of study findings. Furthermore, no long-term data could be collected within the short time-frame for the feasibility study. However, responses on intervention acceptability were consistent across the 4 interviewees.

C**hapter summary:**

This feasibility study was conducted to evaluate whether patients at the back pain clinic would accept tDCS as an intervention and participate in the main trial. In addition, it was designed to test the proposed trial design and procedures before commencement of the full trial. The observed low levels of pain and disability at baseline informed the incorporation of additional inclusion criteria on minimum levels of pain and disability for the main trial. All other procedures from the research protocol fulfilled practicability and feasibility criteria. Participants accepted trial procedures and tDCS as an intervention for NSCLBP.

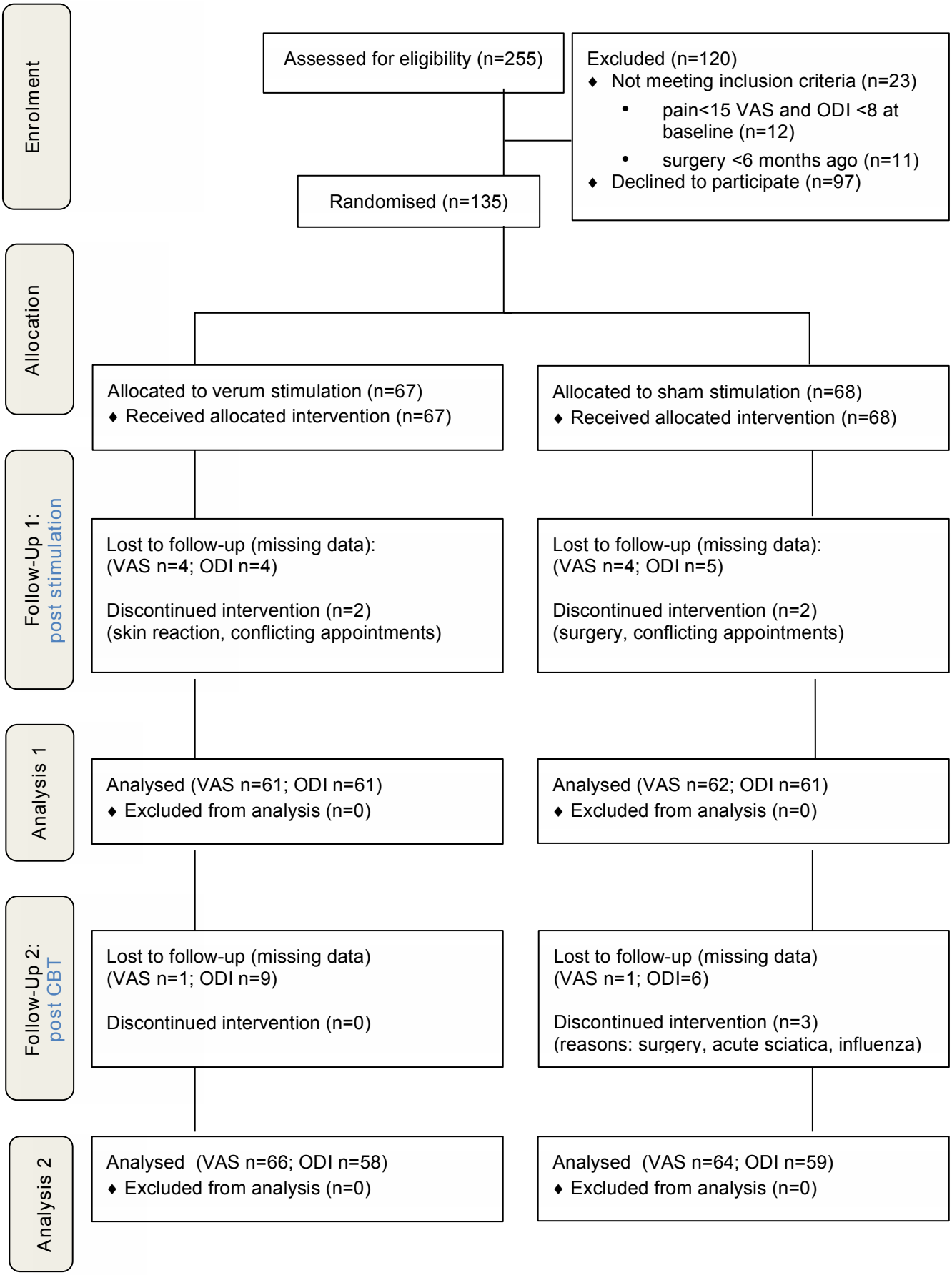
6. CHAPTER

RESULTS FROM THE RCT

This chapter details the participant flow through the RCT, states numbers and reasons for losses and exclusions, reports summaries of data collected on participant characteristics and all outcome measures at each time-point, and presents the results of the statistical analyses of primary and secondary outcome measures. It also states the frequency and type of side effects. The presentation of trial results followed the recommendations and format of the CONSORT Statement (Moher et al., 2010; Schulz et al., 2010).

6.1 Recruitment period and participant flow

Recruitment took place over 26 months (01.01.2011 to 01.03.2013). Two hundred and fifty five NSCLBP patients were telephoned and assessed for eligibility (Section 4.3) to recruit the required 135 participants. Of 232 eligible patients (ineligibility was due to recent spinal surgery and pain intensities lower than 15 mm on a 0-100 mm VAS), 97 declined to participate due to the additional time and travel required for the extra 5 visits to the back pain clinic (Figure 6.1). Two participants in each group discontinued the intervention during the stimulation phase. Reasons provided were skin reactions (n=1), conflicting appointments (n=2) and spinal surgery (n=1). None of the participants from the verum group and 3 participants from the sham group discontinued the CBT (reasons: acute sciatica, influenza, spinal surgery). Eighty nine participants (47 in the verum group and 42 in the sham group) completed assessments at all time-points (Figure 6.1). Telephone calls to participants who did not return questionnaires at follow-ups elicited reasons for non-intervention related health issues, and, did not want to complete any further questionnaires.


Enrolment
Assessed for eligibility (n=255)
Excluded (n=120)
♦ Not meeting inclusion criteria (n=23)
• pain<15 VAS and ODI <8 at baseline (n=12)
• surgery <6 months ago (n=11)
♦ Declined to participate (n=97)
Randomised (n=135)
Allocation
Allocated to verum stimulation (n=67)
♦ Received allocated intervention (n=67)
Allocated to sham stimulation (n=68)
♦ Received allocated intervention (n=68)
Follow-Up 1: post stimulation
Lost to follow-up (missing data):
(VAS n=4; ODI n=4)
Discontinued intervention (n=2)
(skin reaction, conflicting appointments)
Lost to follow-up (missing data):
(VAS n=4; ODI n=5)
Discontinued intervention (n=2)
(surgery, conflicting appointments)
Analysis 1
Analysed (VAS n=61; ODI n=61)
♦ Excluded from analysis (n=0)
Analysed (VAS n=62; ODI n=61)
♦ Excluded from analysis (n=0)
Follow-Up 2: post CBT
Lost to follow-up (missing data)
(VAS n=1; ODI n=9)
Discontinued intervention (n=0)
Lost to follow-up (missing data)
(VAS n=1; ODI=6)
Discontinued intervention (n=3)
(reasons: surgery, acute sciatica, influenza)
Analysis 2
Analysed (VAS n=66; ODI n=58)
♦ Excluded from analysis (n=0)
Analysed (VAS n=64; ODI n=59)
♦ Excluded from analysis (n=0)

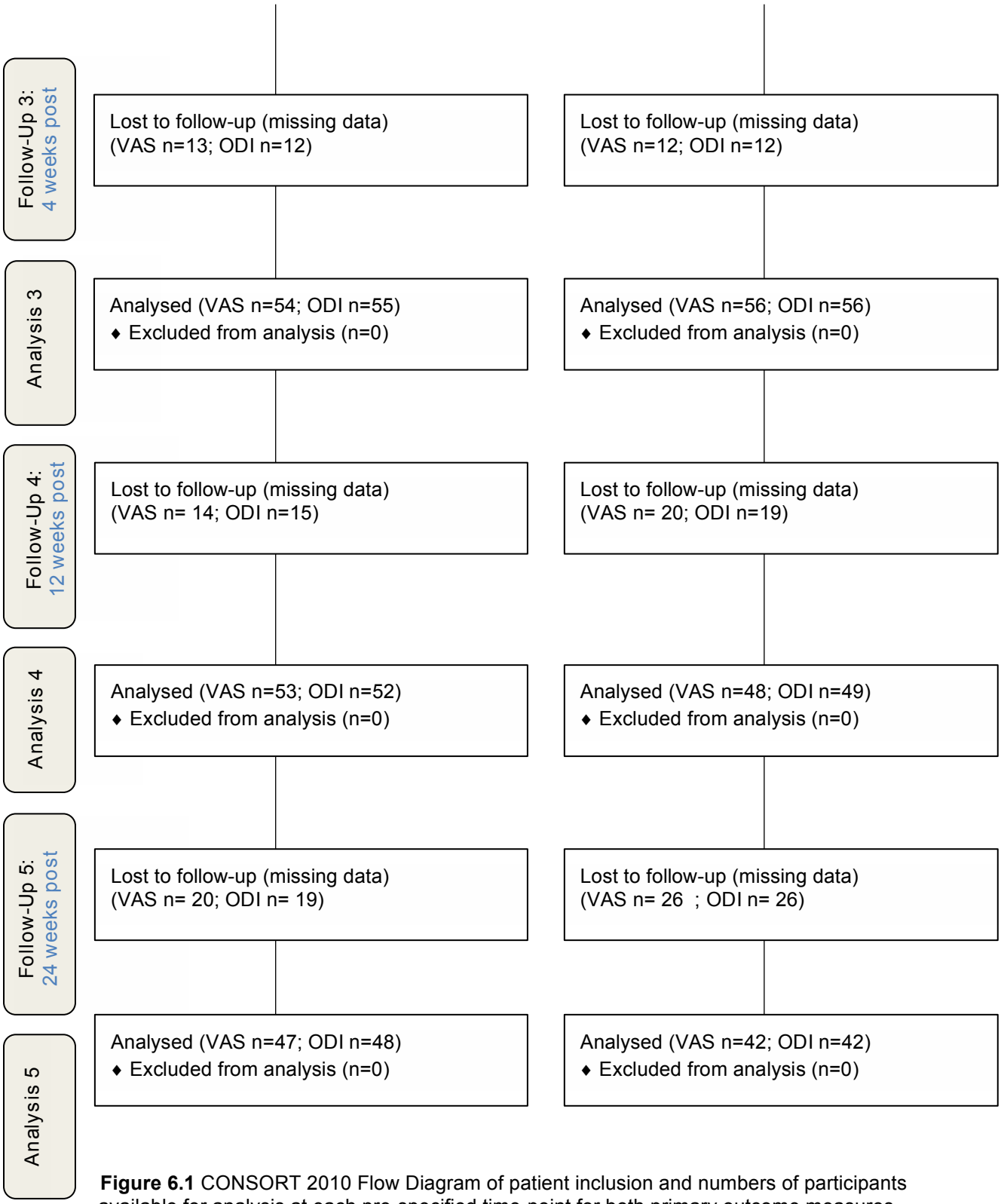


Figure 6.1 CONSORT 2010 Flow Diagram of patient inclusion and numbers of participants available for analysis at each pre-specified time-point for both primary outcome measures (Moher et al., 2010)

Footnotes: ODI=Oswestry Disability Index; **VAS**= visual analogue scale for pain

6.2 Baseline participant characteristics

6.2.1 Participant demographic and clinical characteristics

Sixty three (47%) of the 135 participants were female. The mean age of all participants was 45 years (SD 9 years; range 26-64 years). The mean duration of the current episode of LBP across all participants was 21 months (SD 40 months; range 6-240 months) and the mean first onset of LBP was 95 months ago (SD 115 months; range 6-600 months). Participant characteristics for each intervention group are given in Table 6.1

Table 6.1 Participant demographic and clinical characteristics at baseline

Participant characteristics		Intervention group	
		verum (n=67)	**sham (n=68)**
Females	n (%)	33 (49)	30 (44)
Age at study entry (years)	Mean (SD) Min^m, Max^m	45 (9) 26, 64	44 (10) 27, 62
First onset of back pain (months ago)	Mean (SD) Min^m, Max^m	98 (106) 6, 600	93 (125) 6, 384
This episode of back pain (months)	Mean (SD) Min^m, Max^m	23 (49) 6, 156	19 (29) 6, 240

Medication	**Pain medication:** n (%)		
	NSAIDS	43 (64)	34 (50)
	Week opioids	6 (9)	4 (6)
	Strong opioids	7 (10)	6 (9)
	Adjuvant medication n (%)		
	Antidepressants	3 (4)	3 (4)
	Muscle relaxants	1 (1)	1 (1)
	Anticonvulsiva	3 (4)	0 (0)
	Glucocorticoids	1 (1)	0 (0)
	Other medication: n (%)		
	Cardiovascular	9 (13)	9 (13)
	Asthma	3 (4)	2 (3)
	Thyroid	1 (1)	1 (1)
	Restless legs	1 (1)	0 (0)
	Hormone replacement	3 (4)	1 (1)
	Malaria	1 (1)	0 (0)

Footnotes: Max^{m} = maximum value; Min^{m}= minimum value; n=number; NSAIDS=Non-Steroid Anti-Inflammatory Drugs; SD=Standard Deviation.

6.2.2 Baseline data on primary and secondary outcome measures

The mean VAS pain intensity across groups at baseline was 48 mm (SD 19 mm). The mean disability across all participants was 16 points on the ODI (SD 6 points). Baseline characteristics by intervention group are shown in Table 6.2.

Table 6.2 Baseline data on primary and secondary outcome measures by intervention group

Baseline data on primary and secondary outcome measures	Intervention group	
	verum (n=67)	**sham (n=68)**
Primary outcome measures	Mean (SD) Min[m], Max[m]	Mean (SD) Min[m], Max[m]
VAS		
(0-100 mm)	48 (21) 15, 89	48 (18) 15, 84
ODI		
(0-50 points)	17 (6) 8, 32	15 (5) 8, 29
Secondary outcome measures	Mean (SD) Min[m], Max[m]	Mean (SD) Min[m], Max[m]
FABQ Physical activity		
(0-24 points)	14 (4) 7, 20	15 (7) 2, 24
Work		
(0-42 points)	21 (11) 2, 42	23 (10) 9, 40
FfBH (12-36 points)	22 (4) 12, 29	21 (4) 12, 33
HADS Anxiety		
(0-21 points)	7 (4) 0, 15	6 (4) 0, 18
Depression		
(0-21 points)	6 (4) 0, 15	6 (4) 0, 14
RAND-36 (0-100%)		
Physical functioning	54 (19) 0, 90	58 (23) 10, 100
Role limitations due to physical health	19 (28) 0, 100	15 (28) 0, 100
Pain	31 (16) 0, 74	32 (12) 0, 52
General Health	50 (17) 15, 92	54 (19) 20, 100
Energy / fatigue	38 (19) 0, 85	44 (18) 10, 85
Social functioning	56 (26) 0, 100	61 (26) 0, 100
Role limitations due to emotional	51 (43) 0, 100	49 (43) 0, 100

problems		
Emotional well-being	58 (19) 20, 96	60 (18) 24, 92
	Median (Min^m, Max^m) lower; upper quartile	Median (Min^m, Max^m) lower; upper quartile
Bothersomeness		
(0-4 points)	3 (2, 4) 3; 4	3 (2, 4) 3;4

Footnotes: FABQ= Fear Avoidance Beliefs Questionnaire; FfBH=Funktionsfragebogen Hannover; HADS=Hospital Anxiety and Depression Scale; ODI=Oswestry Disability Index; RAND-36=The RAND 36-Item Health Survey; SD=Standard Deviation; VAS= Visual Analogue Scale for Pain.

6.3 Intention-to-treat-principle and missing data

Numbers analysed at each time-point were detailed in the CONSORT Flow Diagram (Figure 6.1). At the second primary endpoint (post CBT), 5 complete data sets were missing and an additional 13 ODI questionnaires were either not returned or left blank. Withdrawal reasons provided by participants who discontinued the trial were not related to the interventions and did not differ between groups (Section 6.1). Exploration of participant characteristics indicated no statistically significant difference of baseline pain and baseline ODI values for participants who discontinued and participants who continued the trial up to the second primary endpoint (post CBT) (Table 6.3). Hence, according to the definitions in Section 4.13.2, data were considered to be missing at random and ITT principles were met.

Missing data at the 2 primary endpoints (post stimulation and post CBT) were balanced across groups (Figure 6.1). The total amount of missing data was 10% post stimulation and 13% post CBT. This amount was within the anticipated drop-out rate for the sample size calculation (Section 4.9). Hence, according to the missing data strategy in the trial protocol (Section 4.13.3), no data imputation was required.

Table 6.3 Baseline VAS and ODI scores of participants who continued and who discontinued the trial

	Participants continued Mean (SD); n	**Participants discontinued** Mean (SD); n	**Differences between groups** (p-value)
VAS baseline	49 (25); 121	48 (19); 14	0.9
ODI baseline	16 (6); 120	18 (6); 15	0.3

Footnotes: ODI=Oswestry Disability Index; SD=Standard Deviation; VAS=Visual Analogue Scale for Pain. P-value for between group differences according to two-tailed t-tests.

6.4 Primary Analyses

6.4.1 Analyses of primary outcome measures at primary endpoints

All assumptions for ANCOVA analysis as defined in Section 4.13.5 were met.

