

**Non-invasive brain stimulation as a novel approach to
the treatment of chronic non-specific low back pain:**

**A systematic and critical evaluation of the existing
evidence base, an exploration of the efficacy of
transcranial direct current stimulation and an
investigation into the adequacy of commonly used
sham controls.**

**A thesis submitted for the degree of Doctor of
Philosophy**

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ABSTRACT

Chronic non-specific low back pain (CNSLBP) is a widespread but poorly understood condition that places a substantial burden on the sufferer, health services and the wider economy. Existing approaches to management do not demonstrate impressive levels of effectiveness. There is growing evidence that CNSLBP is associated with significant alterations in central nervous system (CNS) structure and function, suggesting a possible role for the brain in the aetiology of the condition, and presenting a case for novel therapies which aim to treat CNSLBP by affecting brain function. One such potential therapeutic approach is non-invasive brain stimulation (NIBS).

Following a literature review discussing the epidemiology and management of low back pain, the evidence for altered CNS function and the potential role of brain stimulation in CNSLBP and chronic pain generally this thesis includes 3 original scientific studies:

- A Cochrane systematic review of the effectiveness of NIBS techniques for the treatment of chronic pain.
- A randomised double-blind exploratory study of transcranial direct current stimulation of the motor cortex in the treatment of CNSLBP
- Is blinding to the stimulation condition maintained in trials comparing 2mA tDCS with sham stimulation? A randomised cross-over study.

RESULTS

There is limited existing evidence that some forms of NIBS may have a beneficial effect on chronic pain, though caution is warranted. Exploratory data from study 2 is not suggestive that tDCS to the motor cortex is effective for treating CNSLBP. Commonly used sham controls in trials of tDCS do not ensure adequate blinding, and so introduce a potential source of bias to the existing evidence base.

CONCLUSION

Further research is required to establish the value of NIBS as a treatment for chronic pain and CNSLBP. Future research in tDCS will need to develop and employ fully validated sham controls to ensure adequate blinding. NIBS cannot currently be recommended for the treatment of CNSLBP.

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LIST OF ABBREVIATIONS

BRAIN STIMULATION METHODOLOGY ABBREVIATIONS

CES	cranial electrotherapy stimulation
ECT	electroconvulsive therapy
Hz	hertz
mA	milliamps
MCS	motor cortex stimulation (epidural)
MEP	motor evoked potential
NIBS	non-invasive brain stimulation
TES	transcranial electrical stimulation
TMS	transcranial magnetic stimulation
rTMS	repetitive transcranial magnetic stimulation
tRNS	transcranial random noise stimulation
tDCS	transcranial direct current stimulation

DIAGNOSTIC ABBREVIATIONS

ALBP	acute low back pain
CLBP	chronic low back pain
CNSLBP	chronic non-specific low back pain
CPSP	chronic post stroke pain
CRPSI	complex regional pain syndrome type I
LBP	low back pain
NSLBP	non-specific low back pain
OA	osteoarthritis

IMAGING/ BRAIN IMAGING/ NEUROPHYSIOLOGY METHODS

BOLD	blood oxygen level dependant (signal)
EEG	electroencephalography
fMRI	functional magnetic resonance imaging
MEG	magnetoencephalography
MRI	magnetic resonance imaging
MRS	magnetic resonance spectroscopy
NP	neuropsychological
PET	positron emission spectroscopy
PPT	pressure pain threshold
rCBF	regional cerebral blood flow
RMT	resting motor threshold
SEP	somatosensory evoked potential
VBM	voxel based morphometry

NEUROANATOMICAL/ NEUROPHYSIOLOGICAL ABBREVIATIONS

ACC	anterior cingulate cortex
DLPFC	dorsolateral prefrontal cortex
DMN	default mode network
GABA	gamma-aminobutyric acid
ICI	intracortical inhibition
M1	Primary motor cortex
MCC	mid cingulate cortex
mPFC	medial prefrontal cortex
NAA	n-acetyl aspartate
NMDA	n-methyl-d-aspartate

OFC	orbitofrontal cortex
pACC	perigenual anterior cingulate cortex
PAG	periaqueductal grey
PFC	prefrontal cortex
PMA	premotor area
RAS	reticular activating system
S1	primary somatosensory cortex
S2	secondary somatosensory cortex
SMA	supplementary motor area

RESEARCH METHODS/ OUTCOME MEASURE ABBREVIATIONS

ADL	activities of daily living
ANOVA	analysis of variance
HADS	Hospital anxiety and depression scale
MCID	minimally clinically important difference
NRS	numerical rating scale
RCT	randomised controlled trial
RMDQ	Roland & Morris Disability Scale
SD	standard deviation
SE (SMD)	standard error of the standardised mean difference
SMD	standardised mean difference

VAS	visual analogue scale
VRS	verbal rating scales

INSTITUTIONAL ABBREVIATIONS

ACP	American College of Physicians
ACS	American College of Surgeons
APA	American Pain Association
CSAG	Clinical Standards Advisory Group (UK based)
EFNS	European Federation of Neurological Sciences
IASP	International Association for the Study of Pain

IMPACT	Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials
NICE	National Institute of Health and Clinical Excellence
PaPaS	Cochrane Pain Palliative and Supportive Care group

MISCELLANEOUS ABBREVIATIONS

CBT	cognitive behavioural therapy
MeSH	medical subject headings
NSAIDS	non-steroidal anti-inflammatory drugs

CHAPTER 1. INTRODUCTION

1.1 INTRODUCTION

The purpose of this introduction is to offer the reader a map of this thesis, outlining the broad themes of each chapter. Figure 1.1 illustrates the structure of the thesis in the form of a flow diagram.

The primary subject of this thesis is chronic non-specific low back pain (CNSLBP). The thesis outlines the current state of knowledge of CNSLBP, considers the growing evidence of a role for the central nervous system in the development and persistence of chronic pain and CNSLBP specifically. It considers electrical brain stimulation as an emerging potential intervention for chronic pain, and reports on and considers the results of three original research studies that contribute to knowledge in this field.

1.2 OUTLINE OF THE LITERATURE REVIEW

1.2.1 CHAPTER 2. THE EPIDEMIOLOGY AND CURRENT MANAGEMENT OF CNSLBP

The first chapter of the literature review considers the current state of knowledge regarding the epidemiology and management of CNSLBP. Back pain is almost ubiquitous in Western industrialised countries and a small but not insubstantial proportion of back pain sufferers go on to develop persistent disabling symptoms, placing a substantial burden on health systems and society as a whole. While there are many models of diagnosis available for non specific low back pain (NSLBP), none have been broadly accepted and none have yet demonstrated comprehensive validity. While traditional structural-anatomical and biomechanical spinal models of low back pain demonstrate poor correlation with clinical presentation or prognosis, other factors such as psychosocial variables appear to have some, albeit low, predictive value. Prognostic models generally have failed to explain most of the variance seen in clinical outcomes. The persistence of the diagnostic label NSLBP to account for most cases of low back pain, a diagnosis of exclusion rather than an adequate explanation of presenting symptoms, speaks to the lack of tangible progress in this area. Similarly while clinical guidelines variously recommend an array of treatments for CNSLBP, no approach has yet demonstrated impressive levels of efficacy. It could be argued that such recommendations promote “the best there is” rather than a genuinely effective solution to the problem. Consequently there is a pressing need for the development and testing of novel approaches to treating this condition.

1.2.2 CHAPTER 3. THE BRAIN IN CHRONIC BACK PAIN

Historically, diagnostic models have adopted a traditional structural-anatomical view of back pain focused on the health of specific spinal tissues and a biomechanical perspective which focuses on proposed dysfunctional and damaging loading of these tissues. In more recent decades substantial attention has been given to the play of psychosocial variables. Concurrently modern neuroscience has begun to revolutionise our understanding of pain, particularly chronic pain, revealing a pain system that, rather than simply producing an experience/ sensation that directly reflects the state of the tissues in which it is perceived, can, at multiple levels of the nervous system, regulate nociceptive input. This offers a new perspective in which pain can be conceptualized as an output of the brain (Moseley, 2007) wherein a distributed network within the central nervous system (CNS) assesses perceived threats to the tissues and in response produces the experience of pain which subsequently alters behaviour to promote survival and recovery. This process must integrate nociceptive input, previous experience, beliefs, mood and affect, and the immediate environmental context. Importantly this model places the brain at the heart of pain perception.

There is growing recognition that persistent pain is associated with altered function of the central nervous system. Early models of abnormal central processing focused on neuroplastic changes observed in the dorsal horn of the spinal cord in animal models but modern neuroimaging technology has allowed the investigation of brain activity, function and structure in vivo, in humans. Chapter 3 reviews the growing evidence that CLBP and other chronically painful conditions are characterized by significant and diverse changes in brain structure and function and considers, with a critical perspective, what implication this may have for our understanding of the condition. The possibility that, at least in part, CNSLBP might be a condition driven by abnormal central nervous system function is discussed, as is the logical corollary that the brain may be a legitimate target for novel therapies for this condition. One such therapeutic possibility is electrical brain stimulation.

1.2.4 CHAPTER 4. BRAIN STIMULATION AS A TREATMENT FOR CHRONIC PAIN

Over the last 3 decades interest has revived in the proposition that electrical stimulation of the brain may be a useful treatment for pain. Modern brain stimulation techniques as methods for treating pain were born of the observations of Penfield and Boldrey (1954) and the observation of chronic and severe “thalamic” pain following stroke. The most commonly considered site of stimulation has been the motor cortex, in part by virtue of its strong thalamic projections. Neuroimaging studies have revealed a network of brain areas that appear to be correlated with pain relief following invasive brain stimulation and these

provide a tacit theoretical model for such an approach. The development of non-invasive, tolerable forms of brain stimulation such as rTMS and tDCS has reduced the likely risks and costs of the procedure and allowed the study of brain stimulation as a treatment for chronic pain to expand considerably. Some reviews of the evidence conclude that these techniques may be a promising tool for the treatment of chronic pain. Whether CNSLBP is driven primarily by altered CNS processing or ongoing nociceptive drive from spinal tissues it is plausible that by altering pain processing at the central level through electrical stimulation the experience of pain could be modulated.

Chapter 4 examines the various methods of stimulation, the evidence that they alter brain activity and function, the theoretical models by which they might reduce pain, and the literature regarding their efficacy. That the existing literature regarding efficacy is found to be difficult to interpret provides the rationale for the first study in the thesis.

1.3 OUTLINE OF THE ORIGINAL RESEARCH STUDIES CONTAINED IN THIS THESIS

Each of the three research studies contained in this thesis will be discussed in a separate chapter that clearly outlines the research aims, methodology, and results and contains an in depth discussion of the study findings and limitations.

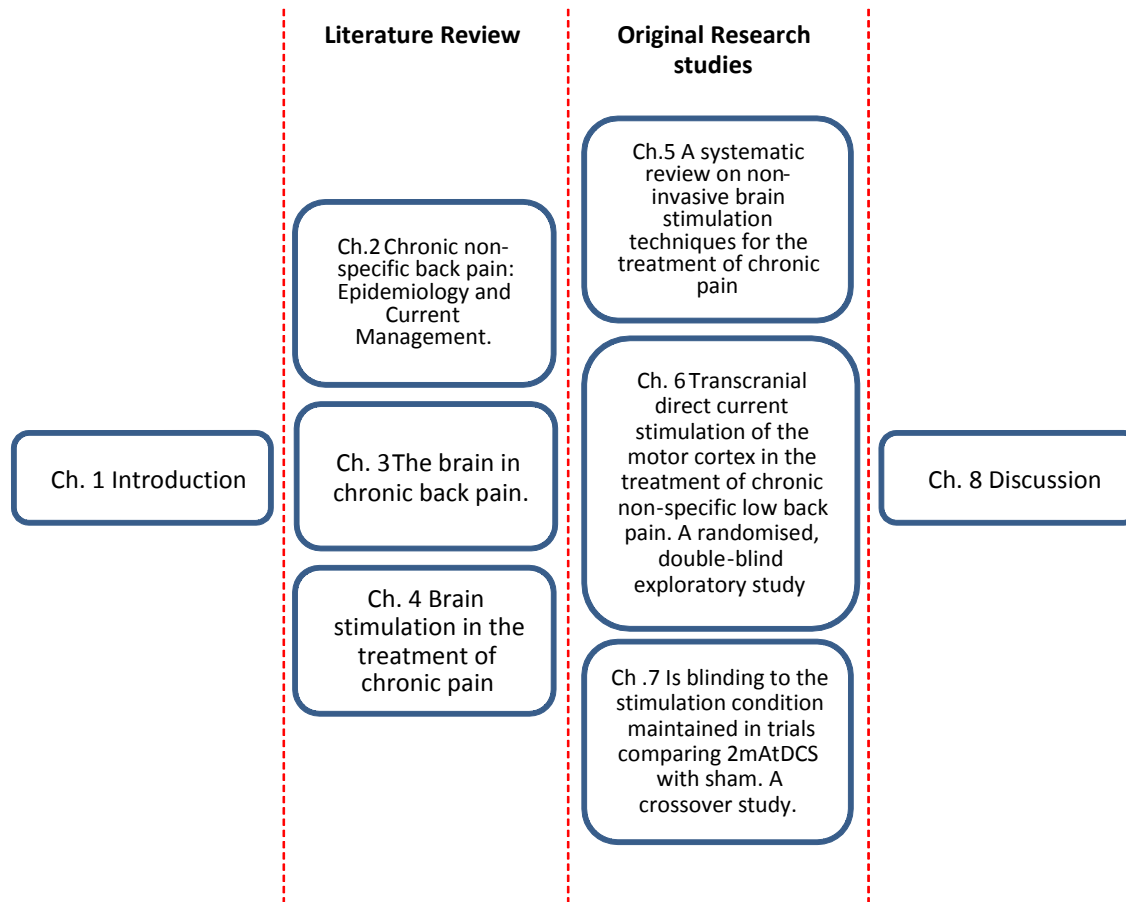
1.3.1 CHAPTER 5. A COCHRANE SYSTEMATIC REVIEW ON NON-INVASIVE BRAIN STIMULATION TECHNIQUES FOR THE TREATMENT OF CHRONIC PAIN

The first research study in this thesis is a systematic review meeting the standards of the Cochrane Collaboration and undertaken for publication in the Cochrane library. The primary aims of the review were to:

- critically evaluate the efficacy of non-invasive cortical stimulation techniques compared to sham controls for chronic pain.
- critically evaluate the influence of altered treatment parameters (i.e. stimulation method, parameters, dosage, site) on the efficacy of non-invasive cortical stimulation for chronic pain.