6.4.2 Effect of tDCS on VAS pain

Mean VAS pain post tDCS was 42 mm (SD 24; n=61) in the verum group and 41 mm (SD 23; n=62) in the sham group. There was no statistically significant effect of tDCS on mean VAS pain post tDCS: F(1,119)=0.18, p=0.68 (99% CI for the between group difference -8.69 to 6.3) (Table 6.4 Figure 6.3).

6.4.3 Effect of tDCS on ODI

Mean ODI post tDCS was 15 points (SD 7; n=61) in the verum group and 14 points (SD 6; n=61) in the sham group. There was no statistically significant effect of tDCS on mean ODI post tDCS: F(1,119)=0.31, p=0.86 (99% CI for the between group difference -1.73 to 1.98) (Table 6.4, Figure 6.4).

6.4.4 Effect of tDCS & CBT on VAS pain

Mean VAS pain post CBT was 26 mm (SD 23; n=66) in the verum group and 23 mm (SD 18; n=64) in the sham group. There was no statistically significant effect of tDCS on mean VAS pain post CBT: F(1,127)=0.30, p=0.58 (99% CI for between group difference -10.32 to 6.73) (Table 6.4, Figure 6.3).

6.4.5 Effect of tDCS & CBT on disability

Mean ODI post CBT was 7 points (SD 6; n=58) in the verum group and 7 points (SD 5; n=59) in the sham group. There was no statistically significant effect of tDCS on mean ODI post CBT: F(1,114)=0.01, p=0.92 (99% CI for between group difference -2.45 to 2.62) (Table 6.4, Figure 6.4).

Table 6.4 Mean scores for VAS pain and ODI at the primary endpoints post tDCS and post CBT

	Post tDCS Mean (SD); n		p-values	post CBT Mean (SD); n		p-values
	Sham	Verum		Sham	Verum	
VAS pain	41(23); 62	42(24); 61	0.68	23(18); 64	26(23); 66	0.58
ODI	14(6); 61	15(7); 61	0.86	7(5); 59	7(6); 58	0.86

Footnotes: CBT=cognitive behavioural therapy; ODI=Oswestry Disability Index; SD=standard deviation; tDCS=transcranial direct current stimulation; VAS=visual analogue scale for pain. P-values for between group differences according to ANCOVA results.

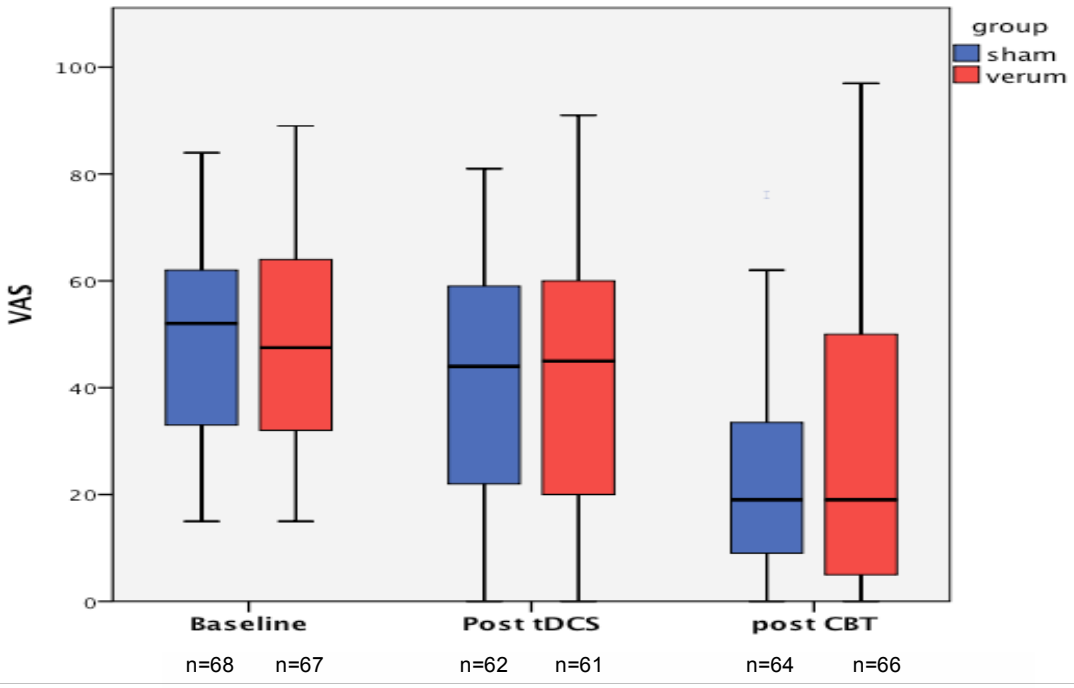


Figure 6.3 Box plot of VAS pain values at baseline and primary endpoints

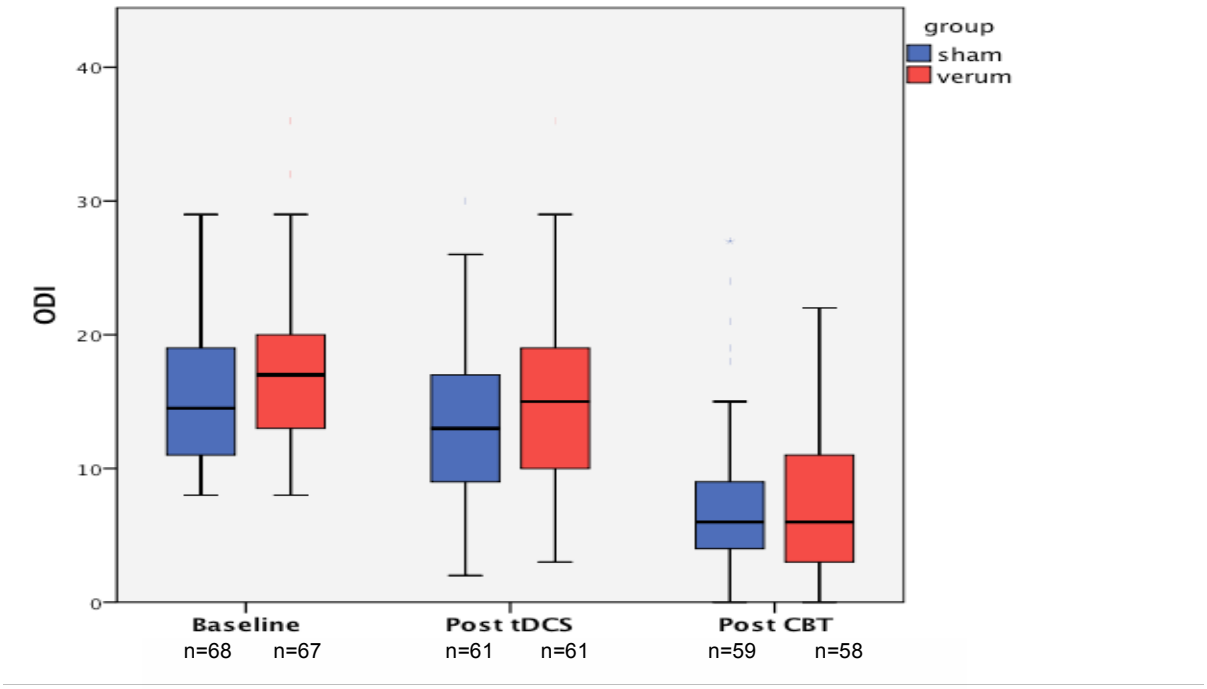


Figure 6.4 Box plot of ODI values at baseline and primary endpoints

6.5 Secondary analyses

6.5.1 Analyses of secondary outcome measures at primary endpoints

Data for all secondary outcome measures met the requirements for ANCOVA analysis detailed in Section 4.13.5. There was no statistically significant effect of tDCS on any secondary outcome measure at either the post tDCS or the post CBT endpoint when assessed by ANCOVA analyses (Table 6.5).

Table 6.5 Mean values, standard deviations and results from ANCOVA for all secondary outcome measures post stimulation and post CBT

	Post stimulation					Post CBT				
	verum Mean (SD); n	**sham** Mean (SD); n	**95% CI** (lower to upper)	**F-values** (degrees of freedom)	**p-values**	**verum** Mean (SD); n	**sham** Mean (SD); n	**95% CI** (lower to upper)	**F-values** (degrees of freedom)	**p-values**
FABQ										
Physical activity	15 (4); 62	15 (4); 61	-3.24 to 3.14	(1,22) 0.00	0.98	9 (4); 54	10 (7); 55	-4.75 to 5.32	(1,20) 0.01	0.91
Work	21 (12); 62	21 (12); 61	-5.92 to 4.74	(1,22) 0.05	0.82	16 (9); 54	14 (11); 55	-8.47 to 5.96	(1,20) 0.13	0.72
FfBH	21 (4); 62	20 (5); 61	-0.70 to 1.39	(1, 120) 0.43	0.51	16 (4); 54	16 (4); 55	-1.58 to1.11	(1,106) 0.12	0.73
HADS										
Anxiety	7 (4); 59	6 (4); 58	-0.95 to 0.51	(1,114) 0.35	0.56	5 (4); 52	4 (3); 52	-1.10 to 0.88	(1,101) 0.05	0.83
Depression	6 (4); 59	6 (4); 57	-1.10 to 0.69	(1,113) 0.21	0.65	4 (4); 52	4 (3); 51	-0.85 to 1.15	(1,100) 0.09	0.77
Bothersomeness	3 (1); 61	3 (1); 61	-0.18 to 0.30	(1,119) 0.23	0.63	2 (1); 54	2 (1); 55	-0.47 to 0.30	(1,106) 0.19	0.67
PPSI	1 (1); 61	2 (1); 61	-0.29 to 0.55	(1,97) 0.38	0.54	3 (1); 54	3 (1); 55	-0.57 to 0.21	(1,81) 0.85	0.36
RAND-36										
Physical Activity	57 (19); 62	62 (21); 61	-2.64 to 8.45	(1,120) 1.07	0.30	81 (19); 58	85 (18); 59	-3.51 to 8.64	(1,114) 0.70	0.41
Role limitations due to physical health	23 (32); 61	21 (32); 61	-5.90 to 11.53	(1,119) 0.41	0.52	53 (46); 53	59 (44); 54	-7.09 to 23.71	(1,104) 1.15	0.29
Pain	33 (13); 61	33 (14); 61	-3.12 to 4.35	(1,119) 0.11	0.77	49 (18); 53	53 (17); 55	-1.44 to 11.31	(1,105) 2.36	0.13
General Health	52 (19); 58	55 (19); 61	-5.52 to 4.37	(1,116) 0.05	0.82	60 (20); 53	63 (21); 55	-5.36 to 5.54	(1,105) 0.00	0.97
Energy / Fatigue	43 (20); 59	47 (18); 61	-7.02 to 2.87	(1,117) 0.69	0.41	56 (16); 54	58 (19); 54	-4.59 to 6.87	(1,105) 0.16	0.69
Social Functioning	59 (26); 62	64 (28); 59	-3.82 to 7.24	(1,118) 0.38	0.54	77 (22); 54	75 (22); 53	-13.25 to 0.88	(1,104) 3.01	0.09
Role limitations due to emotional problems	47 (45); 62	52 (46); 61	-3.62 to 21.13	(1,120) 1.96	0.16	70 (42); 54	78 (37); 54	-5.78 to 19.53	(1,105) 1.11	0.28
Emotional well-being	60 (19); 60	63 (17); 60	-1.83 to 5.83	(1,117) 1.07	0.30	73 (18); 53	73 (16); 53	-7.89 to 2.03	(1,103) 1.38	0.24

Footnotes: CI=Confidence Interval; FABQ=Fear Avoidance Beliefs Questionnaire; FfBH=Funktionsfragebogen Hannover; HADS=Hospital Anxiety and Depression Scale; PPSI=Patient Perceived Satisfactory Improvement.

6.5.2 VAS pain on each day of the stimulation

Mean VAS pain was reduced over time during the stimulation for participants in each group. There was a trend towards a lowest mean value on day 4 of the stimulation. The reduction in mean VAS pain on day 4 compared to baseline was statistically significant ($F(129)=4.187$ $p<0.05$) in both groups (verum and sham). There was no statistically significant difference between mean VAS pain for the 2 groups on any specific day (Table 6.6, Figure 6.5).

Table 6.6 Mean VAS pain for both groups on each day of the stimulation

Group / Time	Baseline	Day 1	Day 2	Day 3	Day 4	Day 5
	Mean(SD)	Mean(SD)	Mean(SD)	Mean(SD)	Mean(SD)	Mean(SD)
sham	48(18)	49(22)	45(22)	43(23)	40(23)	41(23)
verum	47(21)	46(21)	42(22)	41(22)	33(22)	42(24)
p-values for differences between groups	0.82	0.55	0.56	0.52	0.66	0.86
95% CI for differences between groups	-5.99 to 7.36	-5.16 to 9.16	-5.33 to 9.86	-5.25 to 10.33	-6.07 to 9.62	-9.05 to 7.68

Footnotes: CI=Confidence Interval; SD=Standard Deviation; P-values and CIs indicate between group differences according to two-tailed t-tests.

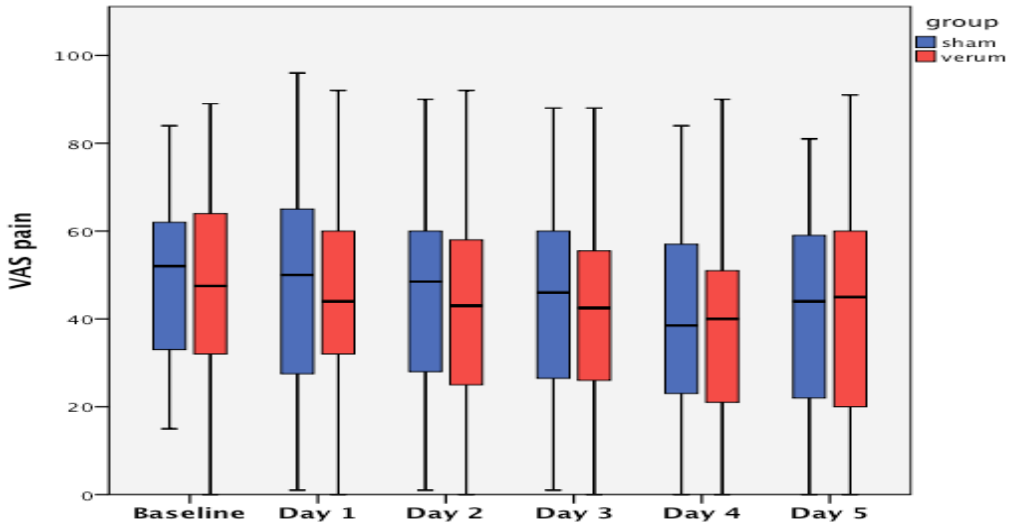


Figure 6.5: Mean VAS pain for both groups on each day of the stimulation period

6.5.3 Exploratory analysis of VAS pain and ODI

The graphical illustration of mean VAS pain and mean ODI over the period of the trial, indicated an improvement for both groups after the CBT that seemed to remain stable at all follow-up time-points (Figures 6.6 and 6.7). No statistically significant interaction of the factors group and time was found using a multilevel model analysis on VAS pain (CI 95% for the estimates of group*time as a fixed effect -0.84 to 0.20; p=0.23) or on ODI (95% CI for the estimates of group*time as a fixed effect -0.16 to 0.11; p=0.72) (Table 6.7). The final model for VAS pain included the fixed effects Time + $Time^2$ + $Time^3$ + FABQ_PA + FABQ_W + gender + VAS_pre + FfBH + RAND36_EWB + ODI_pre + group*time. The final model for ODI included the fixed effects Time + $Time^2$ + $Time^3$ + FABQ_PA + FABQ_W + VAS_pre + FfBH + group*time. Stepwise building of the multilevel models for VAS and ODI are reported in Appendices 6.1 and 6.2.