This review represents the first time that non invasive brain stimulation (NIBS) techniques (rTMS, tDCS and cranial electrotherapy stimulation (CES)) have been submitted to a rigorous systematic review. The conclusions of the review are less positive and more cautious than those of previous published reviews.

1.1 A FLOWCHART OUTLINING THE STRUCTURE OF THE THESIS



One key conclusion was that while there is insufficient evidence on which to base strong recommendations, there is some evidence to suggest that tDCS applied to the motor cortex may be effective in treating chronic pain. None of the identified studies had specifically investigated NIBS for the treatment of CNSLBP and there was little evidence on which to base conclusions regarding the optimal dose. In light of this the next study undertaken was an exploratory pilot study of tDCS for the treatment of CNSLBP.

1.3.2 CHAPTER 6 TRANSCRANIAL DIRECT CURRENT STIMULATION OF THE MOTOR CORTEX IN THE TREATMENT OF CHRONIC NON-SPECIFIC LOW BACK PAIN. A RANDOMISED, DOUBLE-BLIND EXPLORATORY STUDY

Using a double-blind interrupted time-series design this sham-controlled pilot study was the first to explore the possible effect of varying dosage on the efficacy of tDCS in 8 patients with CNSLBP and incorporated the rigour offered by randomisation, allocation concealment and efforts towards double-blinding via the use of a sham stimulation condition. The study was undertaken to test both the principle that tDCS might modulate chronic back pain, but also to provide exploratory data regarding optimal stimulation parameters to inform the design of a future RCT. No effect of tDCS was observed for active stimulation over sham on pain or low back pain-related disability. This result is at odds with those of existing published trials. However the data did suggest, though not conclusively, that participant blinding may have been imperfect. The possibility that tDCS and sham tDCS delivered in this way may not support effective blinding raises significant concerns for this field of research as it casts doubt upon the veracity of studies with positive conclusions that have utilised this method. It followed that prior to proceeding with a larger clinical trial, the assumption of effective study blinding, at the stimulation intensities commonly used in trials for chronic pain, required formal testing. This aim underpinned the third and final study of this thesis.

1.3.3 CHAPTER 7. IS BLINDING TO THE STIMULATION CONDITION MAINTAINED IN TRIALS COMPARING 2MA TDCS WITH SHAM STIMULATION? A CROSS-OVER STUDY

While participant and assessor blinding has been validated at stimulation intensities of 1mA, many clinical studies, and the majority of studies of tDCS for chronic pain have compared stimulation at intensities of 2mA to sham stimulation. The assumption that participant blinding would be maintained at this higher intensity has not been formally tested. 2mA intensity stimulation is associated with more sensory correlates that may compromise blinding, and, in addition the presence of skin redness under the electrode sites post-stimulation may threaten assessor blinding. Given the importance of adequate

blinding to controlling potential placebo effects it was considered vital to formally test the assumption of adequate blinding when comparing 2mA tDCS stimulation with the commonly used sham control stimulation condition.

Chapter 7 describes this study, a randomised cross-over trial in which 100 healthy volunteers were led to believe they were taking part in a trial of tDCS on word memory performance. This deception was planned to direct participants away from the actual research question to reduce the risk that they would overscrutinize the stimulation condition that they were receiving, thereby better mimicking the conditions of a clinical trial of tDCS. The primary outcome was participants' judgements regarding the stimulation condition they had received. The blinded assessor documented when skin redness was clearly noticeable at the electrode sites following stimulation. The results indicate that at intensities of 2mA both participant and assessor blinding are inadequate and that participants can distinguish the stimulation condition greater than would be expected by chance. These results have clear implications for our interpretation of the existing trials of tDCS for chronic pain, and other conditions, and for the design of future trials of tDCS.

1.4 CHAPTER 8. DISCUSSION AND CONCLUSION

Chapter 8 discusses the thesis as a whole, summarises the findings of each study and considers how these studies make a unique contribution to knowledge in this field. In light of the themes that arise from this new evidence recommendations are made for future research.

CHAPTER 2. CHRONIC NON-SPECIFIC BACK PAIN: EPIDEMIOLOGY AND CURRENT MANAGEMENT

2.1 INTRODUCTION AND DEFINITIONS

It is important to begin this discussion by attempting to define what is meant by pain and CNSLBP.

This thesis will be broadly concerned with the construct of pain as defined by the International Association for the Study of Pain (IASP). The IASP define pain as:

“An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage.” (Merskey & Bogduk 1994).

What this definition offers is an acknowledgement of both the sensory and emotional dimensions of the pain experience. The acknowledgement that, rather than simply reflecting actual or potential damage, pain might simply be described in terms of such damage acknowledges the often tenuous relationship between identifiable tissue injury and the experience of pain. As will be seen later in this chapter this is a particular issue in the study of low back pain and in chronic pain generally where pain persists beyond the timescale that would be expected for tissue healing to occur.

In chapter 3 consideration will be given to some of the proposed mechanisms by which the experience of pain may become less reflective of the state of the tissues. The IASP definition has been criticized, particularly for failing to incorporate behaviour. Since pain might be considered to be a stimulus for adaptive behavior to promote safety and recovery it has been argued that this omission leaves the IASP definition incomplete (Main et al. 2008). Nonetheless in the absence of a widely accepted alternative definition this one seems sufficient.

Recently clinical guidelines for the diagnosis and management of CNSLBP have been produced in Europe and the USA, (Airaksinen et al. 2006; Chou & Huffman 2007a; Chou & Huffman 2007b; NICE 2009). These documents are the result of multidisciplinary efforts to synthesise the vast amount of available data on this condition and therefore are a logical place to begin the search for a clear definition.

While there are subtle differences in definition there is little controversy regarding what is meant by low back pain. The European guidelines define lower back pain as “pain and

discomfort, localised below the costal margin and above the inferior gluteal fold, with or without referred leg pain.” (Airaksinen et al. 2006). The NICE guidelines define low back pain as “pain, muscle tension or stiffness affecting the lower back” and specify that the lower back is commonly considered; “the area bounded by the bottom of the rib cage and the buttock creases”. The guidelines state that patients may feel pain in their upper legs but explicitly exclude radicular pain arising from nerve root compression from their definition (NICE 2008). In contrast the American College of Physicians/ American Pain Society (ACP/ACS) do not offer specific guidance of anatomical location beyond the label “low back pain (Chou & Huffman 2007b).

Guidelines do vary in their definitions of ongoing back pain. While the European and the ACP/ACS guidelines define chronicity as pain in the lower back that has persisted for at least 12 weeks, the NICE guidelines refer specifically to “persistent” back pain which is defined as lasting longer than 6 weeks from its onset, but exclude people with severe and disabling back pain for greater than 12 months. Classifying back pain as chronic is less simple than it may initially appear. Chronic persistent LBP may be distinct from recurrent episodic LBP, but such a distinction may not always be easy to make.

All three sets of guidelines state that the label “non-specific” indicates the absence of a recognised patho-anatomic cause or serious underlying condition. A list of possible specific spinal pathologies that these guidelines exclude from the label “non-specific” is presented in table 1.

Specific spinal pathology appears to account for up to 15% of reported cases of low back pain with the large majority of cases falling under the “non-specific” umbrella (Deyo & Phillips 1996). NSLBP is a diagnosis of exclusion and tells us little about the underlying causes of the phenomena. The APA guidelines (Chou & Huffman 2007a) conclude that attempts to identify specific anatomical causes of non-specific low back pain have not been rigorously validated and found no evidence to suggest that labelling low back pain patients with anatomical diagnoses leads to improved clinical outcomes. Similarly a recent systematic review found no evidence that lumbar imaging improved clinical outcomes (Chou et al. 2009). Indeed there is indirect evidence to suggest the opposite. Briggs et al. (2010) found that chronic low back pain patients with high levels of disability held more patho-anatomic views about their disorder than those with low levels of disability and in a large retrospective study of workers’ compensation back pain cases (Webster and Cifuentes 2010), early MRI of acute back pain cases was associated with poorer clinical

outcome after controlling for the clinical factors that increased patients' propensity to be referred for a scan.

Table 2.1 The specific spinal pathologies that the European, ACP/ACS and NICE guidelines exclude from the label "non-specific low back pain".

Pathology
Cancer/ Tumour
Spinal Infection
Cauda equina syndrome
Spinal stenosis
Radiculopathy
Vertebral Compression fracture/ Osteoporosis
Ankylosing Spondylitis/ Inflammatory Disorder
Rheumatoid Arthritis

The classification of non-specific back pain into distinct subgroups has long been considered a research priority and a substantial amount has been written on this topic. Two systematic reviews of available classification systems identified a wide variety of suggested approaches that focus on varying factors such as putative spinal pathology, clinical symptom profile, psychological features, work status, or a mix of these variables (Riddle 1998; McCarthy et al. 2004). As yet no such approach is universally accepted. The absence of a clear diagnostic framework for non-specific low back pain has inevitably had an effect on the development of appropriate and effective clinical interventions for the condition. It would appear that this lack of diagnostic clarity has led to significant diversity in how the condition is conceptualised and treated, with little consensus within or between groups of clinicians and researchers.

Kent et al. (2005) demonstrated a significant lack of consensus amongst a variety of clinical disciplines in how they classify NSLBP patients into subgroups. Most clinicians sub-grouped

patients based on putative pathoanatomical dysfunction but the specific models used were diverse and conflicting. For example for facet joint pain, one of the most common diagnostic subgroups that clinicians identified, they found less than 10% agreement between clinicians on the 3 most common combinations of signs and symptoms. The same authors then conducted a survey on the beliefs of clinicians and researchers regarding the nature of NSLBP in an attempt to develop a conceptual framework for understanding the condition (Kent et al. 2009). Most participants believed NSLBP to be comprised of multiple conditions which are likely to be best classified based on clinical symptoms and signs rather than patho-anatomy, and that unlike acute NSLBP many respondents believed that the degree of pain and disability associated with CNSLBP are predominantly psychological in nature. Despite this apparent consistency the authors could identify no unifying framework for conceptualising the problem. Other studies have confirmed this lack of consensus. Bishop et al. (2008) found that general practitioners and physiotherapists held quite diverse attitudes and beliefs about LBP which, in turn, influenced their practice.

For the purposes of this thesis CNSLBP will be imperfectly defined as pain and discomfort of greater than 3 months duration, localised below the costal margin and above the inferior gluteal fold, with or without referred leg pain in the absence of the specific spinal pathologies outlined in table 1. As such it will be consistent in terms of duration with the ACP/ ACS and European guidelines and in location with the ACP/ACS, the European and the NICE guidelines. In considering the literature relating to CNSLBP a further challenge is the inconsistency of definitions and language used in the literature. Many studies do not clearly classify chronic low back pain (CLBP) as specific or non-specific, and some do not provide clear parameters for the term chronic. As such this literature review will consider studies of CNSLBP and those that relate more broadly to CLBP, though it is acknowledged that such studies at times may include cases of specific spinal pathology. The term CNSLBP will be used only where clearly justified by the studies under discussion, otherwise CLBP will be used.

2.2 EPIDEMIOLOGY OF LOW BACK PAIN

In order to fully understand CNSLBP one must first consider the epidemiological data relating to low back pain as a whole.

2.2.1 PREVALENCE OF BACK PAIN

Prevalence can be defined as the number of people in a population who have a specified condition at a defined point or period in time (Bruce et al. 2008). Many studies of back pain

prevalence are specific to targeted populations, for example by age group (e.g. (Jacobs et al. 2006; Masiero et al. 2008) or occupation (Karahan et al. 2009; Leggat et al. 2008). To better understand the general scale of low back pain it is arguably more useful to consider studies that sample general populations. Multiple studies of LBP prevalence in these populations have produced a somewhat disparate picture.

Loney & Stratford (1998) performed a systematic review of studies of LBP prevalence published between 1981 and 1998. Of the 13 studies that met the criteria set for methodological acceptability there was marked variance in the prevalence of LBP. Point prevalence, defined as the number of people reporting back pain at a single point in time ranged from 4.4% to 33%. The 1 year prevalence varied from 3.9%-63% and the lifetime prevalence between 13.8-84%. Much of this variability could be explained by differences in the duration and definitions of LBP studied and the methodological quality of the included studies. Of three high quality studies included in this review that examined populations from regions of the UK, Denmark and Canada (Cassidy et al. 1998; Biering-Sorensen 1983; Hillman et al. 1996), point prevalence ranged between 13.7-28.7%, 1 year prevalence between 39-68.8% and lifetime prevalence between 59-84%.

A review of Nordic prevalence studies (Leboeuf-Yde & Lauritsen 1995) found that only 10 of 26 identified studies met criteria of methodological acceptability. Within these, heterogeneity in the populations studied and unclear reporting made it impossible to pool results or compare estimates. The same group subsequently performed their own study of a middle aged Danish population (Leboeuf-Yde et al. 1996) and pooled these results with 4 previous studies. They report a 1 year prevalence of 44-54% and a lifetime prevalence of 60-65% for Nordic populations.

Walker (1999) performed a systematic review of all studies of LBP prevalence between 1966 and 1998. Only 54% of identified studies were considered methodologically acceptable. Within these, those studies where results allowed pooling of results produced a range of point prevalence between 12-33%, one year prevalence between 22-65% and lifetime prevalence between 11-84%. Again this variability was underpinned by substantial methodological differences, making firm conclusions difficult and useful comparisons between geographical regions, or developed and developing nations impossible. A high quality study from the same research group examined LBP prevalence in Australia and found an estimated point prevalence of 25.6%, 1 year prevalence of 67.6% and lifetime prevalence of 79.2% (Walker et al. 2004).