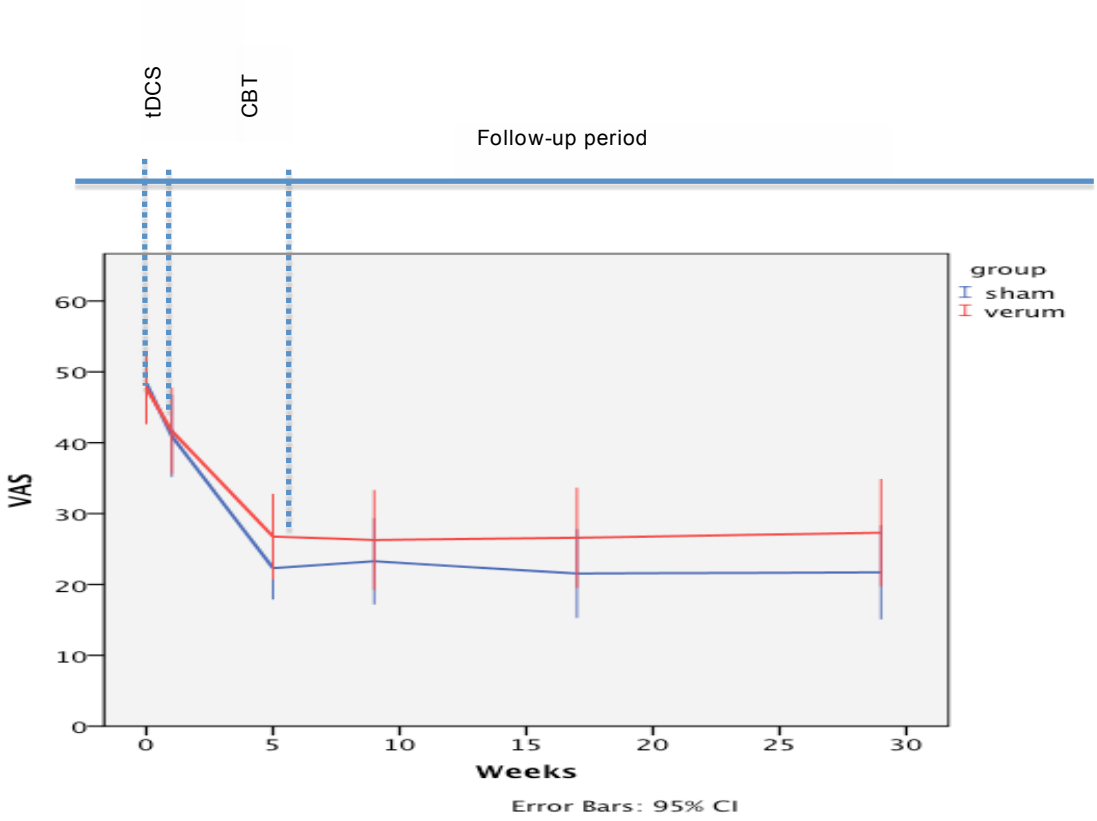


Figure 6.6 Graphical illustration of mean VAS scores over time for each group

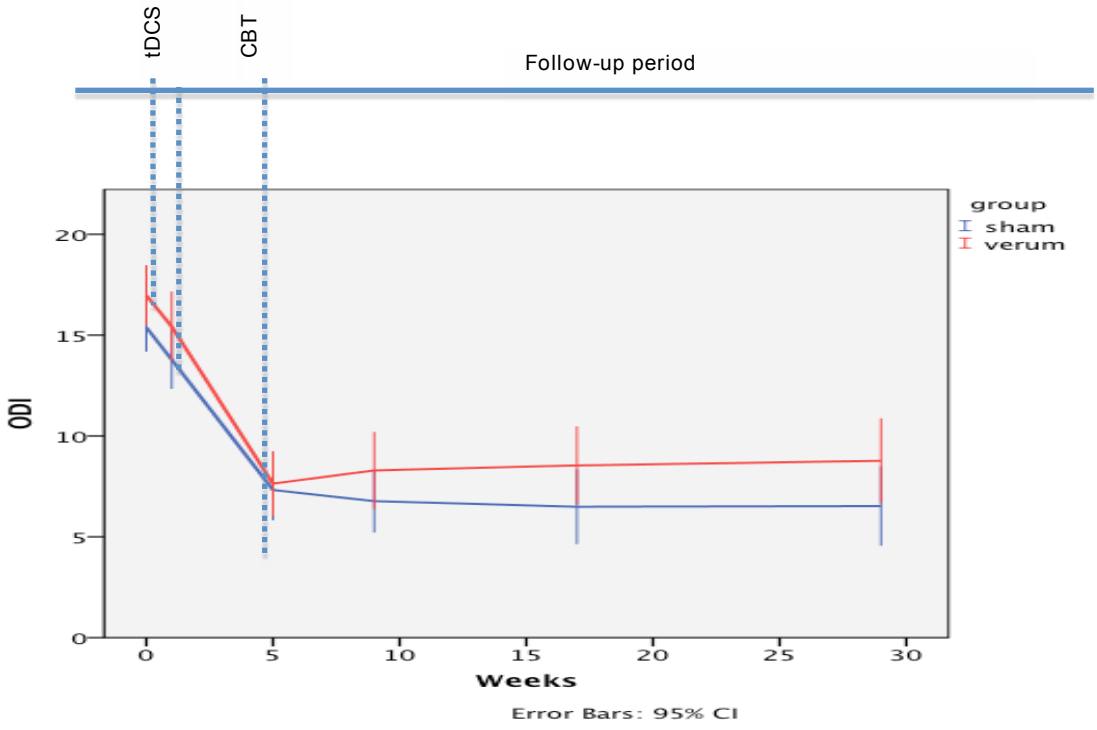


Figure 6.7 Graphical illustration of mean ODI over time for both groups

Table 6.7 Primary outcome measures at 4, 12, and 24 weeks follow-up and results of multilevel model analysis

		Weeks post CBT				
Outcome measure	**Group**	**4 Mean (SD); n**	**12 Mean (SD); n**	**24 Mean (SD); n**	**95% CI estimates of group*time (lower to upper)**	**p-value group*time interaction**
VAS pain	sham verum	23 (23); 56 26 (26); 54	22 (22); 48 27 (26); 53	22 (21); 42 29 (26); 47	-0.84; 0.20	0.23
ODI	sham verum	7 (6); 56 8 (7); 56	6 (6); 49 9 (7); 52	7 (6); 42 9 (7); 48	-0.16; 0.11	0.72

Footnotes: CBT=Cognitive Behavioural Therapy; CI=Confidence Interval; ODI=Oswestry Disability Index; SD= Standard Deviation; VAS=Visual Analogue Scale for Pain.

6.5.4 Exploratory analyses of secondary outcome measures

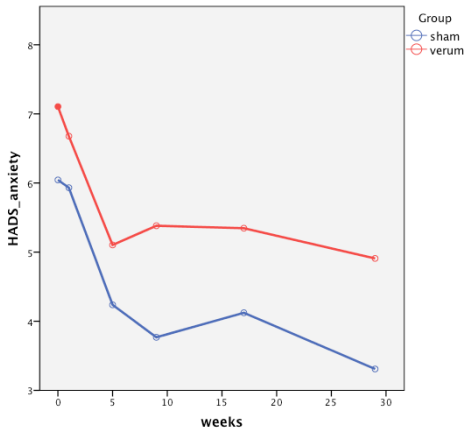
Graphical illustration of secondary outcome measures over time showed results similar to VAS pain and ODI: both groups improved slightly during the stimulation period and significantly after the CBT. Differences between post stimulation and post CBT values for all secondary outcome measures within groups were statistically significant with $p<0.05$. Improvements were maintained throughout follow-up (Figure 6.6). Multilevel models for all secondary outcome measures showed that there was a statistically significant interaction of group*time for the RAND36 subscales *physical functioning*, *general health* and *emotional well-being* (Table 6.8). Post-hoc testing indicated no significant differences between groups at any time-point. The significant interaction was caused by statistically significant reductions in the RAND36 subscales *physical functioning*, *general health* and *emotional well-being* ($p<0.001$ for each subscale) after the CBT observed in both groups.

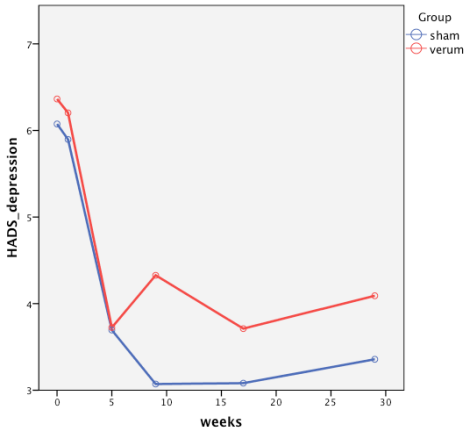
Table 6.8 Secondary outcome measures at 4, 12, and 24 weeks follow-up time-points

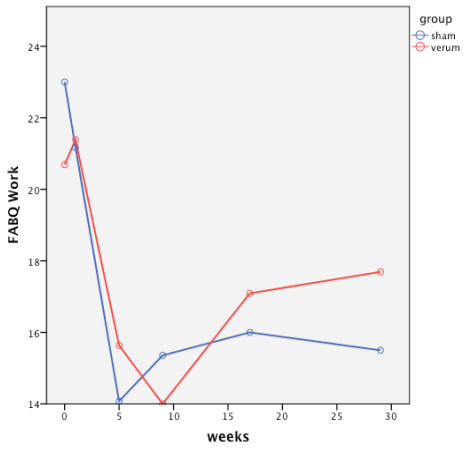
		Weeks post CBT				
Outcome measure	**Group**	**4** Mean (SD); n	**12** Mean (SD); n	**24** Mean (SD); n	**95% CI estimates** of group*time lower to upper	**p-value** group*time interaction
FFBH	sham	15 (4); 56	15 (4); 49	15 (4); 42	-0.11 to 0.01	0.09
	verum	16 (4); 55	17 (4); 52	17 (5); 49		
FABQ	sham	12(7); 52	9 (9); 46	24 (8); 38	-0.37 to 0.01	0.06
Physical Activity	verum	12 (5); 54	12 (4): 52	12 (5); 48		
Work	sham	15 (12); 52	16 (14); 46	16 (15); 38	-0.52 to 0.22	0.41
	verum	14 (11); 54	17 (12); 52	18 (13); 48		
HADS	sham	4 (3); 56	4 (3); 49	3 (3); 42	-0.07 to 0.00	0.06
Anxiety	verum	5 (5); 55	5 (4); 52	5 (4); 49		
Depression	sham	3 (3); 56	3 (3); 49	3 (3); 42	-0.77 to 0.01	0.87
	verum	4 (4); 55	4 (4); 52	4 (4); 49		
RAND-36 Physical functioning	sham	84 (20); 55	83 (22); 49	86 (18); 42	0.03 to 0.64	0.03*
	verum	78 (21); 55	75 (24); 53	75 (25); 49		
Role limitations due to physical health	sham	70 (38); 55	74 (35); 49	78 (35); 42	-0.00 to 1.21	0.05
	verum	63 (39); 55	70 (37); 53	66 (40); 49		
Pain	sham	59 (23); 56	63 (22); 49	64 (21); 42	-0.11 to 0.69	0.15
	verum	58 (27); 55	59 (25); 52	58 (25); 49		
General health	sham	66 (22); 56	67 (20); 49	69 (20); 41	0.07 to 0.57	0.01*
	verum	61 (23); 55	62 (21); 53	59 (24); 48		
Energy / fatigue	sham	64 (20); 56	62 (19); 49	63 (17); 41	-0.10 to 0.41	0.24
	verum	57 (22); 54	57 (19); 52	56 (21); 49		
Social functioning	sham	84 (18); 55	85 (20); 49	84 (20); 41	-0.23 to 0.48	0.49
	verum	77 (25); 55	82 (24); 52	81 (27); 49		
Role limitations due to emotional problems	sham	79 (38); 56	80 (33); 49	83 (29); 42	-0.41 to 0.61	0.69
	verum	72 (40); 55	82 (36); 51	81 (37); 49		
Emotional well-	sham	77 (14); 56	74 (13); 49	77 (15); 42	0.01 to 0.45	0.04*

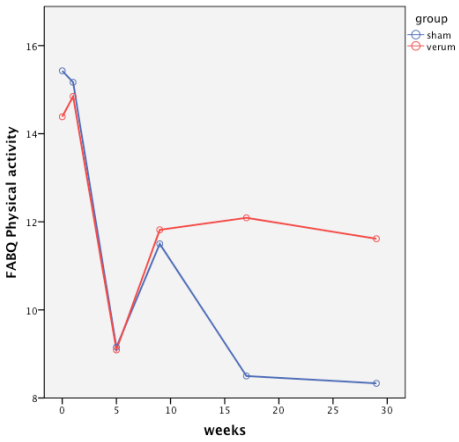
being	verum	71 (20); 55	71 (19); 52	69 (20); 49		
Patient perceived satisfactory improvement	sham	3 (1); 46	3 (1); 47	2 (1); 35	-0.01 to 0.03	0.17
	verum	2 (1); 52	2 (1); 51	2 (1); 45		
Bothersomeness	sham	2 (1); 55	2 (1); 49	2 (1); 41	-0.03 to 0.01	0.16
	verum	2 (1); 53	2 (1); 52	2 (1); 49		

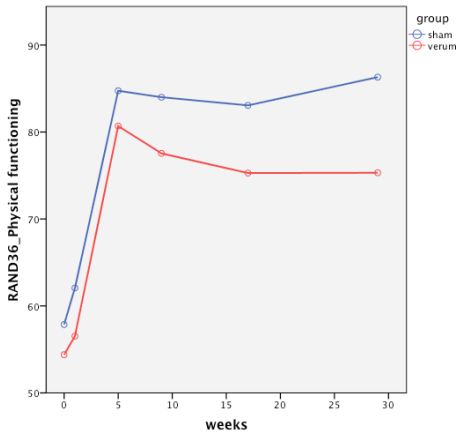
Footnotes: FABQ=Fear Avoidane Beliefs Questionnaire; FFBH=Funktionsfragebogen Hannover; HADS=Hospital Anxiety and Depression Scale; p-values and 95% CI for group differences according to multilevel models for all outcome measures across time. * indicates statistically significant results at p<0.05.

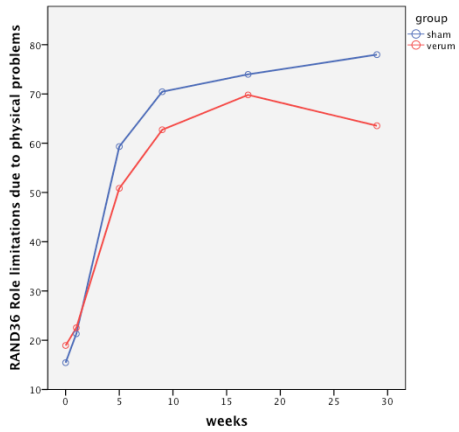

Group
sham
verum
HADS_anxiety
weeks

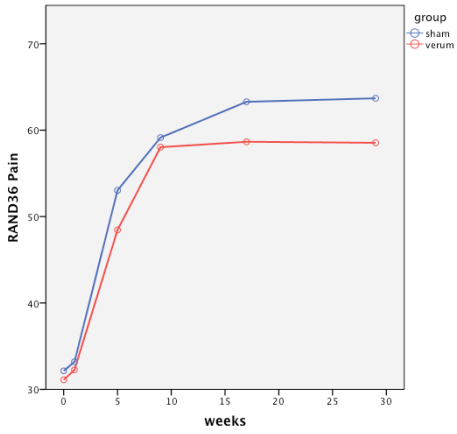

Group
sham
verum
HADS_depression
weeks

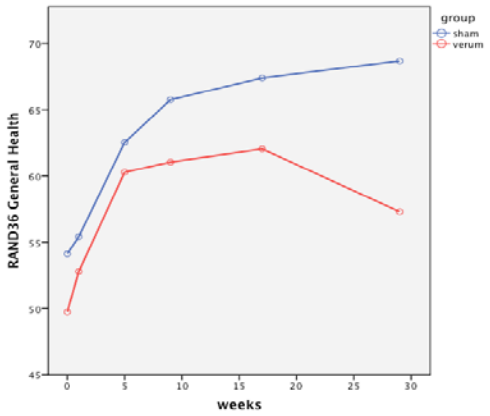

group
sham
verum
FABQ Work
weeks

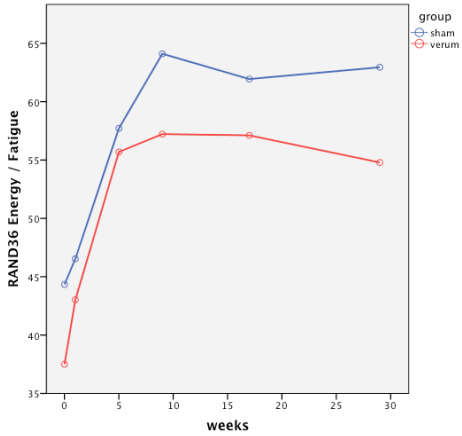

group
sham
verum
FABQ Physical activity
weeks

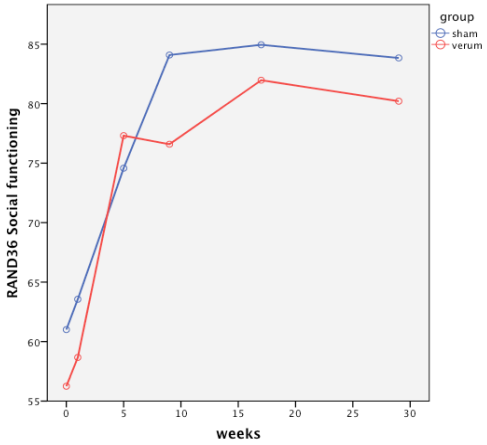

group
sham
verum
RAND36_Physical functioning
weeks

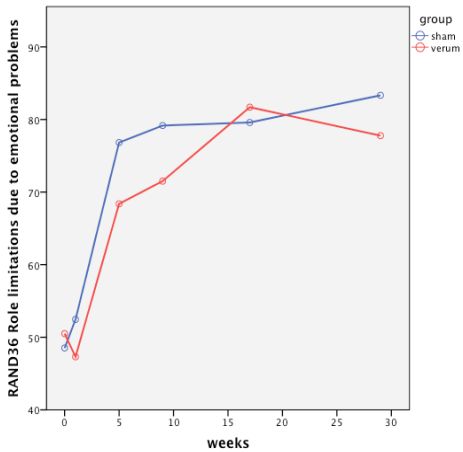

group
sham
verum
RAND36 Role limitations due to physical problems
weeks

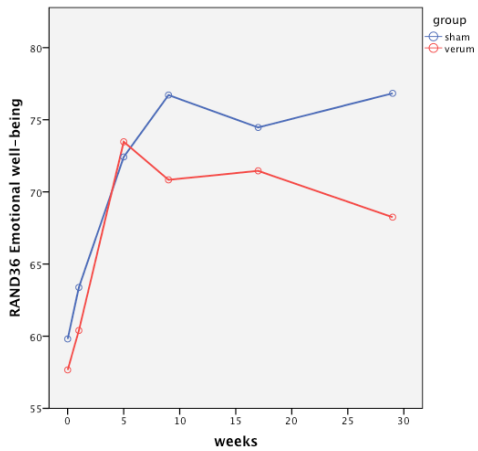

group
sham
verum
RAND36 Pain
70
60
50
40
30
0
5
10
15
20
25
30
weeks

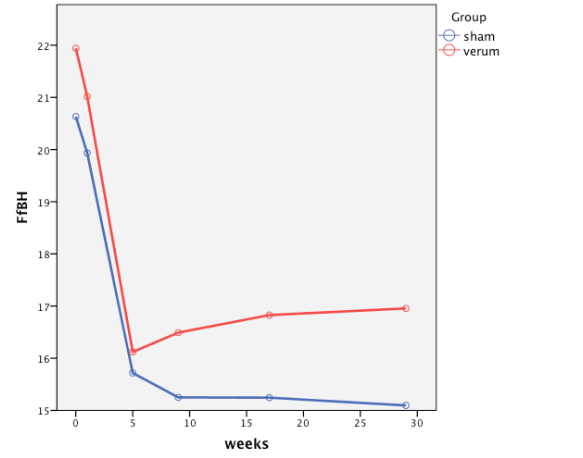

group
sham
verum
RAND36 General Health
70
65
60
55
50
45
0
5
10
15
20
25
30
weeks

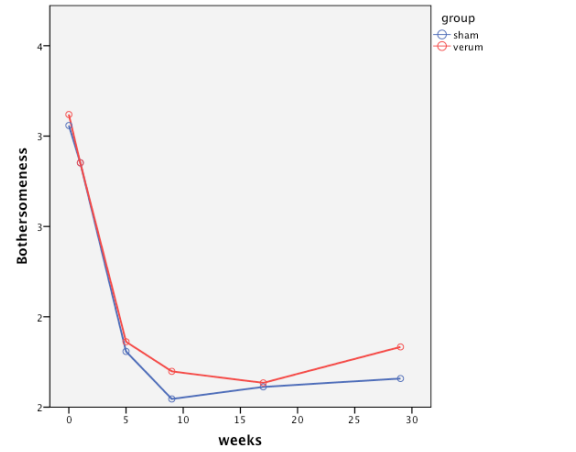

group
sham
verum
RAND36 Energy / Fatigue
65
60
55
50
45
40
35
0
5
10
15
20
25
30
weeks


group
sham
verum
RAND36 Social functioning
85
80
75
70
65
60
55
0
5
10
15
20
25
30
weeks


group
sham
verum
RAND36 Role limitations due to emotional problems
90
80
70
60
50
40
0
5
10
15
20
25
30
weeks


group
sham
verum
RAND36 Emotional well-being
80
75
70
65
60
55
0
5
10
15
20
25
30
weeks





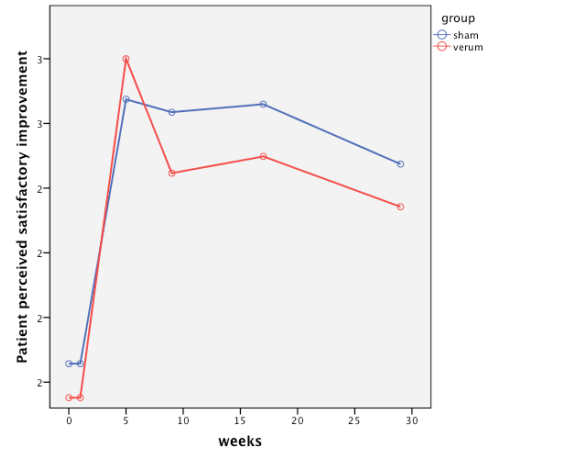


Figure 6.6 Secondary outcome measures by group at each time-point.

Footnotes: Higher ratings for all RAND subscales and PPSI indicate a positive outcome, while lower levels of FABQ, FfBH, bothersomeness and HADS indicate improved results. The CBT was conducted from week 2 to week 5. The round markers indicate the measurement time-points.

6.6 Side effects of tDCS

A total of 587 side-effect evaluation questionnaires from the 135 participants over 5 days of stimulation were evaluated. Participants observed sensory perceptions during and after the majority (75% in the sham group and 89% in the verum group) of the stimulation sessions (Table 6.9). The most frequently observed sensations were

tingling (53% of the sessions in the verum group and 50% of the sessions in the sham group) and a sensation of burning (35% of the sessions in the verum group and 17% of the sessions in the sham group) underneath the electrodes during the stimulation. Further side effects included itching and pain under the electrodes during the stimulation, tiredness during and after the stimulation and headaches after the stimulation (Table 6.9). All of these reported side effects were rated as "mild to moderate" by participants and none of the participants asked for the stimulation to be discontinued.

Table 6.9 Frequencies of participant-reported side effects

Type of side-effect	**Group**	
	sham (n=290)	verum (n=297)
During the stimulation	**n (%)**	**n (%)**
Light flashes	27 (9)	18 (6)
Pain under the electrodes	21 (7)	87 (29)
Tingling under the electrodes	144 (50)	158 (53)
Itching under the electrodes	26 (9)	98 (33)
Burning under the electrodes	48 (17)	104 (35)
Tiredness	21 (7)	32 (11)
Nervousness	4 (1)	3 (1)
Reduced concentration	7 (2)	0 (0)
Impaired vision	12 (4)	12 (4)
Headaches	14 (5)	21 (7)
Other perception	10 (3)	9 (3)
Anything else	11 (4)	10 (3)
Unpleasantness	7 (2)	21 (7)
After the stimulation	**n (%)**	**n (%)**
Pain at stimulation site	6 (2)	10 (3)
Tingling under the electrodes	33 (11)	29 (10)
Itching under the electrodes	14 (5)	34 (11)
Burning under the electrodes	4 (1)	35 (12)
Tiredness	29 (10)	41 (14)
Nervousness	4 (1)	2 (1)

Reduced concentration	11 (4)	6 (2)
Impaired vision	8 (3)	16 (5)
Headaches	35 (12)	31 (10)
Nausea	0 (0)	3 (1)
Vomiting	0 (0)	3 (1)
Impaired sleep	11 (4)	18 (6)
Lifted mood	1 (0)	19 (6)
Cold feeling	9 (3)	17 (6)
Hot flushes	8 (3)	14 (5)
Other sensations	5 (2)	6 (2)
Anything else	9 (3)	9 (3)

Chapter summary:

This chapter has presented the results from statistical analyses conducted on trial data. tDCS alone or in combination with a CBT did not significantly influence VAS pain or ODI when compared to sham stimulation. None of the secondary outcome measures were significantly influenced by the stimulation type (verum or sham) at either of the 2 primary endpoints. The most frequently observed side effects were skin sensations underneath the electrodes. These were observed in the majority of stimulation sessions but rated as mild or moderate.

7. CHAPTER

EVALUATION OF LITERATURE PUBLISHED AFTER THE SYSTEMATIC REVIEW (SEPTEMBER 2010) TO INFORM DISCUSSION

tDCS is still of high scientific interest as indicated by numerous research articles evaluating the effectiveness of tDCS for the reduction of clinical and experimental pain, published since the cut-off date for trial inclusion into the systematic review (Chapter 3). In order to provide an overview of current research in this field and to evaluate how results from the current trial (Chapter 6) will compare with recent evidence, this chapter will present an updated systematic review of the published evidence on tDCS for the reduction of clinical and experimental pain.

7.1 Introduction

The published systematic review of trials on tDCS for the reduction of clinical and experimental pain (Chapter 3 and (Luedtke et al., 2012b)) had a cut-off date for the literature search as Sept 30th 2010. Research interest in non-invasive brain stimulation is still high. An updated version of the 2010 Cochrane Review on non-invasive brain stimulation for the management of chronic pain included 6 new trials on tDCS (O'Connell et al., 2014). The combined effect size from 5 old and 6 new trials was smaller (SMD -0.18 [95% CI -0.46, 0.09]) than the 2010 publication (SMD -0.37 [95% CI -1.01, 0.28]) (O'Connell et al., 2010). The updated review, as in the 2010 review, focused on all types of non-invasive brain stimulation for the reduction of chronic pain but did not include trials on experimental pain.

An updated systematic review was required:

1) To provide a comprehensive overview of current tDCS research, by including and comparing all trials on tDCS for the reduction of clinical and experimental pain;

2) To enable this thesis to discuss the results from the current trial within the context of recent research. For the purpose of facilitating the discussion it was important:

- To identify whether a new stimulation paradigm had emerged as the most efficient for pain reduction;
- To evaluate how results from the current trial compared with the results of recent trials;
- To assess how results from the current trial would influence the combined mean effect for tDCS as an intervention to reduce clinical pain.

7.2 Methods

The methods of this updated review followed those defined for the original systematic review (Chapter 3). Limits for publication dates were set as 2010 to 6th Nov 2013. The search was conducted on 6th November 2013. As suggested by an updated version of the Cochrane Risk of Bias Tool (Higgins et al., 2011b) the risk of bias assessment was revised: One additional column was added to the risk of bias assessment table headed "Assessor blinding" to distinguish between the person who applied the stimulation (therapist) and the person who evaluated the results (assessor). As an accepted limitation, for practicability reasons and time restrictions, the literature search, screening against inclusion / exclusion criteria, risk of bias evaluation and data extraction were conducted by 1 researcher.

Results from trials on clinical pain with no high risk of bias were combined in a meta-analysis to compare the combined mean effect of the 2010 meta-analysis with the combined mean effect of all published clinical trials including those published between 2010 and Nov 2013. A sensitivity analysis was conducted that also included trials with a high risk of bias (in 1 or more domains). Results from the 2 meta-analyses with and without exclusion of high risk of bias trials were compared to evaluate the influence of methodological quality on trial results. In order to evaluate the influence of results from the current trial (Chapter 6) on the combined mean effect of published trials on tDCS for the reduction of clinical pain, a further sensitivity analysis was conducted: a subgroup meta-analysis of all trials that applied anodal tDCS to the M1 to reduce clinical pain was performed with and without entering data from the current trial.

7.3. Results

7.3.1 Search results

The search in Medline (PubMed) resulted in 40 new eligible articles. The same search strategy for OVID added 4 eligible articles and hand searching of reference lists and journal contents added 1 further publication. Title / abstract screening of these 45 articles excluded 18 articles that did not focus on pain as an outcome measure, were not a clinical trial, did not use tDCS as an intervention, were not conducted on humans, or were already included in the last systematic review (Figure 7.1). Full text screening excluded 8 trials: one did not include a control group for tDCS (Vigano et al., 2013); 2 did not assess pain intensity as a primary or secondary outcome (Maeoka et al., 2012; Tadini et al., 2011); 2 trials were excluded since no group received tDCS alone (Moloney and Witney, 2013; Riberto et al., 2011); 2 were excluded because analgesic use was the main outcome measure and varying levels of analgesics made pain as an outcome measure unreliable (Borckardt et al., 2011, 2013), and 1 publication was the abstract for a conference with no full-text available (despite email request) (Lee et al., 2013). This procedure resulted in 19 included new

trials, 10 on clinical pain (Antal et al., 2011; Auvichayapat et al., 2012; Bolognini et al., 2013; DaSilva et al., 2012; Dubois et al., 2013; Jensen et al., 2013; Mendonca et al., 2011; O'Connell et al., 2013; Villamar et al., 2013; Wrigley et al., 2013) and 9 on experimental pain (Borckardt et al., 2012; Grundmann et al., 2011; Hansen et al., 2010; Jurgens et al., 2012; Luedtke et al., 2012a; Mancini et al., 2012; Mylius et al., 2012; Reidler et al., 2012; Zandieh et al., 2013) (Figure 7.1) (Appendix 7.1).

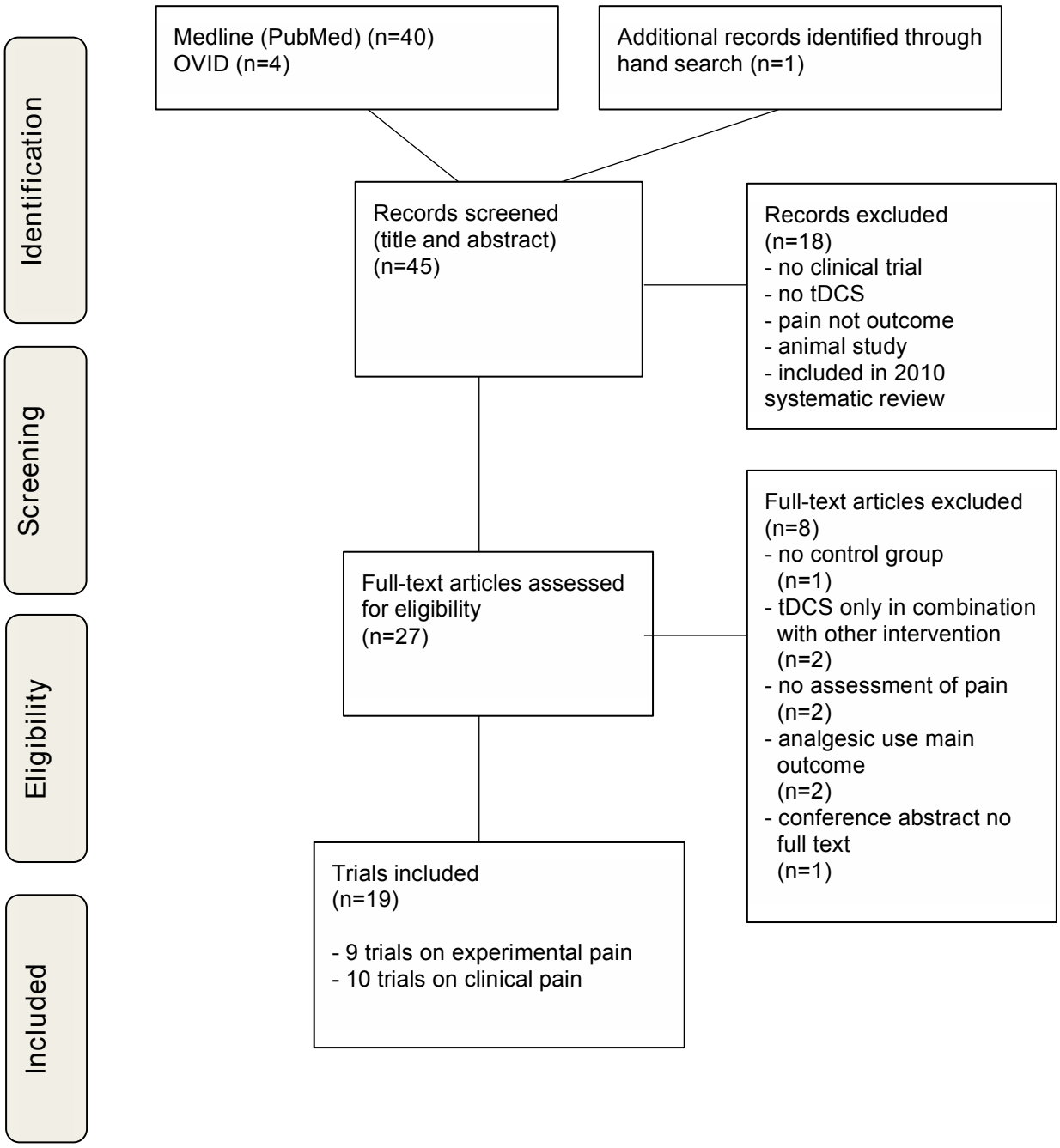


Figure 7.1: Flowchart for study selection process (Moher et al., 2009)

7.4 Risk of bias assessment

The majority of trials used a tDCS machine that had to be actively switched off for the sham stimulation. This resulted in a "high risk of bias" in the column focused to therapist blinding (Table 7.1). None of the included trials had a published research protocol resulting in the rating "unclear" for the domain of selective outcome reporting. Allocation concealment was also rated as unclear in all trials since no methods to conceal participant allocation were described. Further high or unclear risk of bias ratings referred to crossover trials with an unclear carry-over effect.

Table 7.1: Summary assessment of risk of bias for each trial

Author, year country	1	2	3a	3b	3c	4	5	6	Comments
Antal et al. 2011 (Germany)	H	U	L	L	U	L	U	L	Order of entry as randomisation method; allocation concealment not reported; assessor blinding not reported; no study protocol published.
Auvichayapat et al. 2012 (Thailand)	L	U	L	H	L	L	U	L	Allocation concealment not reported; therapist had to switch off machine for sham stimulation; no study protocol published.
Bolognini et al. 2013 (Italy, USA)	L	U	L	H	U	L	U	H	Crossover trial; allocation concealment not reported; therapist had to switch off machine for sham stimulation; assessor blinding not reported; no study protocol published; parametric tests conducted on small sample size.
Borckardt et al. 2012 (USA)	L	U	L	H	U	L	U	L	Allocation concealment not reported; therapist had to switch off machine for sham stimulation; assessor blinding not reported; no study protocol published.
DaSilva et al. 2012 (USA)	L	U	L	U	U	U	U	H	Allocation concealment not reported; therapist had to switch off machine for sham stimulation; assessor blinding not reported; last observation carried forward; no study protocol published. ANOVA on 13 subjects; no correction for multiple comparisons.
Dubois et al. 2013 (Belgium)	L	U	L	L	L	L	U	L	Allocation concealment not reported; no study protocol published.
Grundmann et al. 2011 (Germany)	L	U	L	U	U	L	U	L	Crossover trial; allocation concealment not reported; unclear whether therapist had to switch off machine and who evaluated the data; no study protocol published.
Hansen et al. 2010 (Germany)	H	U	L	H	U	L	U	L	Crossover trial; randomised according to order of study entry; allocation concealment not reported; therapist had to switch off machine for sham stimulation; assessor blinding not reported; no study protocol published.