Studies that have sought to replicate prevalence findings using the same methodology within the same population have found that the results are reasonably stable (Leino et al. 1994; Linton & Ryberg 2000). This suggests that between-study variability in prevalence studies plays an important role in perpetuating heterogeneity in outcomes. Hoy et al. (2012) recently attempted to control for this variance. In a systematic review and meta-analysis of low back pain prevalence studies they identified which risk of bias items influenced prevalence estimates and then controlled for them in their meta-analysis. After this adjustment they reported a point prevalence of “activity limiting low back pain, lasting more than one day” of 11.9% and a one month prevalence of 23.2% and these values were lower than the unadjusted estimates.

There is evidence that reported prevalence may be specific to the culture from which it is sampled. Raspe et al. (2004) surveyed large populations in Britain and Germany with a consistent methodology. German respondents reported a significantly higher prevalence for all timescales, and this difference could not be explained by demographic, lifestyle, educational or anthropomorphic factors. Tentative evidence suggests differences between developing and developed nations. While the review by Walker (1999) highlighted a dearth of evidence on prevalence from developing countries, a non-systematic review of back pain epidemiology data (Volinn 1997) suggested that “low-income” countries demonstrate significantly smaller prevalence of back pain than “high-income” countries and that within low-income countries the prevalence increases in urban compared to rural populations. It should be noted that the review was less systematic than those described above and the quality of the included studies was not systematically addressed.

Studies specific to the UK provide a more consistent picture. Webb et al. (2003) reported a 1 month prevalence of 22.7%. The South Manchester Back Pain Survey found a 1 month prevalence of between 35 and 37% and a lifetime prevalence of 58% (Papageorgiou et al. 1995). Similarly a survey of the population in Bradford (Hillman et al. 1996) reported a 1 year prevalence of 39% and lifetime prevalence of 56%, and a follow up survey of the same population 3 years later estimated 1 year prevalence at 44% and lifetime prevalence at 61% (Waxman et al. 2000) though lifetime prevalence estimates are prone to recall bias and subsequent underestimation. A survey that included eight different geographical areas of the UK reported a 1 year prevalence of 36.1% and a lifetime prevalence of 58.3% with only small geographical differences observed (Walsh 1992). Contrasting these figures with a

recent German study (Schmidt et al. 2007) once again highlights a higher prevalence in Germany, with 1 year prevalence of 76% and lifetime prevalence of 85.5%.

2.2.2 TRENDS IN BACK PAIN PREVALENCE

While these studies provide snapshot data from a given time and place, it is worthwhile to consider whether trends can be observed in back pain prevalence. Harkness et al. (2005) contrasted the findings of 2 population based surveys performed in the Manchester region 40 years apart. Back pain point prevalence measured in the 1990's demonstrated a 2.6-fold increase in males and a 2-fold increase in females compared to data from the 1950's. Whilst methodological and population variations may have influenced the results they are unlikely to have accounted for such a dramatic change. The authors suggest a number of factors that may have contributed to this rise including changes of culture such as an increased awareness of pain syndromes, and increased willingness to report symptoms and an increase in rates of psychological distress.

Palmer et al. (2000) compared 2 large UK population surveys performed 10 years apart, in 1987-8 (Walsh et al. 1992) and 1997-8 (Palmer et al. 1999). They found a 12.7% increase in back pain prevalence but no increase in a specific measure of pain-related disability ("back pain making it difficult to put on hosiery"). However the study involved the comparison of 2 rather different surveys and the response rate was low which may have influenced the results. In contrast a UK based study with a 7 year interval between surveys (Macfarlane et al. 2000) noted a slight decrease in prevalence and Hüppe et al. (2007) demonstrated no increase in point or 1 year prevalence of back pain between 1991/2 and 2003 in Germany. In the north of England Waxman et al. (2000) reported only small increases in the prevalence of back pain generally and the proportion of these with chronic back pain over a shorter 3 year period. However they did observe a large increase in disability related to low back pain: in 1994 half of those categorised with persistent low back pain reported difficulties with activities of daily living (ADL's), but this had increased to 75% in 1997.

A number of large studies undertaken in Finnish populations have failed to demonstrate any strong trends in back pain prevalence. Leino et al. (1994) demonstrated no change in the prevalence of back disorders in the general population between 1978 and 1992, and a large study of farmers (Manninen et al. 1996) also found no evidence of change in back pain related morbidity over a 12 year period. In an extremely large comparison of population surveys (n=20,043 respondents) Heistaro et al. (1998) noted that prevalence was fairly stable with a trend towards decreasing prevalence in male respondents over a 20

year period. In older, home dwelling adults, back pain that interfered with functioning shows a slight and moderately significant decrease (Pitkala et al. 2002). In contrast to these findings the adolescent Finnish population demonstrates evidence of an increase in back pain from 1989-1999 (Hakala et al. 2002).

The data relating to trends in prevalence are broadly equivocal and do not clearly indicate a systematic increase in the prevalence of back pain in western industrialised societies over recent decades. However there is some evidence of an increase in back pain related disability. Waxman et al.'s (2000) results are indirectly supported by various sources. Reviewing the UK data obtained from the Department for Work and Pensions pertaining to the payment of sickness and invalidity benefits relating to back pain, Waddell (2004) notes a large increase between the mid 1950'S and the 1990's. While this measure cannot be considered a direct measure of LBP-related disability since the trends seen will be the result of a myriad of influences including welfare policy changes, they do indicate a drastic rate of increase in sickness certification and benefit payment through the 1980's and 1990's; although there was some evidence of the beginnings of a decline from the mid 1990's. This increase in back pain related sickness and incapacity benefit was far greater than that seen for numerous other debilitating conditions, both musculoskeletal and non-musculoskeletal (CSAG 1994). More recent data is scarce. However Hüppe et al. (2007) found no marked increase in the prevalence of disabling back pain between 1991/2 and 2003 in Germany and suggest that the peak of any epidemic of back pain related disability may have passed.

2.2.3 PREVALENCE OF CHRONIC LOW BACK PAIN

The data discussed above consider the prevalence of back pain in its entirety rather than the specific prevalence of CLBP. In a large survey in the USA, Hardt et al. (2008) reported a 10.1% point prevalence of CLBP. Another large population study performed in Holland (Picavet et al. 1999) demonstrated a 12 month prevalence of 16-27%. Within this group 11.6-18.2% reported back pain associated activity limitations and 0.7-6.2% reported back pain associated work disability. Both studies defined CLBP as pain lasting for 3 months or more. Hillman et al. (1996) found that of the 39% of respondents reporting back pain in the last year, a quarter could be classified as having CLBP, defined as pain on most days for over 3 months.

In the UK Webb et al. (2003) conducted a population study in the Pennines region. They used a significantly higher threshold for defining chronic pain, of pain that first occurred 5 or more years ago. Disabling pain was defined as pain with an associated Oswestry

Disability Score (Fairbank and Pynsent 2000) of 25 points or greater and intense pain as that graded “moderate” or worse. They reported a 1 month prevalence of 11.3% for CLBP, 8.9% for disabling LBP and 5% for intense and disabling CLBP. This study suggests that defining chronic low back pain by its duration alone does not reflect its impact and consequences and that intense pain and disability is not an inevitable consequence of lasting back pain. Consistent with these findings a Belgian study (Goubert et al. 2004) found an overall back pain 6 month prevalence of 41.8%, although there was only an 8.2% 6 month prevalence of disabling pain. In Australia Walker (2004) found that 12.8% of respondents reported LBP every day over a 6 month period with 10.5% of those reporting LBP with high disability.

What seems reasonably clear from the prevalence literature is that LBP will affect a majority of the population in Western industrialised societies at some point in their lifetime and a significant proportion of the population at any given time. Most of these people will not go on to develop disabling CLBP but a small but significant proportion will.

2.2.4 THE INCIDENCE OF LOW BACK PAIN

Despite the abundance of evidence relating to prevalence, estimates of incidence (the number of new cases in the given time period) are harder to come by, in large part because by early adulthood the incidence is already high. In a systematic review Hoy et al. (2010) identified twelve studies relating to incidence. These studies were characterised by variation in case definitions and many were at risk of bias. The 1 year incidence for a first ever episode of back pain ranged from 6.3% to 15.4% and for any episode of back pain the range was from 1.5% to 36%. More recently (Waterman et al. 2012) reviewed a national population database in the United States between 2004 and 2008 to estimate the incidence of back pain related visits to hospital emergency departments. They found an incidence rate of 1.39 per thousand person years, with a high peak in the 25 to 29 year age group (2.58 per thousand person years). Compared with the black and white population, Asians had lower rates of back pain. Emergency department admissions only reflect a subgroup of the wider back pain population, most likely comprised of participants at the more severe end of the spectrum, and so these data can be expected to be substantially lower than the total incidence of back pain.

2.2.5 THE NATURAL HISTORY OF LOW BACK PAIN

Acute LBP has historically been considered to be a benign and self-limiting condition from which the vast majority of sufferers recover (Waddell 2004). A number of systematic

reviews of prospective cohort studies have scrutinised the natural history of LBP and their findings offer a clear challenge to this assumption.

In a review of studies of the course of back pain in primary care Von Korff & Saunders (1996) found that back pain is typically a recurrent condition. Most patients with an acute episode of LBP improved considerably during the first 4 weeks after seeking treatment although up to 75% continued to experience pain of at least mild intensity at 1 month from initial care seeking, 33% of whom reported pain of at least moderate intensity. Up to 25% of patients reported significant activity limitation at this stage. At follow-up periods of greater than 1 year, one in seven patients reported severe pain and one in five substantial activity limitations. These findings are supported by a systematic review of prospective inception cohort studies of acute low back pain (ALBP) (Pengel et al. 2003). Rapid improvements were seen in the first month in both pain and disability. The trend towards improvement continued up to 3 months from initial care-seeking. Most patients (68-86%) who were off work due to back pain had returned to work within one month with 93% returned to work at 6 months. However there was a 26% risk of at least one recurrence of low back pain within 3 months, and that increased to 73% within 12 months. Most people continued to experience low levels of pain and disability at 12 months. In a review of the long-term course of low back pain that included studies with a follow-up period of at least 1 year, Hestbaek et al. (2003) noted between 42 and 75% of subjects still experience pain at one year, 44 to 78% of patients will experience a relapse in that time and between 3 and 40% of patients continued to be off sick from work at 6 months from inclusion into the study. Stanton et al. (2008) argue that the true rate of recurrence after acute low back pain has been exaggerated by previous studies since they were unable to differentiate genuinely recurrent back pain from flare-ups of ongoing pain and persisting pain. The same group and others (Stanton et al. 2009; Kamper et al. 2011; Wasiak et al. 2003) have highlighted that recovery and recurrence is often loosely defined in studies and that this has affected results. Stanton et al. (2008) recruited a cohort of patients who had recovered (defined as a pain-free period of at least one month) from an acute episode of low back pain and monitored recurrence (defined as LBP that had lasted for over 24 hours) over a year. They found a much lower rate of recurrence with an upper limit of 33%. Still these results suggest that recurrence of back pain after an acute episode is far from rare.

Croft et al. (1998) studied patients presenting to their GP with LBP for the first time over a 12 month period at two GP practices in the UK and followed up patients from inception and

at 1 week, 3 months and a year. After the initial visit 59% did not consult their doctor again in the following 6 months. At 3 months following the first visit 90% no longer consulted for their back pain. Despite this seemingly encouraging picture on follow up interview at 3 months only 21% had completely recovered (no pain or disability) increasing to 25% at 1 year. This study selected patients by their first visit to a GP for LBP in a 12 month period, recruiting patients with a mix of acute, sub-acute and chronic LBP and this mixture is likely to have significantly affected prognosis. However a population based study (Cassidy et al. 2005) confirms back pain as a common recurrent condition. While most new and recurrent cases were classified as mild, less than a third resolved within a year and the 6 month recurrence rate was 29%. These findings suggest that the popular image of low back pain as a rapidly self-resolving condition may be an illusion underpinned by a lack of care-seeking and high rates of return to work.

Inception cohort studies that have specifically recruited recent onset low back pain cases present a slightly more positive view of prognosis. Coste et al. (2004) recruited patients with NSLBP of less than 72 hours duration and followed them for 3 months. Defining recovery as “the near disappearance of both pain and disability” using low cut-offs on a pain Visual Analogue Scale (VAS) and the Roland and Morris Disability Questionnaire (RMDQ) (Roland and Morris 1983), 87% of patients had recovered by one month and at 3 months only 5% of subjects had not recovered and were classified as having CLBP.

Schiøttz-christensen et al. (1999) recruited patients presenting to their GP in Denmark with back pain lasting for less than 2 weeks and followed them over a 1 year period. 97% of patients had returned to work at 1 month and at 12 months only 2% remained on sickness absence. Importantly, while 84% of people considered themselves recovered (defined by the question “feeling of well being with regard to low back problems yes/no”) at that stage, at 6 months this had dropped to 47%, remaining fairly stable at 12 months (54%). While these results suggest a greater probability of early and rapid improvement and full recovery than those of Croft et al. (1998) they remain supportive of the notion of a fluctuating and recurrent course of LBP over the long term.

More recently Henschke et al. (2008) studied patients presenting with LBP of recent onset (less than 2 weeks duration) in Australian primary care. 83% of patients who had taken sick leave had returned to their previous work status by 3 months, increasing slightly to 89.5% at 1 year. 73.3% reported no disability at 3 months, increasing to 83.3% at one year. 58.2% had no pain at 3 months increasing to 72.5% at one year. “Complete recovery” was defined

as a combination of all of these parameters, apart from return to work for those who were not seeking work. At 3 months 57.4% were considered completely recovered, increasing to 71.8% at one year.

These data are suggestive of a relatively good prognosis, with most patients with recent onset back pain initially experiencing rapid improvements in pain and disability and the majority returning to work. However it seems that a significant proportion can expect to experience a recurrence in their symptoms at some stage and many will continue to experience low levels of pain and disability. It remains difficult to distinguish patients with persistent disabling NSLBP from those with recurrent episodic LBP since time-point specific measures inevitably include both types of patient.

Carey et al. (2000) noted that 7.7% of patients who sought care for an episode of LBP (of less than 10 weeks duration) went on to develop CLBP, defined as symptoms persisting for 3 months following the first consultation and found that the majority of these still had CLBP 2 years later. Of this group 61% were characterised as having “unremitting low back pain” which was functionally disabling at all of the time intervals studied from inception to 22 months. Similarly Klenerman et al. (1995) found that 7.3% of ALBP patients had not recovered at both the 2 month and 1 year follow up, and van den Hoogen et al. (1998) demonstrated that 10% still suffered from LBP at one year.

A recent systematic review of inception cohort studies confirms that whether patients present with acute or persistent low back pain they demonstrate marked improvement in the first six weeks, after which improvement slows, and, particularly in cohorts with persistent pain, low to moderate levels of disability are still present at one year (Costa et al. 2012).

Perhaps the most accurate description of the natural course of low back pain has been offered by Croft et al. (1998) who recommend that it should be viewed as “a chronic problem with an untidy pattern of grumbling symptoms and periods of relative freedom from pain and disability interspersed with acute episodes, exacerbations and recurrences”.

2.3 THE CONSEQUENCES AND COSTS OF LOW BACK PAIN

2.3.1 ECONOMIC COSTS

A condition as prevalent as back pain inevitably incurs significant costs to society. Maniadakis & Gray (2000) estimated the direct annual costs to the UK in 1998 (the specific costs of healthcare) of back pain in pounds sterling to be over £1.6 billion. This figure was

dwarfed by their estimate of the indirect costs in terms of employment consequences, production loss and informal care which reached over £10.6 billion. These costs have a significant impact on society, the individual back pain sufferer and those around them. Comparison with other common health conditions demonstrated that while the direct costs were similar to those of coronary heart disease, the indirect costs far exceeded those of most common chronic illnesses.

In the USA the national Medical Expenditure Panel Survey demonstrated that self-reported back and neck pain accounted for a significant proportion of health care expenditure and that these costs had increased significantly from 1997 to 2005 (Martin et al. 2008). More recently a systematic review of cost of illness studies of low back pain internationally (Dagenais et al. 2008) found that variation in the methods used in studies lead to gross differences in the estimated costs although it was clear that back pain represents an enormous economic burden. The authors estimate that the costs to the USA (both direct and indirect) range between 19.6-118.8 billion US dollars with these costs heavily skewed by back pain with the longest duration, indicating that CLBP accounts for the majority of the costs of back pain to society. That CLBP sufferers comprise a small minority of low back pain but account for the largest percentage of costs is confirmed by a separate review (Maetzel and Li 2002a).

2.3.2 DISABILITY

Beyond the costs to society it is important to consider the costs to the individual. Whilst crude, back pain related disability and work loss provide 2 measures of the gross impact that the condition has on sufferers (Dionne et al. 1999).

The data on the prevalence of back pain related disability in Westernised countries is remarkably consistent. Walker et al. (2004) found that in Australia one in ten adults reported activity limitation as a result of low back pain over a 6 month period. Similarly in the UK population studies have shown a 10% one month prevalence and a 10-24% one year prevalence of back pain-related activity limitation (Mason 1994; Walsh 1992; Waxman, et al. 2000) and in Canada Cassidy et al. (1998) found a 6 month prevalence of high-disability back pain of 10.7%. Recently Schmidt et al. (2007) also confirmed a population estimate of 11.2% for disabling back pain in Germany.

2.3.3 WORK ABSENCE

In the 1990's Hillman et al. (1996) found a one year prevalence of back pain related work absence of 6.4% amongst the UK population. However taken as a proportion of employed

respondents with back pain this figure rose to 21.8%. Walsh et al. (1992) estimated the life time and one year population prevalence of work absence due to back pain at 34% and 10% respectively for men and 23% and 7% respectively for women. Similar figures are seen in Switzerland (Santos-Eggimann et al. 2000). In Sweden Linton et al. (1998) noted the annual prevalence of work loss at 12.6% for official sick leave, but “unofficial” work absence accounted for an additional 10%. As already discussed, Waddell (2004) reported a significant increase in related work absence and incapacity benefit from the 1950’s to 1990’s and in the early 2000’s back pain accounted for 13.5% of all UK incapacity benefits.

The social and individual costs of low back pain are vast. While most back pain has a fairly good prognosis, the high prevalence of acute back pain leads to substantial healthcare and social costs, but the majority of costs are related to the small proportion who go on to develop persistent chronic symptoms (Dagenais et al. 2008; Maetzel & Li 2002b).

2.4 PREDICTING CHRONICITY – WHO DEVELOPS CHRONIC SYMPTOMS AND WHY?

There has been an enormous research effort to attempt to define the factors and characteristics of ALBP that predict poor recovery and prognosis and the development of CLBP. Such investigations may reveal clues to the underlying mechanisms of chronic low back pain, and where risk factors are potentially modifiable, highlight targets for treatment and allow screening of acute low back pain patients by risk. Both cross-sectional and prospective observational study data have been generated on a wide range of potential factors. While cross-sectional data can inform us of variables that associate with outcome, we require prospectively gathered data in an ALBP population to confirm whether such associations have a predictive value for the future development of chronicity. In order to make sense of the mountain of data it is perhaps easiest to begin with the findings of systematic reviews of studies that have investigated populations of ALBP patients.

In 1996 Von Korff et al. reviewed studies of prognostic variables for back pain outcomes and concluded that methodological variability between studies had led to a failure to identify a set of prognostic variables that allow reliable prediction of back pain outcomes. Similarly a recent review of studies investigating prognostic factors for poor recovery from “recent onset” (less than 3 months duration) NSLBP (Kent and Keating 2008) found contradictory and inconsistent results. Many factors had been shown to be associated with recovery when considered in isolation but few were retained in multivariate models. More worryingly the authors found an inverse correlation between measures of study quality and the size of statistically significant odds ratios, strongly suggesting that lower quality studies

tend to overestimate the influence of various risk factors. They conclude that despite a significant body of studies there is uncertainty regarding which factors are predictive of outcome and the strength of those associations. Recently Hayden et al. (2009) have also highlighted the problem of significant methodological variation in systematic reviews of low back pain prognosis. As such, any consideration of risk factors for chronicity must be viewed in the light of these limitations.

The following discussion will attempt to group risk factors in to the following categories: structural/ pathological factors, symptom based factors, back pain history, back pain related disability, work related factors, psychological factors, and general and physical health.

2.4.1 STRUCTURAL/ PATHOLOGICAL FACTORS

As discussed above, in the vast majority of back pain cases no accurate diagnosis can be made. Nevertheless commonly used clinical investigations such as imaging techniques provide an assessment of the state and integrity of a number of spinal structures, and discern the presence of abnormalities which might plausibly account for or be intimately related to the phenomena of low back pain.

A number of studies have confirmed the presence of intervertebral disc abnormalities found by lumbar spine imaging in a large proportion of asymptomatic subjects (Boos et al. 1995; Weishaupt et al. 1998; Beattie et al. 2000; Jarvik et al. 2001). Jarvik et al. (2001) found that the presence of disc bulges, facet joint degeneration, changes in the disc endplates and mild spondylolisthesis identified by MRI increased with age but not with a history of back pain. In this study disc extrusion was the only finding to be significantly linked with previous episodes of back pain though trends were observed towards an association with moderate to severe central canal stenosis and nerve root compromise. Beattie et al. (2000) studied the association between lumbar spine MRI scans and patient self-reported back symptoms in a large sample (n=408) of LBP patients. Again only marked lumbar disc extrusion (adjusted Odds ratio (OR) 2.72 95%CI 1.50 to 4.9) and severe nerve compression (adjusted OR 3.34, 95%CI 1.51 to 7.38) were strongly predictive of leg pain extending below the knee (as a result of radiculopathy). Disc degeneration, bulging and spinal stenosis were not associated with any specific pain pattern. Kalichman et al. (2009) demonstrated an increasing prevalence of central canal spinal stenosis with age but found that only severe or "absolute" stenosis was associated with an increased risk of low back

pain, again they found no association between other degenerative features and pain (Kalichman et al. 2010).

Using lumbar spine magnetic resonance imaging (MRI), Borenstein et al. (2001) recruited a group of 67 asymptomatic subjects who were subsequently followed up 7 years later. At the initial MRI scan 31% of subjects demonstrated an identifiable abnormality of the lumbar disc or spinal canal. At the follow up no association was seen between the incidence of disc or spinal canal pathology and the development or duration of low back pain. A study of spondylolysis and spondylolisthesis prevalence examined computerised tomography imaging of the lumbar spine in 188 subjects regardless of back pain status (Kalichman et al. 2009). They found that the prevalence of spondylolysis was almost double that which had been previously found using less sophisticated imaging techniques such as radiography. Once again no significant association was seen between the occurrence of low back pain and spondylolysis or spondylolisthesis at any spinal level.

The few prospective longitudinal studies that have included lumbar imaging measures reinforce this low predictive value. Jarvik et al. (2005) recruited a cohort of 148 subjects who reported no back pain and performed spinal MRI scans at baseline and at 3 year follow up. The presence and course of any back pain was monitored at 6 monthly intervals. Over the study period MRI findings were found to change little. Importantly, no association was found between new low back pain, disc degeneration, endplate changes, annular tears or facet joint degeneration as diagnosed by MRI. Carragee et al. (2005) recruited subjects with mild persistent LBP without disability, and a subgroup of patients with any chronic regional pain syndrome. Subjects underwent lumbar MRI and those who were willing underwent lumbar discography. Subjects were followed at 6 monthly intervals over a 5 year period. Again no association was found between any feature of MRI or discography and clinical outcome.

As well as adding little or no predictive value in their own right, Shambrook et al. (2011) demonstrated that the presence or absence of spinal pathology identified on MRI had no relationship with the prevalence of known physical or psychological risk factors for the development and persistence of LBP. MRI findings of structural abnormalities in a group of 53 CNSLBP patients also had no significant influence on clinical outcome after a course of exercise therapy (Kleinstück et al. 2006).

Apart from clear disc extrusion, radiculopathy and severe central canal stenosis (all of which can be classified as “specific” low back pain), a range of structural features and anatomical abnormalities of the lumbar spine that are identifiable through imaging techniques appear to offer little or no diagnostic value in NSLBP, do not predict the presence or distribution of back pain and are not predictive of future LBP or of adverse outcome from existing LBP. Recently Hancock et al. (2011) have argued for more research into the possible structural causes of LBP and advised against dismissing the importance of structural pathology. Nevertheless beyond the implications of these findings for clinical practice these data suggest that the structural abnormalities that are currently detectable are unlikely to be major players in the development of CNSLBP.

2.4.2 SYMPTOM BASED FACTORS

A number of studies have considered the location and severity of pain as possible predictors of chronicity. A systematic review of cohort studies (Mallen et al. 2007) found that pain at multiple sites or widespread pain was a significant indicator of poor prognosis as was higher pain intensity at baseline in the majority of studies reviewed. The negative influence that high pain intensity at baseline has on outcome has been confirmed in cross-sectional (Lefevre-Colau et al. 2009) and many prospective studies (Jones et al. 2006; Henschke et al. 2008; Hill et al. 2011; Dunn et al. 2010).

Gheldof et al. (2007) demonstrated that the risk of long term LBP was positively associated with current pain severity and pain radiating into the ankle/feet. This finding is borne out by data from other prospective cohort studies. Macfarlane et al. (1999) found that the absence of pain in the leg was predictive of good outcome in male subjects, and sciatica, defined as radiating leg pain extending to the knee or below has been shown to be predictive of poor outcome from ALBP (Carey et al. 2000). Pain radiating below the knee is commonly associated with radicular syndrome, a specific spinal pathology. Consistent with this the presence of signs of neurological compromise on clinical examination have been found to be predictive of non-recovery (Grotle et al. 2005; Grotle & Brox 2007). In a review of systematic reviews Hayden et al. (2009) confirmed that nerve root examination findings and sciatica were consistently related to poor outcome and the European guidelines for the management of CNSLBP found moderate evidence that radicular signs were risk factors for chronicity (Airaksinen et al. 2006).

In their review of reviews Hayden et al. (2008) found insufficient evidence to suggest any other physical clinical examination findings as determinants of prognosis. The same

conclusion was reached in the European guidelines for the management of CNSLBP (Airaksinen et al. 2006). Restriction of spinal mobility on examination in the acute stage was identified as predictive by Thomas et al. (1999) and Enthoven et al. (2006) whereas similar studies (Coste et al. 1994; Schiøttz-christensen et al. 1999) found no predictive value for movement restriction. Importantly the 2 negative studies restricted their inclusion to strictly acute back pain, whereas the 2 positive studies included long-duration back pain. It seems reasonable to infer from this that restriction of movement in the acute stage does not play a strong role in the development of CLBP from the acute stage.

2.4.3 BACK PAIN HISTORY

The literature is supportive of the intuitive notion that more episodes of back pain and a greater duration of back pain impact negatively on prognosis. In a post-hoc analysis of data derived from a randomised controlled trial, Bekkering et al. (2005) found that the most robust prognostic factor in low back pain was the duration of the current episode, a longer duration predicting a poorer prognosis. This finding is reinforced by data from large prospective cohort studies (Dunn & Croft 2006; Henschke et al. 2008) confirming that longer duration of the LBP episode prior to consultation is predictive of a longer time to recovery. In their systematic review Mallen et al. (2007) confirmed that both a history of previous episodes of LBP and a longer duration of the presenting episode were predictive of poor recovery from LBP.

2.4.4 BACK PAIN RELATED DISABILITY

The level of self reported disability that a patient demonstrates at initial consultation may also have a bearing on their clinical outcome. Carey et al. (1995) followed an inception cohort of 1633 patients who consulted primary care clinicians for ALBP over a 6 month period. They found that the strongest predictor of delayed return to normal function was the baseline level of functional impairment. This finding is supported by systematic reviews. Mallen et al. (2007) identify higher baseline disability as an important prognostic factor in LBP. In their review of systematic reviews of LBP prognosis Hayden et al. (2008) found that despite significant methodological barriers to accurate data synthesis, baseline functional disability was consistently reported as an important prognostic factor. In contrast a recent inception cohort study by Henschke et al. (2008) did not find that functional interference was predictive of outcome, although pain intensity was. Conversely Epping-Jordan et al. (1998) found that in a subacute back pain population high levels of disability at baseline were predictive of subsequent high levels of pain, but high baseline pain intensity did not predict subsequent disability.