Jensen et al. 2013 (USA)	L	U	L	H	U	L	U	U	Crossover trial; allocation concealment not reported; unclear whether therapist had to switch off machine and who evaluated the data; no study protocol published; carry-over effects unclear.
Jürgens et al. 2012 (Germany)	U	U	L	L	U	L	U	L	Crossover trial; randomisation unclear and allocation concealment not reported; unclear who evaluated the data; no study protocol published.
Luedtke et al. 2012 (Germany)*	L	U	L	L	U	L	U	L	Crossover trial; allocation concealment not reported; unclear who evaluated the data; no study protocol published.
Mancini et al. 2012 (Italy)	U	U	L	H	U	L	U	L	Crossover trial; counterbalanced order but how randomised? Allocation concealment not reported; therapist had to switch off machine; unclear who evaluated the data; no study protocol published.
Mendonca et al. 2011 (Brazil, USA)	L	U	L	H	L	L	U	H	Allocation concealment not reported; therapist had to switch off machine; no study protocol published; 6 participants per group.
Mylius et al. 2012 (Germany)	L	U	L	H	U	L	U	L	Crossover trial; allocation concealment not reported; therapist had to switch off machine; unclear who evaluated the data; no study protocol published.
O'Connell et al. 2013 (UK)	L	L	L	H	L	L	U	H	Therapist had to switch off machine; no study protocol published; statistical tests conducted on small sample size.
Reidler et al. 2012 (USA, Brazil, Canada)	L	U	L	U	L	L	U	L	Crossover trial; allocation concealment not reported; unclear whether therapist had to switch off machine; no study protocol published.
Villamar et al. 2013 (USA, Ecuador, Thailand)	L	U	L	H	L	L	U	L	Crossover trial; allocation concealment not reported; therapist had to switch off machine; no study protocol published.
Wrigley et al. 2013 (Australia)	U	U	L	U	L	L	U	H	Crossover trial; allocation concealment not reported; unclear whether therapist had to switch off machine; no study protocol published; multiple t-Tests, no correction for multiple testing, small sample size (n=10); no primary outcome defined.
Zandieh et al. 2012 (Iran)	L	U	L	H	U	L	U	L	Crossover trial; allocation concealment not reported; therapist had to switch off machine; unclear who evaluated the data; no study protocol published.

Footnotes: Components of risk of bias: 1 Sequence generation; 2 Allocation concealment; 3a Blinding of participants; 3b Blinding of therapist; 3c Blinding of outcome assessor; 4 Incomplete outcome data; 5 Selective outcome reporting; 6 Other sources of bias. Levels of risk of bias: H= high risk of bias; U=unclear risk of bias; L= low risk of bias.
* pilot study conducted prior to PhD on tDCS for the reduction of experimental pain in chronic low back pain patients

7.5 Risk of bias assessment of current trial

The current trial has a low risk of bias in all domains of the Cochrane Risk of Bias Tool (Higgins et al., 2011b).

7.5.1 Random sequence generation

Computer randomisation was used to generate lists of stimulation codes that automatically triggered either a sham or a verum stimulation. Two lists were produced: one for participants with baseline levels of pain between 20 mm and 50 mm on a 0-100 mm VAS and the second for baseline VAS pain between 51 mm and 100 mm (Section 4.11.2). This randomisation approach allowed for balanced baseline pain levels in the 2 intervention groups. This random sequence generation resulted in a low risk of bias to correctly guess the order of interventions.

7.5.2 Allocation concealment

Participants were allocated to an intervention group by receiving the next unused stimulation code from the randomisation list pertinent to their baseline level of pain intensity (Section 4.11.2). Neither participants nor researchers could identify the stimulation mode triggered by the code. This procedure resulted in a low risk of bias to correctly guess the group allocation.

7.5.3 Blinding

The study mode of the tDCS machine used in the current trial allowed for participant and researcher blinding by delivering a pre-programmed verum or sham stimulation triggered by a 5-digit number code (Section 4.12). Blinding was evaluated after every stimulation by asking participants which stimulation mode they thought they had received (Section 4.12). Groups were coded A and B by an independent researcher

to ensure assessor blinding during the statistical analysis of the data (Section 4.12). Consequently blinding of participants, researchers and assessors was regarded as of low risk of bias.

7.5.4 Incomplete outcome data

Evaluation of the number of participants who discontinued the trial showed that the number of drop-outs was within the range used for the sample size calculation (Section 6.3). Participant did not switch intervention groups. Reasons for withdrawal and evaluation of baseline data indicated no systematic loss of data due to factors directly associated with the intervention (Sections 6.1 and 6.3). Hence, there was a low risk of bias due to incomplete outcome data in the current trial.

7.5.5 Selective outcome reporting

A trial protocol was developed and published in an open access (Luedtke et al., 2011) (Appendix 4.7). The protocol pre-specified all trial procedures including primary and secondary outcome measures. No alterations were made to the protocol. This category was therefore rated as low risk of bias.

7.5.6 Other sources of bias

There were no relevant differences at baseline between groups, all assumptions for statistical testing were met, and there were no conflicts of interest or other potential sources of bias. This category was therefore rated as low risk of bias.

7.6 Study characteristics

7.6.1 Experimental pain

All trials on experimental pain evaluated the effect of a single session of tDCS (Table 7.2). Stimulation paradigms varied regarding the stimulation site (M1, S1, DLPFC, centroparietal and occipital cortex), the stimulation intensity (1 mA or 2 mA), the duration (10, 15, 20 minutes), and the stimulation mode (anodal, cathodal). Pain related outcomes included pain thresholds (thermal, mechanical, electrical), ratings to an experimental pain paradigm and pain evoked potentials. Most trials applied tDCS to healthy participants, while 1 trial investigated the effect of tDCS on experimental pain intensity in patients already experiencing chronic pain (Luedtke et al., 2012a).

7.6.2 Clinical pain

Trials evaluated either a single session or repeated sessions (up to a maximum of 20 sessions) of tDCS for the reduction of clinical pain. The most frequently used stimulation paradigm was 2 mA for 20 minutes over M1 (DaSilva et al., 2012; Jensen et al., 2013; Mendonca et al., 2011; O'Connell et al., 2013; Villamar et al., 2013; Wrigley et al., 2013) (Table 7.3). Three trials applied an intensity of 1 mA (Antal et al., 2011; Auvichayapat et al., 2012; Dubois et al., 2013), 4 trials additionally or exclusively targeted a different cortical area (visual cortex, S1, DLPFC) (Antal et al., 2011; Bolognini et al., 2013; Dubois et al., 2013; Mendonca et al., 2011), and 2 trials applied tDCS for a duration of 15 min (Antal et al., 2011; Bolognini et al., 2013). One trial used a new type of tDCS (HD-tDCS) (Villamar et al., 2013) and 1 trial exclusively used the cathodal stimulation mode (Antal et al., 2011). Four trials applied both anodal and cathodal stimulation (Bolognini et al., 2013; Dubois et al., 2013; Mendonca et al., 2011; Villamar et al., 2013). Trial participants were diagnosed with migraine, phantom limb pain, post-operative pain, spinal cord injury, fibromyalgia, and CNSLBP.

Table 7.2: Characteristics of trials on experimental pain

Authors, Year (Country)	Type of pain	Number of participants	Mean age (SD) or range (years)	Mode of active stimulation	Control	Site	Intensity (mA)	Duration (min)	Side effects	Pain related outcome measures
Borckardt et al. 2012 (USA)	thermal, mechanical	24	27 (6)	HD tDCS	sham	M1	2	20	none	cold pain thresholds, heat pain thresholds, thermal wind up pain, mechanical thresholds
Grundmann et al. 2011 (Germany)	thermal, mechanical	12	30 (22-42)	anodal cathodal	sham	S1	1	15	not reported	heat pain thresholds, cold pain thresholds, mechanical thresholds
Hansen et al. 2010 (Germany)	pain related EPs	19	30 (7)	anodal cathodal	sham	M1	1	20	initial itching	Pain related evoked potentials: latency of N2 and peak-to-peak amplitude
Jürgens et al. 2012 (Germany)	thermal, mechanical	17	25 (3)	anodal cathodal	sham	M1	1	15		heat pain thresholds, cold pain thresholds, mechanical pain thresholds, VAS ratings
Luedtke et al. 2012 (Germany)	thermal, electrical	15	49 (30-70)	anodal cathodal	sham	M1	1	15	not reported	thermal pain thresholds, VAS ratings to pain paradigm
Mancini et al. 2012 (UK, Italy)	electrical	24	23 (4)	anodal, cathodal	sham	cp, Occ	2	10	not reported	experimental pain intensity while viewing own hand
Mylius et al. 2012 (Germany)	thermal	26	25 (3) and 24 (4)	anodal, cathodal	sham	DLPFC	2	20	headaches	thermal pain thresholds

Reidler et al. 2012 (USA, Brazil, Canada)	mechanical	15	37 (11)	anodal	sham	M1	2	20	itching, tingling, skin redness, scalp pain, scalp burning, headache, pins and needles	pressure pain threshold
Zandieh et al. 2012 (Iran)	thermal (cold)	22	23 (5)	anodal, cathodal	sham	M1	2	max.15	tingling	cold pain thresholds and cold tolerance / intensity

Footnotes: cp= centro-parietal; DLPFC= dorsolateral prefrontal cortex; EPs=evoked potentials; LEPs= laser-evoked potentials; M1= primary motor cortex; NRS= Numerical Analogue Scale; Occ=occipital; S1= primary somatosensory cortex; SD=standard deviation; VAS=visual analogue scale.

Table 7.3 Characteristics of trials on chronic clinical pain

Author, year (Country)	Type of pain	Number of participants	Mean age (SD) or range	Mode	Control	Site	Intensity (mA)	Duration	Side effects	Pain related outcome measures
Antal et al. 2011 (Germany)	migraine	30	33 (10) 32 (12)	cath.	sham	V1	1	15 min 3 per week for 3 weeks	tingling, itching, fatigue, headache	Pain intensity during migraine attack
Auvichayapat et al. 2012 (Thailand)	migraine	37	23 (8)	anodal	sham	M1	1	20 min, 20 days	first degree burn, skin rash	VAS
Bolognini et al. 2013 (Italy, USA)	Phantom limb pain	8	59 (19)	anodal cath.	sham	M1 PPC	2	15 min	assessed but not reported	VAS for phantom limb pain, VAS for stump pain
DaSilva et al. 2012 (USA)	migraine	13	46 (6)	anodal	sham	M1	2	20 min 4 weeks, every 2nd day	headache, neck pain, tingling, skin redness, sleepiness, scalp pain	Pain intensity during migraine attack
Dubois et al. 2013 (Belgium)	post OP pain	59	50 (16)	anodal, cath.	sham	DLPFC	1	20 min	itching, visual flash	VAS, morphine consumption
Jensen et al. 2013 (USA)	SCI	30	49 (22-77)	anodal	sham	M1	2	20 min	not reported	NRS

Mendonca et al. 2011 (Brazil, USA)	fibro-myalgia	30	43	anodal, cath.	sham	M1 supra-orbital	2	20 min	no adverse reactions	VNS, pressure pain thresholds
O'Connell et al. 2013 (UK)	CNSLBP	8	45 (10)	anodal	sham	M1	2	20 min 3-15 days	dizziness, headaches, ear ache, less cravings for high-fat content food	VAS
Villamar et al. 2013 (USA, Ecuador, Thail.)	fibro-myalgia	18	50 (9)	anodal, cath.	sham	M1	2	20 min	tingling, itching	VNS overall pain, pressure pain thresholds
Wrigley et al. 2013 (Australia)	SCI	10	56 (15)	anodal	sham	M1	2	20min, 5 days	redness, tingling, fatigue, light-headedness, headache	Neuropathic Pain Scale (Pain intensity and unpleasantness)

Footnotes: BPI= brief pain inventory; cath=cathodal; DLPFC= dorsolateral prefrontal cortex; M1= primary motor cortex; NRS= numerical rating scale; PPC=posterior parietal cortex; S1=primary somato-sensory cortex; SD=standard deviation; Thail=Thailand; V1= visual cortex; VAS= visual analogue scale: VNS=visual numerical scale

7.7 Syntheses of results

7.7.1 Experimental pain

Although most trials on experimental pain used pain thresholds as a primary or secondary outcome measure, a meta-analysis of the results was not possible. Pain thresholds referred to different modalities (mechanical, thermal or electrical) that used different scales. Furthermore, publications reported percentage of change, normalised or standardised values that could not be entered into a meta-analysis. An email response from the research group that published the majority of trials stated that data could not be provided due to limited time and limited access to stored study files.

7.7.2 Clinical Pain

To compare the results from current evidence with the combined mean effect reported by the 2010 systematic review, a meta-analysis was conducted that included all (previously included and new trials) published trials with a low risk of bias on clinical pain, independent of localisation and mode of stimulation. The result indicated a small favourable effect of tDCS of -0.82 [95% CI -1.10 to -0.53] on a 0-10 VAS (Figure 7.2). Including trials with a high risk of bias in 1 or more domains resulted in a combined mean effect of -0.68 [95% CI -0.96 to -0.40] on a 0-10 VAS (Figure 7.3).

The subgroup analysis of trials that applied anodal tDCS to M1 indicated a comparable combined mean effect of -0.82 [95% CI -1.44 to -0.20] (Figure 7.4). When results from the current trial were entered into the subgroup analysis of trials on anodal tDCS over M1, this result was reduced to a combined mean effect of -0.72 [95% CI -1.28 to -0.16] (Figure 7.5).

Table 7.4 Main results of trials on experimental pain

Author, year (Country)	Between group differences (verum vs. sham) Statistical significance at p<0.05
Borckardt et al. 2012 (USA)	Heat / cold pain thresholds & mechanical pain not statistically significant. Statistically significant difference in thermal pain wind-up slope
Grundmann et al. 2011 (Germany)	Thermal pain and mechanical pain thresholds not significantly altered by tDCS
Hansen et al. 2010 (Germany)	Cathodal: significantly decreased PPA, anodal significantly increased PPA (trigeminal and extracranial nociceptive system); latencies unaltered
Jürgens et al. 2012 (Germany)	No statistically significant response to suprathreshold heat pain paradigm; no statistically significant increase in pain thresholds
Luedtke et al. 2012 (Germany)	No statistically significant change of pain thresholds or of an experimentally induced suprathreshold pain paradigm
Mancini et al. 2012 (UK, Italy)	Occipital tDCS resulted in statistically significant enhanced visually induced analgesia
Mylius et al. 2012 (Germany)	Anodal tDCS over right DLPFC significantly increased pain heat thresholds; cathodal tDCS over left DLPFC significantly increased cold pain thresholds
Reidler et al. 2012 (USA, Brazil, Canada)	Anodal tDCS significantly increased pressure pain threshold
Zandieh et al. 2012 (Iran)	Anodal stimulation significantly increased pain threshold and tolerance (seconds of cold water immersion)

Footnotes: DLPFC=Dorsolateral Prefrontal Cortex; PPA= Peak-to-Peak Amplitude; tDCS=transcranial Direct Current Stimulation.