2.4.5 WORK RELATED FACTORS

Occupational factors have also received significant attention. Iles et al. (2008) reviewed studies that examined predictors of failure to return to work. They found that job satisfaction was a consistent work-related factor that influenced this outcome. In the review by Hayden et al. (2008) many work related occupational factors were not consistently reported across systematic reviews as prognostic indicators. Specifically, the occupation category, work history, availability of modified duties, size of the firm, absenteeism policy, job satisfaction and risk of poor working postures were not consistently reported. Heavy physical demands of work and poor relations with colleagues were consistently reported and found to be associated with outcome.

In a prospective study of workers presenting to primary care with low back pain Dionne et al. (2007) found that different factors were predictive of “return to work in good health” between male and female participants. In females increasing job seniority, the lack of a unionized job and an increase in work-related fear avoidance beliefs determined failure to recover. In males a belief that the job is below the participant’s qualifications, the perceived likelihood of losing the job, the job status and work-related fear avoidance beliefs were all related to poor outcome but the physical demands of work were not. In a recent cross-sectional survey of 4,522 respondents with CLBP, low job satisfaction and a perceived lack of recognition at work were identified as predictive of poor outcome (Airaksinen et al. 2006; Lefevre-Colau et al. 2009). Dunn et al. (2010) demonstrated that unemployment at the time of presentation to primary care was a risk factor for disabling pain at 12 month follow up.

Following an extensive review of the literature the European guidelines for the management of CNSLBP (Airaksinen et al. 2006) concluded that there was strong evidence that low work place support is a predictor of chronicity in acute back pain patients. They also concluded that strong evidence indicates that difficulty in returning to work at 4-12 weeks from presentation to primary care significantly decreases the chance of ever returning to work, and that the chances of returning to work reduce with increasing back pain-related sickness absence. Moderate evidence was found indicating that shorter job tenure and heavy occupations with no modified duty are predictors of poor outcome (Airaksinen et al. 2006).

2.4.6 PSYCHOLOGICAL, COGNITIVE AND BEHAVIOURAL VARIABLES

It is widely accepted that psychosocial factors play a key role in the clinical picture of back pain (Waddell 2004). Many factors have been posited as playing an important role although the mechanisms linking cause and effect remain obscure. Pain has a clear and direct influence on emotion and behaviour but conversely psychological and emotional factors can directly influence the experience of, and reaction to, pain (Linton & Shaw 2011; Hill & Fritz 2011). In a broad review of studies with prospective designs that included studies of back pain as well as other musculoskeletal pain problems, Linton (2000) concluded that there was good evidence that a number of psychological factors play a key role in determining clinical status for both acute and chronic pain and in the transition from acute to chronic pain. The author was unable to clearly state which psychological factors were the most influential in determining prognosis although attitudes to pain, cognitive style, fear avoidance beliefs, depression, anxiety, distress, health perceptions and a history of sexual or physical abuse were all found to be related to pain and disability. Prospective cohort studies by Burton et al. (1995) and Klenerman et al. (1995) which investigated a range of psychosocial and physical predictor factors both concluded that psychosocial factors were the most powerful predictors of outcome from acute back pain. Similarly Carragee et al. (2005) found that psychosocial variables predicted both short and long term outcomes in a population with mild persistent back pain in contrast to structural pathological variables which offered minimal or no predictive value. The relative contributions of different psychological variables will now be considered.

2.4.6.1 PSYCHOLOGICAL: DISTRESS, DEPRESSION AND SOMATISATION

Emotional distress is a blanket term that encompasses anxiety, depression and anger (Truchon and Fillion 2000). Main et al. (2008) define depression as characterized by emotional distress, negative thinking, motivational deficit and vegetative symptoms. Somatisation is the process of heightened awareness of somatic symptoms and can be indicative of somatic anxiety.

The literature consistently identifies these phenomena as risk factors for poor outcome. In a systematic review of prospective cohort studies that specifically investigated the literature on psychological predictors of chronicity in LBP patients Pincus et al. (2002) concluded that distress, depressive mood and somatisation were consistently identified as predictors of chronicity, although the heterogeneity of study methods confounded efforts to distinguish psychological distress from depressive symptoms and depressive mood. A large study of 860 workers with non-specific back pain (Dionne 2005) found that indices of distress were the best predictors of outcome at 2 year follow up and Mallen et al. (2007)

found that anxiety was identified as a predictor in 5 out of 6 studies identified in their systematic review. Of the 2 studies included in that review which specifically investigated heightened somatic perceptions and distress, both found them to be predictive of chronicity. In their critical review Hayden et al. (2008) concluded that increased psychological stress was one of the few predictors of poor outcome that consistently arose from the literature. Similarly the European guidelines for the management of CNSLBP conclude that there is “moderate evidence” that psychosocial distress and depressive mood are predictors of chronicity (Airaksinen et al. 2006).

2.4.6.2 COGNITIVE: FEAR AVOIDANCE BELIEFS AND BEHAVIOURS

The fear avoidance model was suggested by Lethem et al. (1983) and has been developed further by Vlaeyen & Linton (2000) to attempt to explain the transition from acute pain to chronic pain and disability. The basic premise of this model is that fear and catastrophic beliefs regarding the meaning of painful symptoms leads to hypervigilance and over-attending to the symptoms, fear related avoidance of activity and movement (kinesiophobia) and subsequent disuse, depression and disability. Conversely where pain is not perceived as threatening and does not induce fear and anxiety patients continue to engage in normal activities and functional recovery is optimised. A logical prediction of this model is that pain related fear and associated avoidant behaviours in the acute stages of injury will be predictive of future chronicity.

Klenerman et al. (1995) found that fear avoidance variables were most successful in predicting outcome at 2 and 12 month follow up following acute low back pain. However they used a composite measure of fear avoidance that included other factors such as disability that may have influenced the results. In acute work-related back pain Fritz et al. (2001) found that fear avoidance was a significant predictor of disability and work status at 4 weeks post-injury independent of initial pain and disability levels. In 2002 Pincus et al. argued that fear avoidance and catastrophising were underrepresented in the research literature and that there was insufficient evidence to support its role at that time in the development of CLBP. Since that review several prospective studies have provided data pertinent to this issue. From a population based sample Picavet et al. (2002) demonstrated that in respondents reporting limiting back pain at baseline, high levels of catastrophising (adjusted OR 3.7, 95%CI 1.9 to 7.3) and kinesiophobia (adjusted OR 3.6, 95%CI 1.9 to 6.7) were modestly predictive of chronic back pain and were more strongly predictive of severe or disabling back pain at 6 month follow up. Similarly in a large cohort of acute LBP patients Swinkels-Meewisse et al. (2006) found that baseline fear of movement and re-

injury was the strongest predictor of future disability. In a systematic review of factors predicting failure to return to work (Iles, et al. 2008) found moderate evidence that fear avoidance beliefs and behaviour were predictive of outcome.

Despite this the case remains for caution in accepting fear and fear avoidance as clear risk factors for the development of CLBP. Following their call in 2002 for more research specifically investigating the influence of fear avoidance, Pincus et al. (2006) conducted a systematic review of studies of fear avoidance. 9 studies were identified of varying methodological quality. The evidence demonstrated either no link between fear and prognosis or, in some studies with “acceptable” methodology, weak evidence for a link with a small effect size. Boersma & Linton (2005) found that in subjects who have experienced pain for less than one year, fear of movement did not explain any variance in pain or disability, although in patients with back pain of a longer duration fear of movement did exercise an influence. In a cohort of ALBP patients (Sieben et al. 2005a) only modest correlations were seen between pain related fear, avoidance behaviour, pain intensity and disability. The same authors subsequently found in a prospective longitudinal study that the only fear avoidance-related variable that contributed to prediction of CLBP was negative affect (Sieben et al. 2005b) and other prospective studies in ALBP patients (Grotle et al. 2005; Grotle, Vøllestad, and Brox 2006) have found no prognostic value, or a moderate predictive value that failed to reach significance when distress was accounted for in the regression model. Boersma & Linton (2006) found that negative affect and fear avoidance beliefs did demonstrate a unique predictive value but that the effect was small.

2.4.6.3 COGNITIVE: PATIENTS EXPECTATIONS OF RECOVERY

Patients own expectations of recovery may influence their outcome. Across back pain systematic reviews Hayden et al. (2008) identified insufficient evidence to confirm expectations as a predictive factor due in part to a paucity of studies that investigated it. Conversely in a systematic review of psychosocial predictors of failure to return to work due to back pain, Iles et al. (2008) concluded that patients own expectations of their recovery was the only factor with strong supporting evidence. In a subsequent review focusing on patient’s recovery expectations the same authors confirmed that where the outcome to be predicted was well defined, expectations were found to be strongly predictive of outcome (Iles et al. 2008). The evidence in support of patient expectations as a predictor of chronicity was judged as “moderate” in the European guidelines (Airaksinen et al. 2006). A more recent systematic review (Ramond et al. 2011) found that of 4 studies that investigated expectations of recovery as a risk factor for chronicity 3 studies supported

their role as an independent predictor of which 2 were rated as being of high quality. Similarly even when studies judged at high risk of bias were excluded, Hallegraef et al (2012) found that inception cohort studies consistently demonstrated that negative expectations of recovery in acute and subacute back pain were a risk factor for work absence due to chronic low back pain (pooled OR 2.52 (95%CI 1.47 to 4.31).

2.4.6.4 PSYCHOLOGICAL VARIABLES: METHODOLOGICAL CONSIDERATIONS

A recent study that examined the predictive value of a comprehensive battery of psychological factors in a large prospective population (Foster et al. 2009) demonstrated 11 factors that reached significance in a univariate analysis. In the multivariate model only 4 factors retained their significance as predictors of outcome: perceptions of personal control, acute/chronic timeline, illness identity and pain self-efficacy. The authors argue that this demonstrates a substantial degree of redundancy in the various psychological variables commonly measured in back pain research. However combined these factors were able to explain just 6% of the total variance in outcome leading some commentators to question whether psychological factors have more than a minor influence on outcome (Roelofs et al. 2010).

While a number of psychological variables appear to be indicated in CLBP their predictive value appears to be small in prospective studies. Studies typically use self-reported pain and disability as key outcome measures, and these tools can, in part, be considered to be constructs of the patient's psychological and cognitive state. As such, individual psychological factors may fail to uniquely predict outcome in statistical models as their influence may be washed out by the large influence of self reported pain and/or disability. It is therefore possible that the effect of these variables are underestimated in such studies.

2.4.7 OTHER FACTORS

A number of other factors have been identified as predictors of outcome. Patient involvement in back pain related compensation cases was found by Hayden et al. (2008) to be one of the few predictors that was consistently identified in systematic reviews. Older age was identified as being consistently related to poorer outcome as was poor general health in that review.

2.4.8 PREDICTING CHRONICITY – SOME TENTATIVE CONCLUSIONS

Despite the enormous amount of data on the issue of predicting CLBP generated a lack of clarity persists. In part this can be explained by methodological variation in the factors

studied, the measures used, the cohorts examined and the methodological rigour observed. However this variation may also reflect the complexity of the problem and the absence of any clear pathway from acute to chronic low back pain. Some common themes do arise from the literature. Measures of the mechanical and structural integrity of the back offer little in determining prognosis. The absence of clear mechanical or tissue-based factors that influence this transition arguably suggests that the development of CNSLBP is not driven primarily by tissue-based changes in the spine. The severity and functional impact of an episode of acute back pain has an influence on outcome and pre- and co-existing distress and depression, and to some extent fear of the pain and subsequent maladaptive behaviours all increase the chances of making the transition from acute to chronic LBP. Nonetheless the relative contributions of these factors and the degree of risk that each pose is not clear. As noted in a recent review by Apkarian et al. (2009) when these risk factors are statistically modelled in large populations they typically demonstrate a low predictive power.

2.5 EVIDENCE BASED MANAGEMENT OF CLBP

Given the difficulty in determining the factors that contribute to the back pain experience or predict transition to chronicity it is perhaps unsurprising that the management of CNSLBP presents a significant challenge. Indeed CNSLBP might be defined as LBP that not only persists but is refractory to clinical treatment. Treatment costs contribute significantly to the overall economic burden of low back pain, so the successful management of CNSLBP offers potential benefits beyond those to the individual sufferer. This section will review the current evidence surrounding the efficacy of contemporary treatment approaches for CNSLBP.

2.5.1 RECENT CLINICAL GUIDELINES

There has been a vast research effort to assess the clinical efficacy of a wide range of therapies for CNSLBP and summarising this is an enormous task. Recent clinical guidelines from the USA and Europe (Chou & Huffman 2007a; Chou & Huffman 2007b; Airaksinen et al. 2006) have attempted to systematically gather and summarise this evidence and develop guidelines based on the findings.

In terms of pharmaceutical approaches to management both guidelines conclude that for chronic low back pain there is “good” or “strong” evidence that tricyclic antidepressant drugs offer small to moderate effects for pain relief in CLBP. The European guidelines additionally concluded that there was “strong” evidence that benzodiazepine muscle

relaxants, non-steroidal anti-inflammatory drugs (NSAIDs), weak opioids and topical capsaicin pain plasters are effective for short term pain relief.

In their review of non-pharmacologic therapies (Chou & Huffman 2007b) concluded that there was “good evidence” of “moderate” efficacy for cognitive-behavioural therapy (CBT) approaches, exercise, spinal manipulation and interdisciplinary rehabilitation. The European guidelines (Airaksinen et al. 2006) are in broad agreement suggesting “strong evidence” in favour of exercise therapy, CBT approaches, brief educational interventions and intensive multidisciplinary biopsychosocial rehabilitation and “moderate evidence” in favour of spinal manipulative therapy in the treatment of CNSLBP. The most recent guidelines have been issued by the UK’S National Institute of health and Clinical Excellence (NICE) (2009) and are again in broad agreement, only substantially differing in their recommendation of acupuncture.