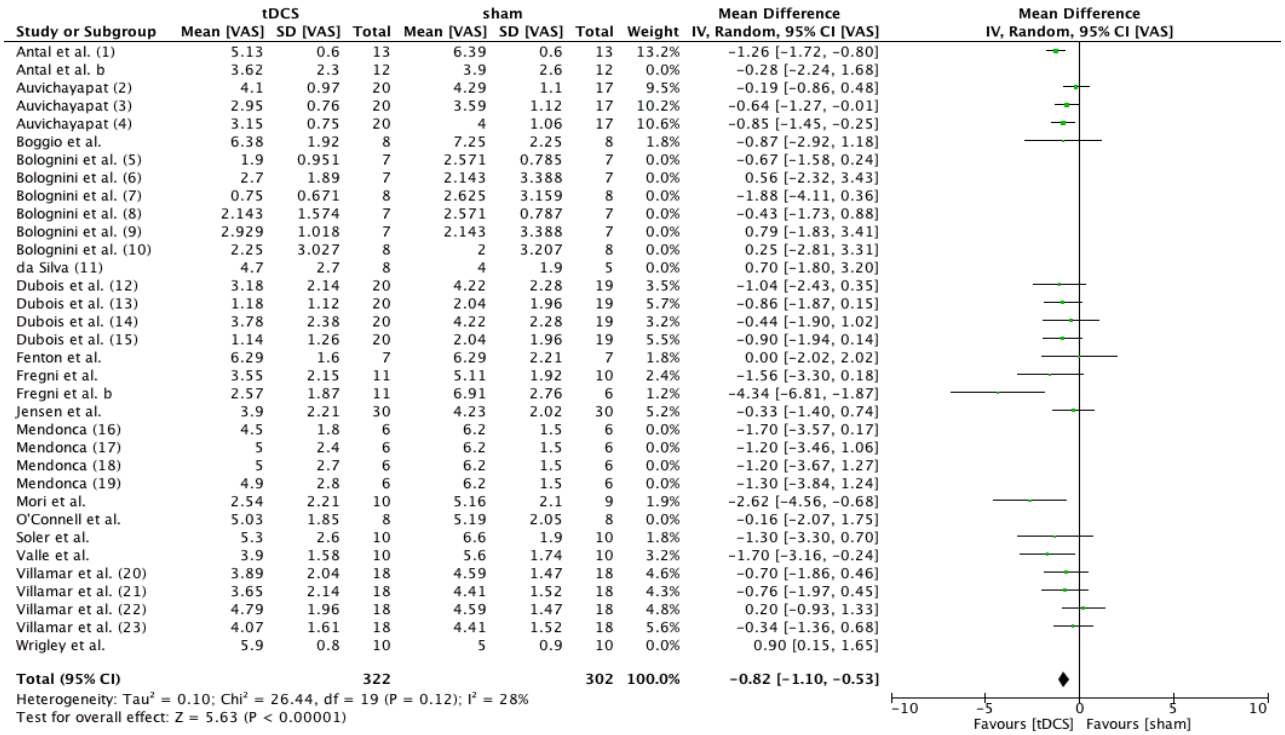
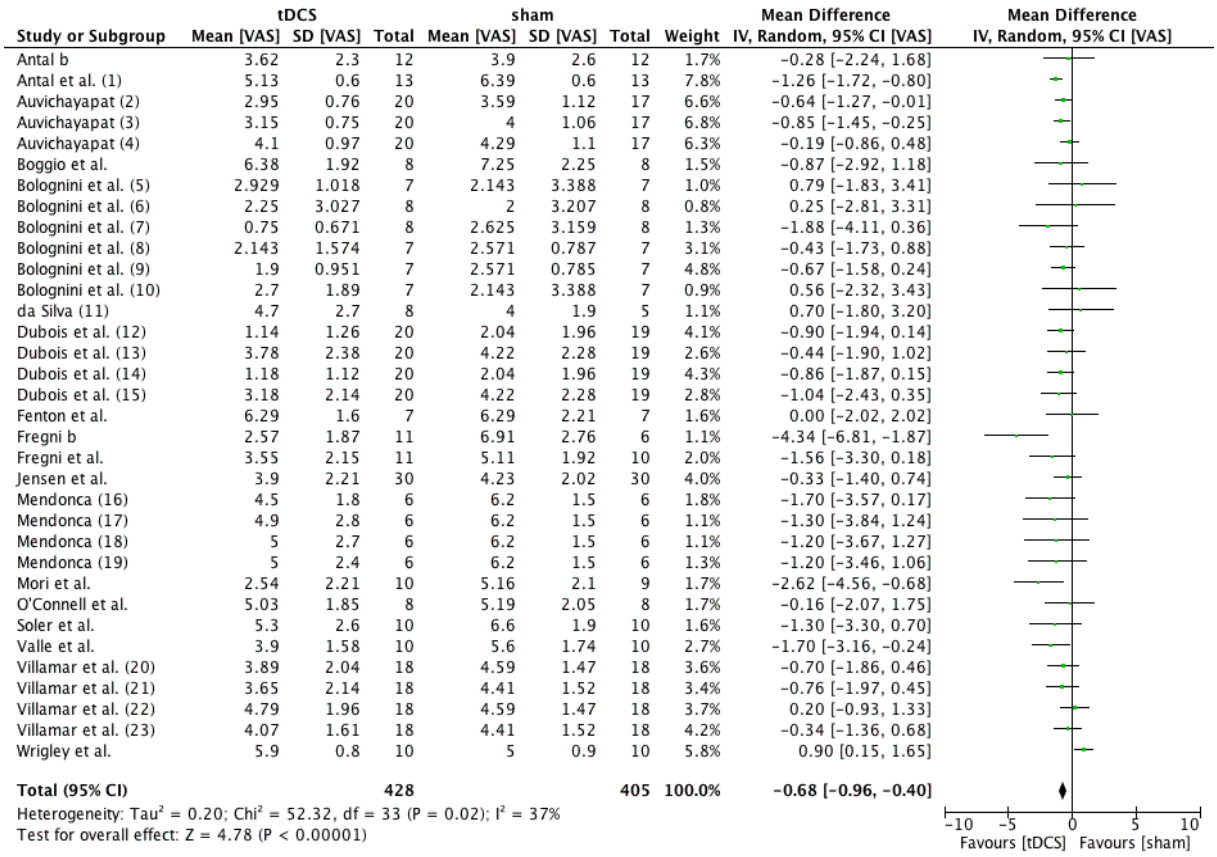


Figure 7.2: Meta-analysis of all trials on clinical pain with an unclear or low risk of bias independent of stimulation paradigm



(1) cathodal visual cortex
(2) week 4
(3) week 8
(4) week 12
(5) anodal PPC; stump pain
(6) anodal M1; stump pain
(7) anodal M1; phantom limb pain
(8) cathodal PPC; phantom limb pain
(9) anodal PPC; phantom limb pain
(10) cathodal PPC; stump pain
(11) Day 15
(12) VAS rest cathodal
(13) VAS dynamic anodal
(14) VAS rest anodal
(15) VAS dynamic cathodal
(16) cathodal supraorbital
(17) cathodal M1
(18) anodal supraorbital
(19) anodal M1
(20) cathodal; immediate effects
(21) cathodal; effects after 30 mins
(22) anodal; immediate effects
(23) anodal; effects after 30 mins

Figure 7.2: Meta-analysis of all trials on clinical pain independent of stimulation paradigm and risk of bias

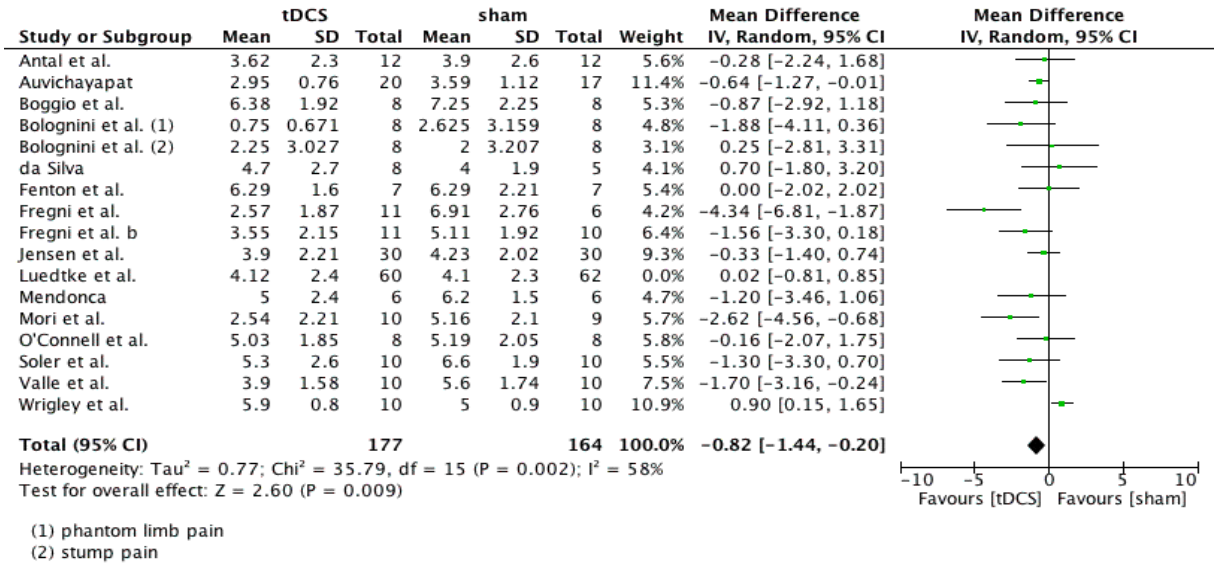


Figure 7.4: Subgroup analysis of trials that used anodal stimulation over M1 (excluding current trial)

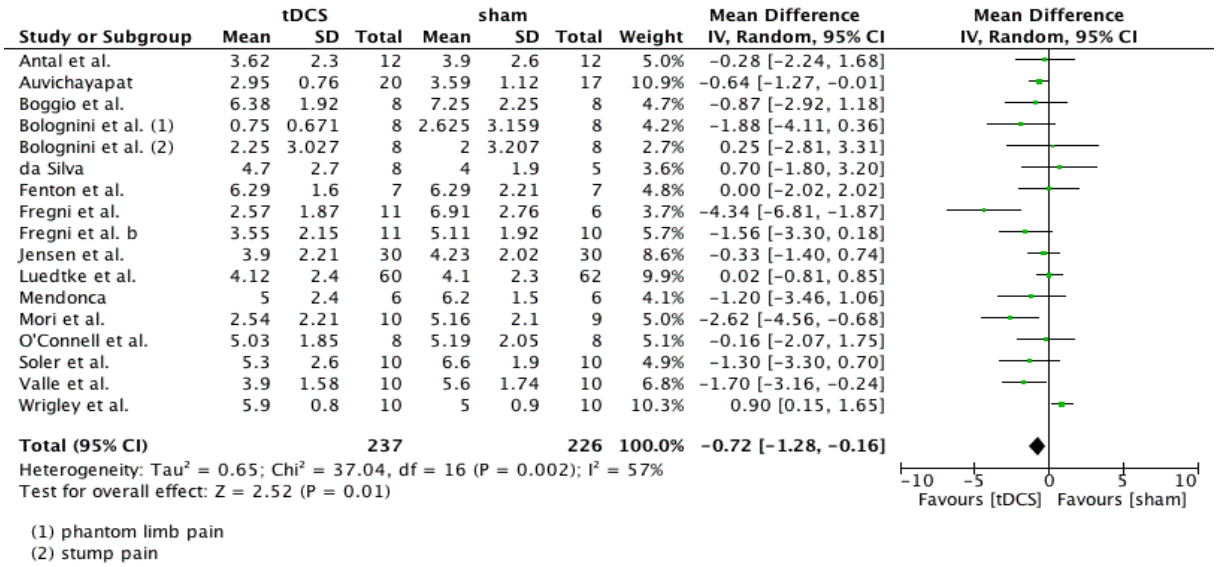


Figure 7.5 Meta-analysis of subgroup anodal stimulation over M1 including results of current trial

7.8 Discussion

The number of included trials indicated the ongoing scientific interest in tDCS as an intervention for pain reduction in clinical and experimental pain trials. The risk of bias analysis showed that the methodological quality of published trials and the quality of reporting had not improved since the 2010 systematic review. In particular, allocation concealment and randomisation procedures were rarely reported in detail and no trial protocols pre-specifying planned procedures were available for any included trial. Sample sizes were still too small to provide adequate statistical power. Moreover, mean values and standard deviations were rarely reported but were substituted by percentage of change or by data reported graphically. The analysis of the stimulation parameters of new trials on experimental pain indicated that higher intensities had been applied to healthy participants than in the earlier trials. Research on tDCS for the reduction of experimental pain was not conducted with a homogenous stimulation paradigm. Furthermore, outcomes on pain thresholds or responses to a suprathreshold stimulation paradigm showed mixed and conflicting results. An emerging area of research was the investigation of experimental pain in patients already experiencing chronic pain. Such investigations might be useful to assess the effect of tDCS in patients with altered pain processing due to a clinical pain condition. By applying an experimental pain paradigm rather than investigating the clinical pain itself, the type and intensity of pain is easier to standardise. In the only experimental pain trial that included chronic pain patients, tDCS failed to influence experimental pain thresholds and suprathreshold perception (Luedtke et al., 2012a).

Trials on clinical pain indicated that research had been conducted on new pain syndromes such as migraine, CLBP, and phantom limb pain. A new area of scientific interest had emerged that applied tDCS for the reduction of acute clinical pain. The stimulation paradigm used by most researchers on clinical pain was still the paradigm that had been used for the current trial. The meta-analysis of all trials on clinical pain showed that the combined mean effect was lower than in the meta-analysis conducted in 2010. This indicated that recent trials had reported neutral or negative

results for tDCS on pain reduction while early research had exclusively reported statistically significant pain reduction. The sensitivity analysis that included trials independent of risk of bias did not alter this result. A subgroup analysis on anodal tDCS over M1 resulted in a comparable combined mean pain reduction. It was the stimulation paradigm applied in the majority of trials. The combined mean effect of anodal tDCS over M1 was slightly reduced when data from the current trial were included. Combined mean effect sizes from all meta-analyses did not reach minimum clinically relevant change levels of 1.5 points for VAS pain (0-10 mm scale) (Ostelo et al., 2008).

The overall level of published evidence was still regarded as "low" according to GRADE (Schunemann et al., 2008) (Section 3.2.11) since all published trials had to be downgraded by 2 levels due to limitations in design, imprecision of results (wide confidence intervals), unexplained inconsistency of results and a high possibility of publication bias. Hence, current evidence is based on publications of an overall low methodological quality. The current trial had a low risk of bias in all domains. Following GRADE no downgrading was required. If the current trial were added to the systematic review, the GRADE approach would be based on 1 RCT with a low risk of bias. According to GRADE this is defined as a high level of evidence and can be interpreted as "further research is very unlikely to change the confidence in the estimate of effect" (Guyatt et al., 2008, p.926). However, this high level of evidence, since it is based on a single RCT, can only apply to the stimulation paradigm used and to NSCLBP.

Chapter summary

This chapter provided a systematic review of the methodological quality and characteristics of recent trials on tDCS for the reduction of clinical and experimental pain. tDCS had been applied to new areas of research (experimental pain reduction in patients with chronic pain and acute clinical pain) and intensities in experimental pain trials had increased from 1 mA to 2 mA. The meta-analysis of trials on clinical pain resulted in a lower combined mean effect than in the 2010 systematic review and meta-analysis. Results from the current trial further reduced the combined mean effect size. The overall level of published evidence for tDCS as an intervention for pain reduction was still regarded as low but upgraded to "high" if the current trial was added to the body of evidence. This level of evidence is based on 1 RCT only, hence future research is unlikely to show a pain reducing effect of tDCS in patients with NSCLBP, but may report pain reductions in other pain syndromes or by using different stimulation parameters.

8. CHAPTER

DISCUSSION

Chapter 6 presented the results from a randomised controlled trial that investigated the effectiveness of tDCS alone and in combination with CBT on pain and disability of patients with NSCLBP. Results indicated no effect of tDCS on either pain or disability immediately after the stimulation, after the CBT, or at any of the long-term follow-up time-points at 4, 12, and 24 weeks after the CBT. Participants perceived transient side effects during most stimulation sessions, however, these were of mild to moderate intensity and did not cause participants to discontinue the intervention. This chapter discusses the findings from the current trial within the context of the systematic review (Chapter 3) and the updated systematic review (Chapter 7). It further discusses the limitations of the current trial and outlines research priorities for the future.

8.1 Participant group characteristics at baseline

Following CONSORT recommendations, between group differences at baseline were not evaluated for statistical significance. However, Table 6.1 and 6.2 indicated that patient characteristics and baseline data were largely comparable between groups. Importantly there were no differences in the primary outcome measures VAS pain and ODI. However, the range in duration since the first onset of back pain was larger in the verum group (maximum value of 600 months) than in the sham group (maximum value of 384 months). This value, however, only referred to a single participant and is therefore unlikely to introduce bias to the data. The same applies to

the duration of this episode of back pain where the sham group showed a larger value (240 months) than the verum group (156 months).

11 more patients in the verum group (compared to the sham group) received NSAIDs for pain relief. This is a large difference and might cause concern if the verum group had shown better results than the sham group. Figure 6.6 visualises that the sham group showed overall better results than the verum group therefore NSAIDs did not seem to influence the data towards a better effectiveness in the verum group. That the sham group consistently showed better results than the verum group might be explained by marginally better baseline values in most RAND36 subscales. However, all other primary and secondary outcome measures did not support this notion that the sham group had been generally less affected than the verum group.

8.2 Effectiveness of tDCS for the reduction of pain

Five days of verum tDCS compared to sham stimulation did not result in a reduction of the intensity of pain in participants with NSCLBP. Hence, results from the trial did not support the pain reducing effect of tDCS on chronic pain as reported by the majority of previously published trials and, consequently, reduced the small combined effect size identified in the updated systematic review and meta-analysis (-0.82 [95% CI -1.44 to -0.20]) to -0.72 [95% CI -1.28 to -0.16] (Chapter 7). Differing results on pain between the current trial and previously published trials could be due to issues concerning the stimulation paradigm, trial participants, sample size, or statistical analyses. Disability had not been used as a primary outcome measure in any previous tDCS trial.

8.2.1 Differences regarding the stimulation paradigm

The stimulation paradigm (20 min, 2 mA, 5 consecutive days, anodal, M1) was selected based on the systematic review that indicated this particular paradigm as the most frequently applied and most effective paradigm in trials that reported a pain

reducing effect of tDCS in chronic clinical pain to date (Chapter 3). This allowed a direct comparison of trial results with evidence from the literature but did not exclude the possibility that more intense stimulation paradigms might result in a pain reducing effect. No previous trial used higher stimulation intensities on patients with chronic pain, but 5 trials reported more repetitions (10 stimulation days) (Antal et al., 2011; Auvichayapat et al., 2012; DaSilva et al., 2012; Soler et al., 2010; Valle et al., 2009) and 1 trial used a longer duration of 30 minutes (Boggio et al., 2009).

Neurophysiological studies reported that the duration of the stimulation (Furubayashi et al., 2008; Nitsche et al., 2002) and repetitions of the stimulation (Monte-Silva et al., 2013) increased the duration of the intervention effect. However, without an observed immediate effect, longevity of the results is arbitrary. Only 1 study has compared varying numbers of consecutive intervention sessions on chronic pain patients applied 3-14 sessions to NSCLBP patients, but with no indication that a higher number of stimulation sessions increased the intervention effect (O'Connell et al., 2013). However, only 8 participants were included and 6 participants received more than 5 days of tDCS, therefore, the study can only serve as an indication that a more intense stimulation paradigm is not very likely to result in a pain reducing effect in NSCLBP.

DLPFC and S1 are further accessible brain areas associated with pain processing (Nir et al., 2008; Ringler et al., 2003). Experimental pain trials reported an increased heat tolerance (Mylius et al., 2012) and heat pain thresholds (Boggio et al., 2008), as well as reduced unpleasantness when exposed to images of human pain after DLPFC stimulation (Boggio et al., 2009b). S1 stimulation increased cold detection thresholds in healthy participants (Grundmann et al., 2011). However, clinical pain trials reported no effect of DLPFC stimulation on acute post-operative pain (Dubois et al., 2013) and pain reductions in fibromyalgia patients after DLPFC stimulation were significantly lower than pain reductions after M1 stimulation (Fregni et al., 2006b; Valle et al., 2009). S1 had not been used as a stimulation target in trials on clinical pain. These results indicate that DLPFC and S1 as alternative intervention targets are unlikely to result in more effective pain reduction than M1 stimulation.