2.5.2 GUIDELINE RECOMMENDED TREATMENTS - HOW EFFECTIVE ARE THEY?

From these guidelines it seems reasonable to conclude that effective treatments are available for this condition. However closer interrogation of the literature suggests that the extent to which CNSLBP might be successfully managed is unsatisfactory, even using interventions that are recommended in international guidelines. Machado et al. (2009) systematically reviewed randomized trials that employed a placebo control using analgesic effects as the primary outcome. Only 15% of studied interventions produced a reduction in pain of greater than 20 on a 0-100mm visual analogue scale for acute or chronic back pain, and all of these had only been investigated in a single trial. Of the interventions that have been recommended in clinical guidelines spinal manipulative therapy, exercise therapy, acupuncture, behavioural therapy and muscle relaxants all demonstrated confidence intervals whose lower limit crossed the line of no effect. NSAID’s demonstrated a statistically significant effect with a point estimate that lay around a 10mm pain reduction on a 0-100 scale. The problem of designing adequate placebo control conditions is significant in low back pain research (Machado et al. 2008) and the pooled effect sizes for many complex interventions found in this review may be overestimated due to the inability to employ a credible placebo control.

With regards exercise therapy for chronic low back pain van Tulder et al. (2007) reviewed all trials of exercise therapy that were identified in a recent Cochrane review of exercise therapy for CLBP (Hayden et al. 2005) to see whether any effect reached a level that could be considered clinically important. They set the threshold for a “minimally clinically

important difference" (MCID) as an improvement of 20% or more from baseline for pain and 10% or more for function. While 43% of identified RCTs found statistically significant differences in favour of the exercise therapy group for pain and 44% for function and reported positive conclusions, only 11% (4 studies) found both statistically and clinically significant changes for pain and 18% for function. While there are no universally agreed cut-offs for MCID in CLBP studies as yet, these results suggest that the effect sizes for exercise therapy are small and that many trial reports may overstate their significance. Indeed a recent review of exercise therapy for back pain that updated the existing Cochrane review on this topic (van Middelkoop et al. 2010) found that while exercise appeared to be effective when compared with usual care, it was not more effective in comparisons with no treatment, and no type of exercise (in a broad church of approaches) demonstrated superiority. Meta-analyses demonstrated small effect sizes of around a 1 point decrease on a 0-10 pain visual analogue scale. The value of meta-analyses of such a diverse range of studies is open to debate and the presented estimates of effect are rather imprecise. Nonetheless the observed effect sizes are modest and since many of the included studies were assessed as being at risk of bias they might also be exaggerated.

It is plausible that the positive effects of exercise could reflect the detrimental effects of usual care approaches rather than a specific effect of exercise, though such a proposition is speculative. A meta-regression of exercise therapy from data taken from the Cochrane review of that topic (Hayden et al. 2005) demonstrated that certain characteristics of exercise programmes are associated with improved outcome, such as higher dose, individualised and individually supervised programmes. However their analysis suggested that the probability of achieving a clinically important difference with an exercise programme incorporating these features was 29% for pain and 4% for function compared to no treatment and just 3% and 1% compared with other conservative treatments.

Keller et al. (2007) systematically searched all available Cochrane reviews of non-surgical treatments for non-specific low back pain and estimated the effect sizes in trials where treatments were compared to a no-treatment or sham/placebo control. They found only modest short term effects for exercise, acupuncture, behavioural therapy and NSAIDs and small effect sizes for manipulation. In many of the included trials the true value of the therapies investigated is likely to be less than the results suggest as no-treatment controls are unable to account for non-specific effects of care. The authors concluded that there is a "dire need" to develop more effective interventions.

While NICE guidelines recommend acupuncture in the management of CLBP the most recent systematic review of acupuncture (Yuan et al. 2008) concluded that there was only moderate evidence that acupuncture is more effective than no treatment and strong evidence that acupuncture is no more effective than sham acupuncture for short term pain relief. In a larger systematic review of trials of acupuncture for any painful condition (Madsen et al. 2009) used meta-regression to investigate the impact of varying sham conditions utilised in acupuncture trials and effect size and found no differences whether the sham condition involved deep or superficial needling, evoked sensation or not, or even was non penetrating. These findings are strongly suggestive that the effects of acupuncture are non-specific and may in large part, or perhaps in totality, be attributed to factors such as the placebo effect. Finally a recent review (Rubinstein et al. 2010) found very low quality evidence that suggested that manipulative therapies offer no benefit over sham or other therapies and that they were less effective when compared to no treatment than acupuncture, for which there is strong and consistent evidence of no benefit over sham (Yuan et al. 2008). These results are suggestive that neither therapy boasts an active effect that can be clearly distinguished from placebo.

Study quality also plays a role when assessing the findings of these reviews. In their review of exercise trials Hayden et al. (2005) detected an inflation of effect size seen in poorer quality studies and indications of potential publication bias. van Tulder et al. (2009) investigated the impact of study quality, measured using the Cochrane Back Review Group Internal Validity score tool on effect size in 216 RCTs of non-surgical interventions for low back pain. They found that study quality significantly affected reported effect sizes. Notably studies that met less than 6 of the 11 quality criteria (44% of all of the studies analysed) used reported effect sizes that were on average 50% greater than those meeting 6 or more of the criteria. Again these data suggest that small to moderate effect sizes seen in the clinical trial data may represent an exaggerated estimate of the true efficacy of these interventions.

Behavioural therapies are well represented in the recommendations of clinical guidelines. The most recent Cochrane review on this topic (Henschke et al. 2010) found that no type of behavioural approach appeared superior or offered a short term effect on pain in excess of a one point reduction on a 0-10 pain visual analogue scale. Perhaps more concerning for approaches that seek to facilitate improved function through better management of pain,

rather than pain reduction per se, this review found no effect of behavioural treatments on function, for any comparison.

The Cochrane review of trials of individual patient education for low back pain found it to be less effective than other, more intensive treatments for improving function in CLBP (Engers et al. 2008). A recent systematic review of trials of pain neurophysiology education for CLBP (Clarke et al. 2012), an intervention which aims to improve patients understanding of the nature of their ongoing pain with a view to empowering them to be more active, found statistically significant but small and clinically unimportant improvements in pain.

2.5.3 THE SUBGROUP QUESTION

The failure of existing treatments to demonstrate convincing levels of efficacy has generated much discussion and debate. One explanation for this phenomenon is that interventions in many RCTs have not been targeted effectively to subgroups of patients for whom they are specifically suited. Indeed the identification of distinct subgroups of patients, and the effective targeting of treatments has been identified as a research priority in low back pain (Guccione et al. 2000). Various approaches to subgrouping have been suggested and are under investigation, including grouping patients by clinical findings or proposed diagnosis or by the presence of specific risk factors for poor outcome though no system has yet conclusively demonstrated its utility (Kamper et al. 2010). For example Childs et al. (2004) developed a clinical prediction rule to better target manipulation to participants with acute back pain who were most likely to respond to this treatment and tested this rule in an RCT. While that trial demonstrated impressive results in participants identified as likely responders, a subsequent trial that attempted to replicate this finding failed to do so (Hancock et al. 2008) and in a single arm trial investigating the underlying mechanisms of manipulation a positive classification on this clinical prediction rule did not predict success with manipulation (Fritz et al. 2011). In addition, one of the items on that clinical prediction rule for predicting a positive response was the presence of spinal stiffness. Yet in the study by Fritz et al. (2011) less initial spinal stiffness was associated with a better treatment response. Debate continues as to the various possible interpretations of this inconsistency.

Another example of subgrouping is offered by the recent STaRT back trial (Hill et al. 2011) in which patients were stratified to receive different care packages in relation to their risk of poor outcome. Compared to non-stratified care there were significant improvements in the stratified group, though on the primary outcomes of pain and disability these were

small. While somewhat encouraging it is not clear that such results indicate that targeting treatments more effectively will necessarily result in existing interventions demonstrating dramatic benefits. Some (including this author) (Wand and O'Connell 2008; Smeets et al. 2009) have argued against a lack of subgrouping as a convincing explanation for much of the poor performance of existing treatments in clinical trials, pointing out that there is little evidence from existing trials to support this assertion. To date a definitive conclusion cannot be made.

From these data it might be considered that currently no treatment offers a satisfactory answer to the problem of CNSLBP. The short term effects of treatments are small to moderate and possibly overestimated through methodological and interpretive biases. Guideline recommendations appear to offer an assessment of the "best there is" rather than evidence of treatments with significant clinical utility. Indeed in a recent editorial Buchbinder et al. (2010) suggest that the major challenge facing clinicians is how to avoid unhelpful or harmful treatments for this condition.

2.6 SUMMARY AND CONCLUSIONS

LBP is widespread in the population and to not experience a significant episode of back pain in one's lifetime might be considered abnormal. It currently incurs significant social costs. Beyond a selection of specific spinal pathologies that comprise a minority of back pain cases, no diagnosis can currently be reliably made. Most back pain is relatively benign, involving only short term or no disability and resolving or improving rapidly in the majority of subjects. Recurrence is common although this does not mean that chronic severe and disabling pain will develop and only a minority of those who experience acute low back pain will go on to develop severe symptoms. High severity and duration of pain, psychological distress and depression increase the risk of chronicity but existing measures of physical pathology and the findings of physical examination tests do not appear to be useful in predicting who develops CNSLBP.

It seems fair to argue that existing models of CLBP have failed to adequately address the problem, with neither structural / mechanical, psychosocial nor combined models offering more than modest predictive power in terms of the course and outcome of the condition. Management approaches based upon these models are suboptimal with the best evidence indicating that currently no treatment offers more than small, short term benefits on pain, even when endorsed by clinical guidelines. The development and consideration of alternative models of CLBP and of novel approaches to managing this condition would

seem to be an urgent priority. Emerging research into the role of the central nervous system in chronic pain states including CLBP may suggest such an alternative and will be considered in the next chapter.

CHAPTER 3 THE BRAIN IN CHRONIC BACK PAIN

3.1 A CENTRAL NERVOUS SYSTEM BASIS FOR CNSLBP?

In a recent review Robinson & Apkarian (2009) discuss 2 models of CLBP; the “end-organ” dysfunction model, the central tenet of which is that the symptoms of CLBP result from structural abnormalities of the spine that generate pain, and the “altered nervous system processing” model, in which the ongoing pain experienced is the result of alterations in nervous system encoding and the processing of sensory information. They conclude that while end-organ dysfunction may play a role in CNSLBP, evidence points to a significant role of aberrant nervous system processing in the aetiology of the disorder.

The end-organ model arguably dominates the clinical and research literature relating to CLBP. Many common management approaches, from surgical and interventional pain management techniques such as injection or denervation, to physiotherapy, osteopathy and chiropractic commonly operate within this paradigm. However as seen in the previous chapter such a model does not adequately explain the characteristics or the course of the condition, nor does it offer useful prognostic indicators and treatment approaches informed by an end organ dysfunction model offer little benefit to people with CNSLBP.

Pain that persists beyond the normal healing time or in the absence of any demonstrable peripheral pathology has long been a challenge in the understanding of CNSLBP and chronic pain in general. Modern concepts of pain processing were revolutionised by the publication of Wall and Melzack’s Gate Control Theory (Melzack and Wall 1965). This theory and its subsequent revisions postulated that nociceptive input from high threshold afferent nerve fibres that respond to potentially noxious stimuli could be facilitated or inhibited by other afferent fibres which carried information regarding non-noxious stimuli and also by descending modulatory control systems from higher centres in the central nervous system. The revolution arises from the proposal of mechanisms by which the experience of pain can be dissociated to some degree from the detection of threat or damage in the body tissues. The description of descending modulatory control mechanisms placed the central nervous system, and principally the brain, at the heart of pain processing rather than acting simply as a passive receiver of information.

In the ensuing years a wealth of evidence has been established demonstrating state dependent neuroplasticity in central pain networks (for reviews see Fields et al. 2006;

Woolf 2011). Enhanced synaptic efficiency in nociceptive networks may facilitate increased perception of pain with little or no peripheral nociceptive input (Fields et al. 2006). Work in animal models has demonstrated that nociceptive input causes wind-up of dorsal horn neurones, characterised by an increase in firing response as the input continues, long term, potentiation, characterised by a persistent increase in synaptic excitability after the nociceptive stimulus, and aberrant response of dorsal horn neurones to normally non-noxious input, collectively known as central sensitization (Woolf 2011), resulting in a possible increase in the amplitude, spatial extent and duration of the pain response.

Evidence indicates that there is some degree of sensitisation in CNSLBP patients (Flor et al. 1997; Clauw et al. 1999; Giesecke et al. 2004, Giesbrecht 2005, Kobayashi et al 2009, Blumenstiel et al. 2011, O'Neill et al. 2011, Wang et al. 2012). Theoretically, this may be the result of changes in the periphery, the spinal cord (Apkarian & Scholz 2006), the brain (Flor 2003) or in a combination of these areas. Studies of inflammatory and neuropathic pain models in animals demonstrate extensive structural and functional alterations in the dorsal horn of the spinal cord that represent a relatively specific degeneration of the inhibitory interneurone system, leading to central sensitization and increases in pain-related behaviours (Apkarian & Scholz 2006). Similar changes in the dorsal horn have been demonstrated post-mortem in human subjects who had suffered from post-herpetic neuralgia (Watson et al. 1988; Watson et al. 1991). While it must be considered that CNSLBP develops in the absence of demonstrable peripheral nerve injury it is possible that the initial afferent nociceptive barrage that follows acute spinal injury may induce lasting alterations in dorsal horn function that lead to the maintenance of pain after tissue healing has occurred.

Methodological barriers to studying cord structure and function in humans make it difficult to ascertain the contribution of such changes to CNSLBP. Furthermore, in rodents, the spinal cord represents a far greater proportion of the CNS than in humans, and animal models demonstrate that while cord changes are prevalent in younger animals, brain changes dominate in older animals (Flor et al. 2006). While there is currently no direct evidence of spinal cord changes in CNSLBP patients, there is significant and growing evidence of altered brain function. This chapter will discuss the evidence relating to alterations in brain function, pain processing and related behaviour in CLBP.