8.2.2 Inter-study differences in trial participants

The current trial is the first RCT to exclusively investigate the effect of tDCS on NSCLBP. Only 2 previous publications on tDCS for the reduction of chronic pain included participants with CLBP. Antal et al. (2010) investigated a mixed population of CLBP (n=8) and other chronic pain (n=23) and patients. Results indicated a statistically significant pain reducing effect in the group that received anodal stimulation. However, the CLBP subgroup was too small to draw statistically significant conclusions. Furthermore, patients were not analysed separately, therefore the effect of anodal tDCS on CLBP could not be distinguished from the overall effect (Antal et al., 2010).

A second trial focussed on the reduction of NSCLBP and found no effect of anodal tDCS compared with sham stimulation (O'Connell et al., 2013). The trial used an interrupted time series design, with 8 participants, who received sham stimulation until a randomly allocated day when the stimulation changed to verum mode. This approach resulted in a minimum of 3 and a maximum of 15 stimulation sessions per patient. The design did not allow the evaluation of a specific stimulation paradigm, as stimulation was applied with varying gaps (up to 6 days) between sessions. The small sample size was a further limitation of the trial, hence the effectiveness of tDCS on NSCLBP could not be evaluated.

The current trial was specifically designed to assess the effectiveness of tDCS on pain and disability in NSCLBP. Consequently, the study population was carefully selected by defining clear eligibility criteria to achieve a level of homogeneity that reflected typical participants of a CBT programme and, thereby allowed transferability of the trial results to other CBT settings. This is therefore the first trial that allows clinically relevant conclusions to be drawn regarding the effectiveness of tDCS for the reduction of pain (and disability) in patients with NSCLBP.

8.2.3 Differences regarding assessment of sample size

The current trial is the only tDCS trial to date that was adequately powered (based on a well justified sample size calculation (Section 4.9) to demonstrate a clinically meaningful effect on pain and disability. As critiqued in the systematic review and its update (Chapters 3 and 7) all published trials have been conducted using small and inadequate sample sizes. Sample size calculations (if reported) were based on TMS studies with large effect sizes and small standard deviations (Fregni et al., 2006b), or on previous publications of equally underpowered studies (Boggio et al., 2009a). Small sample sizes generally increase the Type II error (failure to reject a false null hypothesis) (Schulz and Grimes, 2005; Vickers, 2003), but can also lead to false-positive results by inducing chance.

8.2.4 Differences regarding statistical analyses

Methodological problems in previous trials included inappropriate use of parametric statistical tests (e.g. repeated measures ANOVA) on small sample sizes and reported statistically significant results without consideration of the validity of assumptions underlying the use of the statistical tests. Repeated measures ANOVA conducted on small samples can inflate the Type I error (incorrect rejection of the assumption of no difference between groups), indicating a false-positive effect (Vasey and Thayer, 1987). In the current trial, all assumptions for the primary analysis of covariance (ANCOVA) were met (Section 6.4), thereby minimising chances for a Type I error within the limits pre-defined in the sample size calculation (Section 4.9).

8.3 Effectiveness of tDCS on the disability associated with NSCLBP

Five days of anodal stimulation did not result in a statistically significant reduction of disability associated with NSCLBP. Disability was chosen as a primary outcome measure for the current trial to meet the requirements for a clinically relevant indicator of change in NSCLBP following outcome recommendations for trials in CLBP (Section 4.7). Although disability is correlated with pain intensity in patients with LBP (Hout et al., 2001; Kovacs et al., 2004), the effect of tDCS on disability is unknown: Disability has not been previously selected as a primary outcome measure in any published trial on tDCS. Two trials on tDCS for the reduction of pain did evaluate disability measured with the RMDQ as a secondary outcome measure. In a crossover trial on 7 participants with chronic pelvic pain, Fenton et al. (2009) found a reduction of 0.83 out of 24 points that was statistically significant but not clinically relevant. A second trial on 8 participants resulted in a reduction of 0.5 points in the sham group and 1.7 points in the anodal stimulation group (O'Connell et al., 2013). Results were not analysed for statistical significance between groups and recommended minimum clinically relevant change levels for the RMDQ of 4-5 points (Maughan and Lewis, 2010; Ostelo et al., 2008) were not achieved. Similar to these results, a small reduction of ODI of 1 point out of 50 (SD 3) in the sham group and 2 points (SD 4) in the verum group were identified in the current trial, and did not reach statistical significance or clinical relevance (Section 6.4.3).

8.4 Effectiveness of tDCS in combination with CBT (on VAS and ODI)

Although both groups improved significantly after the CBT, there were no statistically significant differences between verum and sham stimulation ($p=0.62$ for pain and $p=0.86$ for disability). One previous trial applied tDCS in combination with a multidisciplinary intervention for the reduction of fibromyalgia pain (Riberto et al., 2011). Twenty three patients were randomly assigned to weekly verum and sham stimulation sessions for 10 weeks during a multidisciplinary intervention. No effect for VAS was found, and disability was not measured. However, the SF-36 subscale for

pain showed a statistically significant effect of anodal stimulation compared to the sham group. This effect, however, should be interpreted with caution since the sample size calculation was based on a large effect size of 3 cm on a 0-10 cm VAS and SDs of 2.5. Furthermore, 2 outcome measures were presented (but not defined a priori) in the results section at an alpha level of 0.05 and a power of 80%. No adjustments for multiple testing were made, hence, reported results were based on an underpowered trial (Bender and Lange, 2001). The stimulation was applied once a week and patients received a total of 10 stimulation sessions. This stimulation paradigm is different from the paradigm used for the current trial, and therefore results are not directly comparable.

Further research was published that combined tDCS with a second intervention, such as TENS for the reduction of chronic pain (Boggio et al., 2009a), motor learning exercises in stroke patients (case report) (Hummel and Cohen, 2005) and healthy participants (Kidgell et al., 2013), working memory training (Fregni et al., 2005), and tDCS as a preconditioning technique for TMS (Lang et al., 2004b; Moloney and Witney, 2013). All trials reported a statistically significant enhancing effect of tDCS on the subsequent intervention. However, a risk of bias assessment identified an unclear risk of bias for the domains sequence generation, allocation concealment, therapist blinding, assessor blinding, and incomplete outcome data for all trials. Sample sizes ranged from 1 to 15 participants. Fregni et al. (2005) applied tDCS to the DLPFC rather than M1; Lang et al. (2004) used a stimulation duration of 10 minutes; and Moloney and Witney (2013) only found a pain reducing effect after cathodal tDCS. A further difference between the above trials and the current trial is that they performed tDCS during or minutes prior to the second intervention and the second intervention was of brief duration. In the current trial the second intervention (CBT) started a minimum of 24 hours after the stimulation and continued for 4 weeks. Based on the results of the current trial and on the results and methodological quality of trials combining tDCS with a second intervention, it is unlikely that tDCS applied immediately prior or during the CBT would change trial results.

8.5 Exploratory analyses of secondary outcome measures

The RAND36 subscales *physical functioning*, *general health,* and *emotional well-being* were the only secondary outcome measures to have a statistically significant time*group interaction. Post-hoc tests did not identify a statistically significant difference between groups at any time-point. The interaction was driven by a tendency towards better *physical functioning*, *general health* and *emotional well-being* in the sham group at 24-weeks follow-up.

8.6 Side effects

No adverse events occurred in the current trial. However, during the majority of stimulation sessions (group sham: 89%; group verum: 75%) participants reported some type of sensory perception such as tingling, burning, or itching underneath the electrodes. These perceptions were rated as mild or moderate in intensity and no participant discontinued the stimulation. An overview of side effects and frequencies was reported (Table 6.9). All side effects reflected those published in previous trials investigating chronic pain populations (Antal et al., 2010; Boggio et al., 2009a; Fenton et al., 2009; Fregni et al., 2006a; Fregni et al., 2006b; Mori et al., 2009; Soler et al., 2010; Valle et al., 2009) but only 1 publication on chronic pain patients reported a similarly high incidence (Antal et al., 2010). A high incidence of sensory side effects was also found in a large trial on healthy participants (Kessler et al., 2012). Both research groups that reported a high incidence of side effects used the same questionnaire as that used for the evaluation of side effects in the current trial. All other publications reported only verbally asking participants about side effects. The questionnaire listed a range of potential side effects, thereby directing a participant's attention to potential side effects including unspecific perceptions such as tiredness or feeling cold. The expectation of side effects increases the likelihood for participants to experience such perceptions (Faasse and Petrie, 2013). This effect is known as the nocebo response (Benedetti et al., 2007; van Laarhoven et al., 2011). Side effects were less frequent but had the same quality and intensity in the

sham stimulation group. In particular, sensory effects under the electrode were perceived in the sham stimulation group because the machine was programmed to intentionally provoke these perceptions in the initial 30 seconds of the stimulation. This indicates the effectiveness of participant blinding in the sham condition.

8.7 Blinding of patients and researchers

Sham stimulation as used in the current trial is regarded as a reliable placebo condition (Gandiga et al, 2006) and has been used by all authors that evaluated the effect of tDCS on chronic or experimental pain (Tables 3.3 and 3.4). Towards the end of the data collection for the current trial, a discussion on the effectiveness of blinding of participants and researchers was triggered by a publication that raised doubt about the reliability of the sham stimulation, mainly due to a higher rate of skin redness underneath the electrodes after the verum stimulation (O'Connell et al., 2012). Some authors further reported that trial participants, who had experienced tDCS before, might be able to distinguish between verum and sham stimulation even at a low intensity of 1 mA, due to skin perceptions (Ambrus et al., 2012); others confirmed effective participant (but not researcher) blinding at 2 mA (Palm et al., 2013).

The effectiveness of therapist blinding was addressed by documenting (for the remaining data collection period) what type of stimulation researchers believed the participant had received. One rating per patient was obtained for the stimulation type that the researcher believed they had applied. Researchers also rated whether they had observed skin redness after the stimulation. Participants rated on each day of the stimulation which stimulation type they believed they had received. To evaluate whether participants and researcher could guess the stimulation type on a greater number of occasions than would be expected by chance and to evaluate skin redness after the stimulation, the answers were analysed by calculating the kappa coefficient of agreement for each day of the stimulation (O'Connell et al., 2012; Landis and Koch, 1977).

Five hundred and eighty seven participant ratings (1 rating per participant per day of stimulation) were available, and indicated what stimulation type participants believed they had received. Seventy five percent of the participant ratings (n=442) indicated that participants believed they had received verum stimulation. Agreement for guessed and received stimulation type was poor to slight, indicating effective participant blinding in the current trial (Table 8.1).

Table 8.1 Effectiveness of participant blinding

	Day 1 (n=112)	**Day 2 (n=120)**	**Day 3 (n=124)**	**Day 4 (n=118)**	**Day 5 (n=120)**
Agreement between guessed and received stimulation	κ=0.111	κ=0.000	κ=-0.014	κ=-0.007	κ=-0.120
Interpretation (Landis and Koch, 1977)	slight agreement	slight agreement	poor agreement	poor agreement	poor agreement

Footnotes: κ=kappa coefficient

Thirty one researcher ratings were available (1 researcher rating per participant). The kappa coefficient for correctly guessed intervention groups was κ= 0.103. This result is interpreted as slight agreement indicating effective researcher blinding (Landis and Koch, 1977). The kappa coefficient for skin reactions observed after the verum stimulation was κ= 0.671 (p= 0.003), which was considered as "substantial agreement" and indicated more skin reactions in the verum group compared to the sham group (Landis and Koch, 1977). Participant and researcher blinding in the current trial was therefore effective despite the higher rate of skin redness underneath the electrodes after verum stimulation. Participants did not guess the stimulation mode more correctly towards the end of the stimulation period. This indicated that participants did not "learn" to detect the stimulation mode during the 5 day tDCS period (Table 8.1).

The literature reporting the reliability of the sham condition referred to different tDCS machines. The machines that applied a brief period of stimulation and had to be

manually switched off by the researchers for the sham condition (Ambrus et al., 2012; O'Connell et al., 2012; O'Connell et al., 2013) were less effective in blinding participants than the machine used by Palm et al. (2013) and for the current trial. This newer machine provided a study mode that for sham stimulation automatically switched off after a ramping up and a brief stimulation phase, while continuing to indicate the time elapsed and impedance on the display. This had the benefit that participants could not detect the "switching-off action" and continued to watch an active display. The study mode further allowed blinding of the person who applied the stimulation. The current trial indicated slight agreement between researcher rating and stimulation type, due to observed reddening of the skin under the electrodes that occurred more frequently in the anodal stimulation group. Other authors reported insufficient blinding due to such skin reactions (O'Connell et al., 2012; Palm et al., 2013) or recommended that the stimulation sites should be covered after the intervention (Palm et al., 2013). In the current trial blinding of the researcher was more effective since the decision whether verum or sham stimulation had been applied was based not only on redness of the skin but also on other issues including tingling and itching reported by the participant.

There was also a difference in the attachment technique between the 2 trials and the current trial that highlighted skin reactions as a risk to researcher blinding (O'Connell et al., 2012; Palm et al., 2013). The 2 trials that reported reddening of the skin only in the verum group used soft elastic straps or rubber bands to secure the electrodes. This had resulted in a large number of automatically terminated stimulations due to impedance levels exceeding the permitted range and automatically switching off the machine in pilot experiments preceding the current trial. To reduce the number of automatically terminated stimulations, elastic bandages were used that allowed for a closer contact of the electrodes to the skin and thereby better impedance levels. The elastic bandages had to be attached very tightly to the head. The compression to the skin left red marks on most participants and made it less likely for researchers to distinguish these from redness due to the stimulation mode.

8.8 Reduction of pain and disability in the sham stimulation group

In the current trial, an improvement of 7 mm (SD 16) on the 0-100 mm VAS pain was found in the sham group immediately after the stimulation, corresponding to a 15% reduction of pain intensity from baseline. Disability improved by a mean difference of 1 point (SD 3) on the 0-50 ODI, corresponding to a reduction of 9% from baseline. This is an interesting finding not attributable to the stimulation itself. Authors have attributed this effect to natural pain fluctuation, regression to the mean, or other influences such as responses influenced by politeness or gratefulness for the chance to try a new treatment approach or to receive extra attention (Ernst and Resch, 1995; Kienle and Kiene, 1997). These influences have previously been referred to as "the healing situation" (Papakostas et al., 2001). The healing situation in the current trial was identical for both groups. Previous trials found a pain reduction after sham tDCS of 18.9% (Antal et al., 2010) and 23.7% (Mori et al., 2009) while O'Connell et al. (2013) reported a negligible reduction in a trial on NSCLBP patients. The negligible reduction in the trial by O'Connell et al. (2013) was explained by the authors through questioning participant blinding.

8.9 Neurophysiological working mechanisms and explanations for the lack of a stimulation effect

Working mechanisms for anodal tDCS over the M1 are still not fully understood (Knotkova et al., 2013; Medeiros et al., 2012). Previous research has identified local and referred working mechanisms, and the resulting pain control mechanisms are hypothetical or inferred from investigations on invasive MCS.

8.9.1 Local working mechanisms

It is generally acknowledged that anodal tDCS results in an excitatory effect on cortical structures underneath the electrode, partially spreading to surrounding tissue (Antal et al., 2010; Lang et al., 2004a; Nitsche and Paulus, 2000; Suzuki et al., 2012). Cortical responses to tDCS have been well documented using various techniques. MEP studies consistently showed altered cortical activation as summarised in a recent systematic review (Bastani and Jaberzadeh, 2012). PET studies indicated an altered regional blood flow (Zheng et al., 2011) that was mainly observed during a task specific for the stimulated region (e.g. motor task during M1 stimulation) (Paquette et al., 2011). Only fMRI studies found conflicting results regarding the measured response in regional brain activation during and after anodal stimulation (Antal et al., 2011; Baudewig et al., 2001; Kwon et al., 2008). Inconsistencies between fMRI and MEP studies were explained by the differences in neurophysiological activity measured by the techniques: MEP measures the synaptic excitability of the pyramidal tract neurones (Rothwell et al., 1991) while fMRI measures the activity within the cortical network (Ogawa et al., 1990).

8.9.2 Referred working mechanisms

Evidence suggested that the application of tDCS influenced neurotransmitter systems, important for the communication within and descending from the brain, including dopamine, acetylcholine, and serotonin (Kuo et al., 2007; Monte-Silva et al., 2009; Nitsche et al., 2009). It was further reported to affect sodium and calcium channels and to interfere with the synaptic modulation (Medeiros et al., 2012). Studies that combined tDCS with pharmacological interventions identified a modifying influence on the neurotransmitter GABA and on NMDA receptors (Liebetanz et al., 2002; Nitsche et al., 2004; Tremblay et al., 2013); both closely linked to pain transmission (Cao et al., 2011).

8.9.3 Hypotheses for pain control mechanisms

8.9.3.1 Activation of the endogenous opioid system

Invasive MCS enhanced the activity of the endogenous opioid system in animal studies (Fonoff et al., 2009). Researchers attributed the effect to the opioid system by abolishing the stimulation induced pain reduction with opioid receptor blocking medication (naloxone). The effect of invasive MCS on the opioid system in humans was hypothesised, based on post stimulation changes of the periaqueductal grey, an area associated with endogenous opioid system observed in PET studies (Chiou et al., 2013; Maarrawi et al., 2007). One case study replicated this effect for tDCS in a PET study using an opioid receptor selective radiotracer. Authors reported changes in the periaqueductal grey and an immediate increase in opioid release post stimulation (DosSantos et al., 2012). Larger studies are required to further investigate the endogenous opioid system as a working mechanism for pain reduction following tDCS.

8.9.3.2 Modulation of the emotional appraisal of pain

Modulation of the emotional appraisal of pain was proposed as a working mechanism based on PET studies that showed a correlation between the level of pain relief during invasive MCS and an activation of the cingulate and orbitofrontal regions (Garcia-Larrea et al., 1999; Garcia-Larrea and Peyron, 2007). The proposed mechanism of action was an activation of these regions due to MCS resulting in a reduction of pain caused by a modulation of the emotional appraisal of pain. However, the cingulate and prefrontal regions have previously been shown to also correlate also with perceived control over pain (Wiech et al., 2006). Reported results, therefore might have been the consequence of the perceived pain reduction and not the effect of the stimulation. Furthermore, it has not been investigated whether tDCS also activates the cingulate and orbitofrontal regions. Further research is required to

clarify the role of specific brain areas for the emotional appraisal of pain and the capacity of brain stimulation techniques to influence activities.

8.9.3.3 Activation of the descending pain inhibiting network

Descending inhibition is the most described working mechanism for invasive MCS and tDCS (Knotkova et al., 2013; Medeiros et al., 2012; Garcia-Larrea and Peyron, 2007). It is also known as central pain modulation and relies on the concept that altered cortical activity leads to a descending cascade of events, consequently resulting in pain relief (Ossipov et al., 2010). M1 is the origin of the descending cortico-thalamic pathway. Polania et al. found an increased functional coupling of M1 and the thalamus after anodal tDCS over M1 (Polania et al., 2011) and further evidence suggested a spreading of electrical currents to subcortical areas distant from the stimulation site (Lang et al., 2005; Reidler et al., 2012). Modulation of the H-reflex in the quadriceps muscle indicated that the cascade of effects from tDCS descended as far down as the leg via the spinal pathway in healthy participants (Roche et al., 2011). However, evidence that these remote neurophysiological effects lead to pain reduction relied on studies with controversial results using experimental pain or pain thresholds (Luedtke et al., 2012; Jurgens et al., 2012; Grundmann et al., 2011; Bachmann et al., 2011; Csifcsak et al., 2009; Boggio et al., 2008; Antal et al., 2008). Recent data showed that healthy participants responded to tDCS during fMRI scanning with distinct cortical activations but did not show a reduction of the perceived intensity of experimental pain measured by a quantitative sensory testing protocol (including pain and perception thresholds and thermal and cold pain) (Ihle et al., 2014). In participants with spinal cord injury, EEG data indicated altered brain activity following tDCS that was not correlated with changes in clinical pain perception (Jensen et al., 2013). In summary, there is sufficient evidence to support a reliable cortical and subcortical neurophysiological response to tDCS, but alterations in pain perception were absent or inconsistent. Consequently, descending mechanisms can be activated by tDCS, but do not consistently result in the modulation of pain perception.

8.10 Implications for the use of tDCS in chronic clinical pain

Chronic pain is associated with multidimensional central and peripheral changes (Apkarian et al., 2010; Baliki et al., 2006, 2011; Cedraschi and Allaz, 2005; Heneweer et al., 2007; Linton, 2000; Martelli et al., 2004; May, 2008). Specific brain areas associated with chronic pain were identified by investigating anatomical changes (e.g. loss of grey matter) (Apkarian et al., 2004; Baliki et al., 2011; May, 2008) and functional changes (activity of brain regions as a response to a painful stimulus) (Baliki et al., 2006; Kobayashi et al., 2009; May, 2007). Both techniques demonstrated a distinct pattern of altered brain regions in chronic pain including the spino-thalamic tract, the lateral thalamus, somatosensory areas and the posterior insula (Moisset and Bouhassira, 2007) that only partially overlapped with those affected by anodal tDCS over M1. Other regions involved in sensory-discriminative pain processing, such as the S1 and secondary somatosensory cortex (Gustin et al., 2013; Kong et al., 2013; Vartiainen et al., 2009), have never been shown to be modulated by anodal tDCS over M1. A simple explanation why tDCS cannot consistently reduce pain is, therefore, that the stimulation cannot alter all brain regions associated with sensory-discriminative pain processing. Depending on the individual's cognitions, emotions and alterations in central pain processing, regions other than M1 (and associated cortico-thalamic tract) might support ongoing pain perception. Secondly, there is no evidence regarding how and to what extent tDCS passes through the thalamus, the brainstem, and the spinal cord, regions known to be important for the processing of pain.

Additionally, a range of psychological factors have been described to be predictive for the transition from acute to chronic pain, such as depression and maladaptive cognitions or work related factors (Carragee et al., 2005; Cedraschi and Allaz, 2005; Heneweer et al., 2007; Linton, 2000; Martelli et al., 2004; Melloh et al., 2009). M1 tDCS does not alter cognitive and affective brain networks: While shown to improve clinical depression when applied to the DLPFC (Berlim et al., 2013), no published research has reported an influence of M1 tDCS on psychological aspects. Consequently, tDCS results in measurable neurophysiological changes within the

brain and in remote areas of the nervous system but does not influence pain perception or disability due to the multi-layered factors that result in and maintain a chronic pain condition.

8.11 Limitations

8.11.1 Limitations of the trial

All care was taken to design and conduct a RCT of high methodological standard. However, the RCT was conducted within a clinical and not a laboratory environment, resulting in practicability issues that limited the trial design but had the advantage of a direct transferability of trial results to clinical practice. Feasibility and ethical considerations required that all participants received CBT after the stimulation. CBT was the standard management for patients at the study site and it was neither feasible nor ethical to deprive patients of this management or to postpone the CBT. Consequently, no long-term effects of tDCS alone were evaluated.

A key limitation is that the trial was conducted at only 1 study centre. This might reduce the generalisability of the results despite the clear definition and description of the inclusion and exclusion criteria and trial procedures. The back pain clinic and the CBT programme were developed following international and national examples of chronic pain management programmes. It can be viewed, therefore, as a representative example of a back pain clinic applying CBT. A final limitation is that cost-effectiveness could not be evaluated due to the German data protection act that does not allow access to patients' health files to evaluate doctor visits and further health care use. Data collected for medication use and number of physician visits based on patient recall have previously been evaluated as unreliable.

8.12. Recommendations for future research

Based on the results of the RCT reported in this thesis and on the systematic review of the currently available literature on tDCS for pain reductions, tDCS is not effective for the treatment of clinical pain and does not consistently reduce experimentally induced pain. It is highly unlikely that altered stimulation paradigms, such as longer duration, higher intensities or a different stimulation target will increase its effectiveness. Future research on tDCS should therefore focus on different clinical conditions such as stroke, Parkinson's disease or dementia. Research in these areas is in its preliminary phase with few small scale trials indicating clinical improvements of the conditions. However, without a low risk of bias and adequately powered RCT, there is only a low level of evidence for its effectiveness.

Regarding chronic pain research, future research should further attempt to identify interventions that might improve the outcomes of CBT. These should continue to target pain processing within the central nervous system and effects of the intervention on pain processing within the brain should be monitored. A range of interventions has been proposed such as graded motor imagery, including left/right recognition and mirror therapy as well as sensory perception interventions.

Chapter Summary

This was the first adequately powered and low risk of bias trial to investigate the effectiveness of anodal tDCS over M1 for the reduction of pain and disability in a population of NSCLBP patients. Trial results indicated that tDCS compared to sham stimulation was ineffective to change both primary outcome measures and did not influence the outcome of a CBT. Participants perceived a range of side effects but these were of mild to moderate intensity. Blinding of participants and researchers was evaluated following a recent discussion on the reliability of sham stimulation. Participants and researchers were effectively blinded in the current trial. Neurophysiological hypotheses as to why tDCS did not effectively reduce pain in NSCLBP patients were based on the multidimensional nature of the pain experience. While the literature reported a measurable response to tDCS in brain regions underneath the electrodes, it was not sufficient to alter the perception of pain or to change perceived disability. Trial results did not support the use of tDCS for the reduction of pain and disability in NSCLBP.

9. CHAPTER

CONCLUSIONS

This PhD aimed to evaluate the effectiveness of tDCS on pain and disability in patients with NSCLBP. It provided an overview of the published literature (overview of reviews and a systematic review of clinical trials) on the effectiveness of tDCS for the reduction of pain. Findings from the systematic review informed the design and methods for a RCT investigating the effectiveness of tDCS for pain and disability in a NSCLBP population. The trial was preceded by a feasibility study that evaluated practical aspects of trial procedures and the acceptability of tDCS as an intervention for NSCLBP. The results of the main trial were presented. The systematic review was updated. Trial results and limitations were discussed within the context of the updated systematic review, representing current evidence. Possible explanations for the non-significant effect of tDCS were explored from a neurophysiological perspective.

The initial systematic review (Chapter 3) revealed a high scientific interest in tDCS as a pain reducing intervention, as indicated by the large number of trials being published each year. Preliminary evidence was provided for a pain reducing effect for a variety of chronic pain disorders that raised hope for a new and effective tool in the management of chronic pain. However, the systematic review and meta-analysis of published trials revealed an unclear or high risk of bias in most trials due to methodological issues such as non-randomised sequence generation or unconcealed allocation to intervention groups. The external validity of reviewed trials was also unclear owing to small sample sizes based on unknown effect sizes of tDCS for the reduction of pain. The meta-analysis of trials on clinical pain showed a small pain reducing effect that was lower than minimum clinically relevant change recommendations. The overall level of evidence was rated as "low" according to GRADE (Guyatt et al., 2008). The systematic review of trials on the reduction of

experimental pain in healthy participants showed that trials could not be combined in a meta-analysis because stimulation paradigms, experimental pain conditions, and outcome measures were too diverse. Based on these results and on doubts about the transferability of data produced by experimental pain studies into clinically meaningful results, a RCT on tDCS for the reduction of NSCLBP was designed (Chapter 4). It was the first RCT that focussed exclusively on NSCLBP and the first clinical trial that showed a low risk of bias. Furthermore, it was the first adequately powered clinical trial on tDCS for the reduction of pain using a sample size calculation that was based on clinically relevant change recommendations and on previous trials on tDCS as well as on NSCLBP.

A feasibility study indicated that planned trial procedures were feasible to conduct in practice and showed good patient acceptability for tDCS as an intervention for NSCLBP (Chapter 5). It further detected that potential trial participants had pain and disability values that were lower than anticipated and that they did not allow for an improvement that satisfied minimum clinically relevant change recommendations. Subsequently, the inclusion criteria for the trial were amended to include a minimum level of VAS pain of 15 mm and a minimum ODI score of 8 points.

The results of the main trial (Chapter 6) indicated that tDCS was not effective to reduce pain or disability in patients with NSCLBP and that tDCS in combination with a CBT did not improve the outcome of the CBT. No adverse events were observed (defined as the participant requiring medical attention) but mild side effects were reported during / after most stimulation sessions. Participant, researcher, and assessor blinding was effective throughout the trial contrary to recently published doubts on the validity of the sham stimulation paradigm in tDCS research (O'Connell et al., 2012).

The systematic review of recent clinical trials on tDCS (Chapter 7) showed that results differed widely regarding the effectiveness of tDCS for pain reduction. Since the cut off date for the initial systematic review, negative results on the effectiveness of tDCS had been published, but the level of evidence was still low due to an unclear

or high risk of bias in all trials. The updated meta-analysis of published trials showed a combined mean effect of tDCS for the reduction of pain that was below 1 mm on a 0-10 mm VAS. Including the results of the current trial into the meta-analysis resulted in an even smaller effect size. Interestingly, all recent positive results were reported by 1 research team, an issue that compromises the credibility of the results in the light of the negative results published by other research teams. The systematic review of recent trials further indicated that experimental pain trials still have not agreed on a stimulation mode, duration, location or intensity that can be regarded as consistently effective for the reduction of experimental pain perception or the increase of pain thresholds. Owing to the diversity in outcome measures it was impossible to combine experimental pain trial results in a meta-analysis.

Trial results clearly indicated that anodal tDCS, applied over M1 with an intensity of 2 mA on 5 consecutive days for 20 min each day, was ineffective for the reduction of the pain intensity and disability in participants with NSCLBP and did not improve the outcome of CBT. Results from the updated meta-analysis additionally showed that the combined effect of anodal tDCS over M1 for the reduction of clinical pain, independent of the intensity, duration and frequency of the stimulation was smaller than 1 mm on a 0-10 mm VAS (Chapter 7). The current trial raised the level of the current evidence from "low" to "high" using the GRADE approach, since evidence was now based on 1 low risk of bias RCT. This can be interpreted as confidence that future research is unlikely to change the combined mean effect of tDCS for the reduction of clinical pain. The clinical use of tDCS can therefore not be recommended.

APPENDICES

Appendix 2.1 Search history for Ovid

Search History (8 searches)

	Searches	Results
1	pain.mp. [mp=ab, ti, ot, bt, hw, sh, tn, dm, mf, dv, kw, ps, rs, nm, an, ui, tx, ct, tc, id, tm]	1224640
2	brain.mp. [mp=ab, ti, ot, bt, hw, sh, tn, dm, mf, dv, kw, ps, rs, nm, an, ui, tx, ct, tc, id, tm]	2597630
3	(tDCS or transcranial direct current or direct current).mp. [mp=ab, ti, ot, bt, hw, sh, tn, dm, mf, dv, kw, ps, rs, nm, an, ui, tx, ct, tc, id, tm]	12784
4	(noninvasive or non-invasive).mp. [mp=ab, ti, ot, bt, hw, sh, tn, dm, mf, dv, kw, ps, rs, nm, an, ui, tx, ct, tc, id, tm]	246025
5	1 and 2 and 3 and 4	177
6	review.mp. [mp=ab, ti, ot, bt, hw, sh, tn, dm, mf, dv, kw, ps, rs, nm, an, ui, tx, ct, tc, id, tm]	4984586
7	5 and 6	117
8	**remove duplicates from 8**	101

Appendix 2.2 Critical appraisal tool for the assessment of the methodological quality of systematic reviews (AMSTAR)

1. Was an 'a priori' design provided? The research question and inclusion criteria should be established before the conduct of the review.	Yes No Can't answer Not applicable
2. Was there duplicate study selection and data extraction? There should be at least 2 independent data extractors and a consensus procedure for disagreements should be in place.	Yes No Can't answer Not applicable
3. Was a comprehensive literature search performed? At least 2 electronic sources should be searched. The report must include years and databases used (e.g. Central, EMBASE, and MEDLINE). Key words and/or MESH terms must be stated and where feasible the search strategy should be provided. All searches should be supplemented by consulting current contents, reviews, textbooks, specialized registers, or experts in the particular field of study, and by reviewing the references in the studies found.	Yes No Can't answer Not applicable
4. Was the status of publication (i.e. grey literature) used as an inclusion criterion? The authors should state that they searched for reports regardless of their publication type. The authors should state whether or not they excluded any reports (from the systematic review), based on their publication status, language etc.	Yes No Can't answer Not applicable
5. Was a list of studies (included and excluded) provided? A list of included and excluded studies should be provided.	Yes No Can't answer Not applicable
6. Were the characteristics of the included studies provided? In an aggregated form such as a table, data from the original studies should be provided on the participants, interventions and outcomes. The ranges of characteristics in all the studies analyzed e.g. age, race, sex, relevant socioeconomic data, disease status, duration, severity, or other diseases should be reported.	Yes No Can't answer Not applicable
7. Was the scientific quality of the included studies assessed and documented? 'A priori' methods of assessment should be provided (e.g., for effectiveness studies if the author(s) chose to include only randomized, double-blind, placebo controlled studies, or allocation concealment as inclusion criteria); for other types of studies alternative items will be relevant.	Yes No Can't answer Not applicable

8. Was the scientific quality of the included studies used appropriately in formulating conclusions? The results of the methodological rigor and scientific quality should be considered in the analysis and the conclusions of the review, and explicitly stated in formulating recommendations.	Yes No Can't answer Not applicable
9. Were the methods used to combine the findings of studies appropriate? For the pooled results, a test should be done to ensure the studies were combinable, to assess their homogeneity (i.e. Chi-squared test for homogeneity, I^2). If heterogeneity exists a random effects model should be used and/or the clinical appropriateness of combining should be taken into consideration (i.e. is it sensible to combine?).	Yes No Can't answer Not applicable
10. Was the likelihood of publication bias assessed? An assessment of publication bias should include a combination of graphical aids (e.g., funnel plot, other available tests) and/or statistical tests (e.g., Egger regression test).	Yes No Can't answer Not applicable
11. Was the conflict of interest stated? Potential sources of support should be clearly acknowledged in both the systematic review and the included studies.	Yes No Can't answer Not applicable

Appendix 2.3 List of included and excluded reviews

Included:

Antal, A and Paulus, W. Transkranielle Gleichstromstimulation: Neues Werkzeug in der Schmerztherapie? Transcranial Direct Current Stimulation: A New Method in the Therapy of Pain? 2007; 34: 530-533.

Antal, A and Paulus, W. [Transcranial magnetic and direct current stimulation in the therapy of pain]. Schmerz 2010; 24: 161-166.

Arul-Anandam, AP, Loo, C and Sachdev, P. Transcranial direct current stimulation - what is the evidence for its efficacy and safety? F1000 Med Rep 2009; 1.

Been, G, Ngo, TT, Miller, SM and Fitzgerald, PB. The use of tDCS and CVS as methods of non-invasive brain stimulation. Brain Res Rev 2007; 56: 346-361.

Fregni, F, Freedman, S and Pascual-Leone, A. Recent advances in the treatment of chronic pain with non-invasive brain stimulation techniques. Lancet Neurol 2007; 6: 188-191.

Fregni, F and Pascual-Leone, A. Technology insight: noninvasive brain stimulation in neurology-perspectives on the therapeutic potential of rTMS and tDCS. Nat Clin Pract Neurol 2007; 3: 383-393.

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