3.2 CORTICAL REPRESENTATION AND ACTIVITY

Plasticity in cortical neuronal networks is well established. For example reorganisation of the cortical representation of the hand body surface in the sensory cortex has been demonstrated in relation to non-painful movement conditions such as focal dystonia (Elbert et al. 1998), immobilisation of the hand (Lissek et al. 2009) and task specific practice such as in string players (Elbert et al. 1995; Schwenkreis et al. 2007) and Braille readers (Sterr et al. 1999; Sterr et al. 1998). A large body of evidence has emerged indicating the presence of cortical reorganisation in chronic pain conditions, including CLBP. The initial work investigating the brain in CLBP was performed by Flor et al. (1997). Using magnetoencephalography (MEG) they demonstrated that the cortical representation of the lower back region in the primary sensory cortex (S1) was altered in patients with CLBP versus healthy controls. CLBP sufferers demonstrated enhanced cortical responses to painful back stimulation and the S1 cortical representation of the back was shifted medially and appeared to be expanded. Importantly the degree of enhanced cortical reactivity was strongly positively correlated with the duration of the symptoms and was specific to stimulation of the back; similar changes were not observed from stimulation of the finger suggesting that the changes were both specific to the painful area and related to the clinical characteristics of the problem.

Cortical reorganisation does not appear to be isolated to the sensory cortex in LBP. Using transcranial magnetic stimulation (TMS) mapping techniques Tsao et al. (2008) found that the motor cortical representation of the transversus abdominus trunk muscle was shifted postero-laterally in patients with recurrent LBP when compared to pain free subjects. A similar posterior shift of the longissimus erector spinae map has been observed in recurrent low back pain patients, with a increase in the degree of overlap between its map and that for the deep multifidus muscle (Tsao et al. 2011). The same group have demonstrated that a motor control exercise programme designed to target transversus abdominus function reversed the shift in its cortical representation in a group with recurrent low back pain over a 2 week training period, while a generalized walking program did not. No relationship was observed in that study between parameters of the cortical maps and clinical features (Tsao et al. 2010) but the results do suggest that altered motor cortical representation is a reversible phenomenon .

Alterations in cortical representations have been demonstrated in other chronic pain conditions in human subjects. Flor et al. (1995) demonstrated S1 cortical reorganization in

patients with phantom limb pain following amputation. Maihöfner et al. (2003) and Pleger et al. (2004) demonstrated altered representation of the hand in patients with complex regional pain syndrome type I (CRPSI). In these studies cortical reorganisation was correlated with clinical signs such as the magnitude of pain (Flor et al. 1995; Pleger et al. 2004) and the degree of mechanical hyperalgesia (Maihofner et al. 2003), although while Juottonen et al. (2002) observed similar reorganization in CRPS patients they could not demonstrate a clear relationship with any clinical feature of the condition. These studies demonstrate that across different chronic pain conditions S1 demonstrates enhanced cortical reactivity. However the precise nature of the cortical reorganisation is less consistent. In CRPS the data suggest a shrinkage of the cortical representation of the affected part (the hand), whereas in CLBP the representation appears to expand. The meaning and relevance of these findings remains unclear (Lotze & Moseley 2007). While the demonstrated relationships with pain suggest that reorganisation of S1 representation may be a relevant feature of CLBP, a review by Moseley (2006) highlighted that similar changes have been reported in non painful conditions such as focal dystonia, and in response to training. S1 reorganisation has also been demonstrated after the infliction of acute pain (Sörös et al. 2001). Additionally Birbaumer et al. (1997) demonstrated a reversal of S1 reorganisation in 3 of 6 phantom limb pain patients who experienced elimination of their phantom pain when the stump was locally anaesthetised. In the remaining three patients no reduction in pain was reported and cortical reorganization was unchanged. Such results raise the possibility that these changes represent correlates of the experience of pain (and other symptoms rather) than a cause.

Enhanced cortical reactivity may be a neurophysiological feature of CLBP. Giesecke et al. (2004) found that patients with CLBP and fibromyalgia demonstrated hyperalgesia to painful pressure testing on the nail of the thumb. Simultaneous functional magnetic resonance imaging (fMRI) revealed activation of a more expansive network of pain related regions in the brain in subjects with chronic pain and a secondary analysis of the data (Giesecke et al. 2006) demonstrated enhanced responses to noxious stimuli in S1 and the secondary somatosensory cortex (SII).

There are inconsistencies within this evidence and the data do not unanimously support the proposition of enhanced cortical reactivity in CLBP. The finding of increased responsiveness to painful stimulation of a site remote from the lower back (Giesecke et al. 2006) is at odds with those of Flor et al. (1997) who found increased responsiveness only

on stimulation of the back itself. Derbyshire et al. (2002), Baliki et al. (2006) and Wasan et al. (2011) found no difference in cortical activation in response to painful thermal stimulation of the hand, lower back and leg respectively. One possible explanation for these apparently conflicting results is that sensitivity may be stimulus specific. Giesecke et al. (2004) used pressure pain stimulation whereas Flor et al. 1997 used electrical stimulation. Similarly the use of thermal stimulation by Baliki et al. (2006) and Derbyshire et al. (2002) may have influenced these results. The psychological disposition of patients may also have an influence. Lloyd et al. (2008) demonstrated lower levels of cortical activation in response to electrical stimulation of the lower back in chronic back pain patients with higher levels of illness behavior. These inconsistencies, and the small size of the studies involved suggests that caution is warranted in drawing firm conclusions regarding cortical reactivity.

As well as alterations in the cortical response to evoked pain, studies have demonstrated altered cortical activity in the resting brain associated with the experience of chronic back pain. The experience of spontaneous back pain in patients with CLBP is reflected by increased activity in the medial prefrontal cortex (mPFC)(Baliki et al. 2006), and compared with healthy participants CLBP patients demonstrate altered oscillatory activity at rest in the mPFC with an increase in high frequency oscillations in the blood oxygen level dependent (BOLD) signal, a measure of change in regional blood flow within the brain. These alterations were synchronous with changes in spontaneous back pain (Baliki et al. 2011)

Alterations in brain function in CLBP do not appear to be isolated to pain processing. CLBP has also been demonstrated to disrupt the “default mode network” (DMN). This is a network of brain regions that are activated in the “resting” brain and whose activation appears to decrease during task performance is believed to represent the baseline state of brain function (Raichle et al. 2001). Significant disruptions in DMN activation at rest in CLBP patients compared to healthy controls have been observed (Baliki et al. 2008; Balenzuela 2010; Buckalew et al. 2010; Tagliazucchi et al. 2010; Baliki et al. 2011) suggesting a possible influence on brain function that goes beyond pain or sensory processing.

3.3 BRAIN CHEMISTRY AND STRUCTURE

The utilisation of a variety of brain imaging methods has revealed further changes in the CLBP brain. Using in vivo proton magnetic resonance spectroscopy (MRS) to interrogate

brain chemistry Grachev et al. (2000) discovered reductions in N-acetyl aspartate (NAA - a chemical precursor to the excitatory neurotransmitter aspartate) and glucose (a marker of general metabolic rate) in the dorsolateral prefrontal cortex (DLPFC) of CLBP patients, which were correlated with aspects of pain perception and anxiety. Follow up studies by the same research group (Grachev et al. 2002; Grachev et al. 2003) confirmed the findings of the original study and found that the concentration of NAA in the orbitofrontal cortex (OFC) could be used to distinguish between subjects with high and low anxiety (measured using the State-Trait Anxiety Inventory, Spielberger et al. 1983), and those with and without CLBP and that the chemical profile of the DLPFC and the OFC combined was best related to the severity of pain. Importantly there was no difference in OFC chemistry between CLBP patients with low levels of anxiety and healthy subjects (Grachev et al. 2002). Similarly depression levels in CLBP patients were highly correlated with NAA levels in the right DLPFC. Back pain levels were also correlated but the relationship was considerably weaker. Given that NAA is considered a marker for neuronal loss and degeneration (Miller 1991) the authors suggest that the changes seen in CLBP may reflect localised neuronal loss and degeneration and conclude that these changes are more advanced in patients exhibiting depression and anxiety and may reflect the neurobiological substrate of these symptoms in CLBP patients.

Reduced NAA levels in CLBP patients have also been demonstrated in the anterior cingulate cortex (ACC), the anterior insula, (Gussew et al. 2011) and in the left primary somatosensory cortex (Sharma et al. 2011) as have reduced glutamate levels in the ACC (Gussew et al. 2011). Siddall et al. (2006) found that altered NAA chemical profiles in the ACC, thalamus and prefrontal cortex recorded using MRS could distinguish back pain patients from controls with high levels of accuracy.

MRI voxel-based morphometry (VBM) allows the examination of structural changes in the brain. Comparing the brain morphology of 26 CLBP patients to matched healthy controls Apkarian et al. (2004) found significant decreases in grey matter density in the bilateral DLPFC and in the right anterior thalamus which were markedly more prominent in patients with neuropathic pain due to lumbar nerve root compromise. However across all CLBP subtypes (neuropathic and non-neuropathic) a combination of sensory and affective dimensions of pain could strongly predict DLPFC grey matter change, demonstrating a clear relationship between these changes and aspects of patients' clinical profile such as pain intensity, duration and negative affect. Unlike the brain chemistry changes demonstrated

by Grachev et al. (2000, 2002, 2003) these changes showed only a weak relationship to depression and anxiety measures. The authors suggested that the reduction in density supported the hypothesis of localised neural degeneration. Schmidt-Wilcke et al. (2006) also identified grey matter loss in the right DLPFC of CLBP patients and more marked loss in brainstem and somatosensory cortex. Their results demonstrated strong correlations between the extent of loss and pain intensity and unpleasantness on the day of scanning but found no correlation with pain duration. They also found an increase in grey matter density located in the thalamus and the basal ganglia. They suggest that this finding is unsupportive of the hypothesis that brain atrophy underpins density changes seen and conclude only that the findings indicate cortical and subcortical structural reorganisation of some kind. Using fMRI to calculate cortical thickness as a measure of reduced grey matter, Seminowicz et al. (2011) found reduced thickness in the left DLPFC, bilateral anterior insula/frontal operculum, left mid/posterior insula, left S1, left medial temporal lobe, and right ACC in patients with CLBP.

Sampling from a broader population based study in Germany, Ruscheweyh et al. (2011) compared a control group, who had never suffered chronic pain, to an ongoing chronic pain group (with a variety of painful conditions), and a past pain group who had suffered pain in the past but not in the preceding 12 months. They again demonstrated regional grey matter decreases centred in frontal regions in patients with ongoing CLBP.

Decreases in white matter density in the middle cingulate cortex and grey matter density in the posterior parietal cortex have been observed in older adults with CLBP (Buckalew et al. 2008), (though these changes were not significant when using a conservative p-value). Older adults with disabling CLBP demonstrate decreased white matter integrity in the splenium of the corpus callosum compared with those with non-disabling CLBP, which post hoc analyses suggested was strongly negatively correlated with pain duration (Buckalew et al. 2010).

These structural changes do not appear to be peculiar to CLBP. A recent review identifies studies demonstrating similar changes in patients with CRPS, irritable bowel syndrome, chronic headache and fibromyalgia although the regional focus of the largest changes differs somewhat between studies (May 2008, Henry 2011) and there are inconsistencies in results both within and between conditions. In a review of this area (Apkarian et al. 2011) argue that while technical differences between studies can explain some of this variability, across a number of chronically painful conditions grey matter decreases are consistently

observed. Moreover they argue that the anatomical pattern of changes is specific to different conditions. In a separate review Schmidt-Wilcke (2008) also identified technical considerations with VBM as a source of between study variance and again suggested that patterns of altered brain morphology may be specific to different conditions.

Direct evidence for this assertion comes from a recent study (Baliki et al. 2011) which directly compared VBM results between healthy participants and patients with CLBP, CPRS and osteoarthritis (OA). The only pain group to demonstrate an overall reduction in grey matter density was the CLBP group. While all pain groups demonstrated reductions in grey matter density in the insular compared with healthy controls, and both the CLBP and OA group demonstrated decreases in the cingulum and both primary and secondary somatosensory cortices (S1 and S2), there were decreases in grey matter density that did not overlap between conditions and the broader patterns of decreases between conditions were distinct.

Recent data challenges the suggestion that these structural alterations represent irreversible neurodegeneration. Rodriguez-Raecke et al. (2009) found that decreased grey matter density observed in patients with pain related to chronic osteoarthritis of the hip partially reversed following successful joint replacement surgery. Only part of the original cohort in this study was followed up after treatment (those who had successful surgery) which may have had some bearing on the results. In chronic back pain patient's improvements in observed reductions in cortical thickness in the left DLPFC, S2 and posterior insula which correlated with improvements in pain and disability have been observed (Seminowicz et al. 2011). Ruscheweyh et al. (2011) found no differences between participants who had recovered from chronic persistent pain for over one year and those with no history of chronic pain.

Given this degree of reversibility it seems unlikely that the observed reductions in grey matter would reflect significant neuronal degeneration or loss, though neurogenesis in the adult mammalian brain is no longer considered to be non-existent (Ming and Song, 2011). The actual mechanism underpinning these observed structural changes is currently unknown though changes in concentration of channels of proteins within neurons and/or glia has been proposed (Apkarian et al. 2011).

Together these studies provide evidence of significant alterations in brain structure and function associated with CLBP. Most of these studies are cross-sectional in design and as

such no causal inferences can be confidently drawn from them. That early longitudinal studies are beginning to demonstrate change that is related to a changing clinical profile (Rodriguez-Raecke et al. 2009; Seminowicz et al. 2011) offers the compelling suggestion that they may at least reflect the cortical effects of chronic pain or possibly an underlying mechanism which is, to some extent, reversible. This possibility is lent further credibility with the recent publication of the first attempt at a longitudinal study in which patients with “subacute” back pain were recruited and followed for one year (Baliki et al. 2012). fMRI imaging was conducted at study entry and at 4 points over the year. The findings were striking. Those whose back pain persisted demonstrated greater whole-brain gray matter decreases in comparison to those who moved toward recovery or healthy controls, and specific decreases in the nucleus accumbens region, insula and left sensorimotor cortex. That these changes occurred over the transition from subacute to chronic pain lead the authors to conclude that differences in grey matter volume are not causal. However they also demonstrated that greater functional connectivity between the nucleus accumbens (NAc) and the mPFC at baseline predicted the persistence of or recovery from back pain. While these results are observational they do provide the first hint of a possible causal mechanism in brain processing for the progression to chronicity. Baliki et al. (2012) speculate that abnormalities in the circuitry between the NAc and mPFC are critical in the transition from acute to chronic pain. However there are grounds for a cautious interpretation of these data. The small size of the study (n=39 back pain patients) that splits neatly in to recovered and persistent back pain by the end of the study (n=20 and 19 respectively) is suggestive of a possible recruitment bias. Participants were categorised as recovering if they achieved a 20% change in pain intensity over the course of the study. It is unclear whether this was a decision taken a priori or a strategy decided upon post hoc in order to ensure an even split. This concern is compounded by high rates of drop out of 28% at 7 weeks, increasing to 46% by week 29 and 55% by week 54. Similarly closer inspection of the initial cohort of “subacute” back pain patients demonstrates that the duration of pain extended from 4 to 16 weeks with an average of 12 -14 weeks suggesting that many were patients who would already be considered to have chronic low back pain. To some degree this undermines the validity of the claim that the results reflect the transition from subacute to chronic pain.

In any event such findings and claims of a causal mechanism for CLBP in the brain require replication in larger studies with fewer potential confounders. At this point it remains possible that the observed brain changes across studies are the result of ongoing

nociceptive activity, may potentially drive the ongoing perception of pain, or indeed may simply be the biological substrate of pain perception. It is also possible that they are merely epiphenomena and of little consequence.

Three recent narrative reviews have emphasised the possible role of abnormal central processing of pain in the pathogenesis and maintenance of chronic pain. Ablin & Clauw (2009) consider chronic idiopathic back pain as one of a number of clinical entities that might be categorised as “central sensitivity syndromes” and suggest that all such syndromes (including fibromyalgia, irritable bowel syndrome and chronic pelvic pain among others) demonstrate a common underlying dysfunction of pain processing and sensory amplification rather than a specific abnormality of the body region where that pain is experienced. A genetic predisposition to developing chronic pain syndromes, including CLBP has been proposed (Gjerstad 2007) though a recent review concluded that the limited results to date are equivocal (Holliday and McBeth 2011). Tracey & Bushnell (2009) also argue that chronic pain may be considered a disease underpinned by abnormal brain structure and function and Apkarian et al. (2009) present a working model for the transition from acute to chronic pain that, while not ignoring the role of ongoing nociceptive input places an emphasis on abnormal central neurological function.

3 broad themes emerge from the literature which may explain the relevance of brain changes to the experience of CLBP: 1. Central disinhibition/ hyperexcitability, 2. Psychological/Emotional/Cognitive Dysfunction, 3. Disrupted cortical representation/ body perception. While none of these themes is mutually exclusive they will be discussed separately for the purposes of clarity.

3.4 CENTRAL DISINHIBITION/ HYPEREXCITABILITY

As discussed numerous (but not all) studies have provided evidence of increased excitability of cortical areas in CLBP (Flor et al. 1997, Giesecke et al. 2004, 2006) suggesting that hyperactivity in pain-relevant brain regions may drive the experience of ongoing and severe pain. Behavioural studies reinforce this finding. Clauw et al. (1999) investigated pain tolerance and thresholds at various sites over the body of patients with CLBP and found tenderness at sites remote from the area of reported pain. Pain sensitivity measured in this way was found to account for a significant amount of the observed variance in back pain and functional status after controlling for other variables, including psychosocial factors, although depression and degenerative changes also demonstrated associations. In a general population pain pressure thresholds (PPT) were neither predictive of the onset of

low back pain, observed in participants with recent onset back pain, nor predictive of developing persistent back pain but lower PPTs were observed in participants with long-lasting LBP both locally over the back and at remote body sites (O'Neill et al. 2011). Similar generalised, non-anatomically specific decreases in PPT have been observed in female CLBP patients in comparison with healthy controls (Giesbrecht and Battié 2005). However in a less clinically severe CLBP population Blumenstiel et al. (2011) found increased pressure pain sensitivity, as well as decreased vibration sensitivity only over the low back, and not on the dorsum of the hand. Jensen et al. (2010) investigated the presence of widespread tender points in a mixed population of sick-listed low back pain patients. While there was a positive association of tender points with low back pain, psychological distress and female gender there was a significant negative correlation between tender-point score and degenerative lumbar disc disease or radiculopathy leading the authors to conclude that diffuse tenderness was likely the result of disturbed pain regulation rather than spinal pathology. Kobayashi et al. (2009) also demonstrated increased tenderness around the lower back region to mechanical stimuli in CLBP patients. When the stimulus intensity was controlled to evoke similar pain intensity between participants, CLBP patients reported greater unpleasantness than healthy controls and fMRI scanning revealed a broader cortical activation pattern.

This widespread sensitivity to pain is suggestive of central hypersensitivity. Curiously changes in sensitivity in CLBP may not be limited to painful mechanical stimuli. Small & Apkarian (2006) tested the perception of sour taste in CLBP patients versus normal controls. Despite no differences in the unpleasantness ratings of sour tastes and no between-group differences in performance of a visual perception task, CLBP patients rated sour taste stimuli as significantly more intense and demonstrated a trend towards lower detection thresholds. The authors point to the shared brain regions (the medial pre-frontal cortex (mPFC), the insula and the thalamus) that have been demonstrated to process both taste and painful stimuli and argue that enhanced gustatory sensitivity may be indicative of hyperactivity in these regions.

This evidence of increased sensitivity might be explicable in part by the brain changes discussed above. The dorsolateral prefrontal cortex has a role in pain perception. In healthy subjects with experimentally induced pain, activity in the DLPFC bilaterally is negatively correlated with reported pain intensity and unpleasantness. Left DLPFC activity is associated with a reduction in the relationship between the perceived unpleasantness of

pain and activity in the anterior cingulate cortex (ACC), mid brain and medial thalamus, and right DLPFC activity with a reduction in the relationship between the anterior insula and perceived pain intensity and unpleasantness (Lorenz et al. 2003). Schmahl et al. (2006) demonstrated elevated activity in the left DLPFC and reduced activity in the ACC in response to painful stimuli in subjects with borderline personality disorder, who characteristically exhibit reduced pain sensitivity, in comparison to the same level of stimulation applied to healthy subjects. When the data was adjusted to control for the subjective report of pain, activation levels were similar across the groups suggesting that DLPFC activity was inversely related to perception of pain.

Research into the neurobiological mechanisms of the placebo effect suggests that the DLPFC has a key role in expectancy-induced analgesia. In a study of placebo analgesia for anticipated pain, Wager et al. (2004) found that during the anticipation of pain, bilateral DLPFC activity was enhanced in subjects who reported reduced pain ratings and vice versa. Zubieta et al. (2005) demonstrated that the level of endogenous opioid activity in the left DLPFC was associated with the size of analgesic effect that subjects anticipated prior to the administration of a placebo. Krummenacher et al. (2010) used repetitive transcranial magnetic stimulation to temporarily disrupt DLPFC function during an experimental condition aimed at evoking expectation-induced placebo analgesia to induced heat pain. They found that placebo analgesia was completely blocked by rTMS but not by sham rTMS. Stein et al. (2012) have demonstrated, using diffuse tensor MRI imaging, which provides an indirect measure of white matter connectivity, that individual differences in placebo response are associated with structural connectivity in the right DLPFC, left rostral ACC and the PAG. In effect lower white matter integrity is associated with a diminished placebo response. These studies together suggest a direct role for the DLPFC in mediating the relationship between expectation and perceived pain and in modulating the conscious experience of pain via intra-cortical and cortico-subcortical pathways (Lorenz et al. 2003).

Baliki et al. (2006) provide further evidence of this specifically in CLBP. They monitored cortical activity in participants with CLBP whilst simultaneously recording their reports of spontaneous pain, and also when responding to painful thermal stimuli (in comparison to pain-free controls). In comparison to painful thermal stimuli, which induced similar activation patterns in both CLBP patients and healthy controls, when CLBP patients experienced spontaneous lasting pain there was an associated increase in activity in the mPFC that was closely correlated with the intensity of the pain. This mPFC activity was

inversely correlated with activity in the DLPFC and the authors speculate that dysfunction of the DLPFC (as suggested by the observed structural and chemical changes in this region) may disrupt inhibitory control over the mPFC leading to an increase in spontaneous pain. In another study CLBP patients who exhibited distress failed to show an increase in right sided DLPFC activity and the ACC in response to non-painful sensory stimuli in comparison to non-distressed patients (Lloyd et al. 2008), again suggesting a disruption of normal top-down sensory modulation possibly associated with psychological distress.

Giesecke et al. (2006) also provide evidence of altered modulatory pain control via descending pathways. Using a pressure pain model they demonstrated significantly reduced blood flow in the periaqueductal grey matter (PAG) of CLBP patients compared to normal subjects to equally painful pressure. The PAG is widely acknowledged as playing a key role in the descending modulation of nociceptive input (Fields & Basbaum 2006) and these findings, and that of reduced grey matter density in the brain stem (Schmidt-Wilcke et al. 2006) are suggestive of a dysregulation of this system in CLBP.

Dysfunction of normal central pain inhibitory controls might plausibly lead to hypersensitivity and excitability of pain-processing brain areas and as such, may play a role in the development and experience of CLBP. Some of the studies discussed suggest that, in part, these changes may be associated with psychological and emotional factors (Clauw 1999; Grachev et al. 2000, 2002, 2003, Jensen et al. 2008, Lloyd et al. 2008). The next section will discuss the evidence relating to CLBP, the brain and psychological, emotional and cognitive function.

3.5 CLBP AND THE BRAIN - EMOTIONAL, COGNITIVE AND PSYCHOLOGICAL CONSIDERATIONS.

Various studies provide evidence of specific emotional, psychological and cognitive abnormalities in patients with CLBP that may result from or directly represent correlates of cortical abnormalities.

Apkarian et al. (2004b) found that compared to healthy controls CLBP patients performed poorly in a task designed to specifically assess emotional decision making. Using a gambling task in which participants are asked to choose between a deck of cards that yields immediate large rewards but subsequent larger losses (the bad deck) and one that yields lower but more consistent gains and fewer losses (the good deck) they found that CLBP patients were more likely to choose the bad deck for longer and over repeated trials they

took longer to learn to choose the good deck. Performance in this task was negatively related to pain intensity in CLBP patients. It appears that this deficit is not one of general attention or cognitive ability as a battery of other cognitive tasks was unaffected. Equally pain intensity was not enough to fully explain the finding as another group with CRPS and similar levels of pain demonstrated greater impairments. Deficits in performing this task have previously been associated with lesions of the orbito-frontal region of the prefrontal cortex (Bechara 2004) and the authors speculate that the deficit indicates abnormal involvement of this area in patients with chronic pain.

Using a different battery of cognitive tasks (Weiner et al. 2006) demonstrated in an elderly population that subjects with CLBP demonstrated significant deficits in neuropsychological (NP) performance compared to those without and that NP performance scores demonstrated a significant but weak negative correlation with pain severity, a positive moderate correlation with physical performance and mediated the relationship between the two. There is also evidence of memory dysfunction on CLBP, though this was correlated with catastrophizing but not pain levels (Jorge et al. 2009) Buckalew et al. (2008) found impairments in attention and mental flexibility in a group of elderly CLBP sufferers compared to those without pain. These findings appear at odds with those of Apkarian et al. (2004b) who found no evidence of a generalised deficit in cognitive performance in CLBP. Given that the correlations in this cohort (n=323) were not strong it seems reasonable that the study by Apkarian et al. (2004b) may have been underpowered to detect them (n=52 excluding CRPS patients). Alternative explanations might be that CLBP has a more global impact on general cognitive performance in elderly sufferers or that the deficits were specific to the tests employed. In a large (n=1400) population based study Gijzen et al. (2011) found that after controlling for a range of variables, subjects with recurrent pain were specifically impaired on the Stroop interference task (which seeks to measure speed of information processing interference control, Stroop 1935) but not a task that measured attentional skills or verbal memory. These results suggest that attentional deficit may be age dependent and speak to a degree of specificity in the cognitive impairments associated with chronic pain. Conversely Ling et al. (2007) found an impairment of short term prospective memory in CLBP patients after controlling for age.

Impairment of attentional processes does appear to be a phenomenon related to chronic pain generally, including chronic low back pain. It has been proposed that chronic pain patients may be unable to exercise voluntary cortical control over nociceptive interference

and be impaired at switching attention away from pain and pain-relevant stimuli (Legrain et al. 2009) and there is direct evidence to support this.

Using a dot-probe task Roelofs et al. (2005) found that both normal subjects and those with CLBP take longer to disengage from pictures of physical activities that they associated with the threat of back injury than from those without threat association. This difficulty in disengaging was significantly increased in the CLBP subjects, although the same was not found for threatening words. In contrast, using a similar task with similar group sizes Haggman et al. (2010) found a significant attentional bias towards words related to sensory aspects of pain, but not affective, disability or threat related words, in both acute and chronic back pain. The reason for these conflicting results is unclear, the participants in the study by Roelofs et al. had higher pain levels on average than those in the Haggman study which suggests against disease severity being a factor. While technical problems in the study by Roelofs et al. did reduce the size of the group considerably, it should be noted that no trend towards a bias to threatening words was observed. In a review of the wider chronic pain literature Pincus & Morley (2001) conclude that there is evidence for attentional biases towards sensory but not affective pain words and Dehghani et al. (2003) found similar results to Haggman et al. in a broader chronic pain group.

It is plausible that DLPFC dysfunction may contribute to attentional problems. The DLPFC is broadly accepted as playing a key role in selective attention and attention switching (Funahashi 2001; Milham et al. 2003; MacDonald III et al. 2000; Smith and Jonides 1999; Wager, Jonides, and Smith 2006; Sylvester et al. 2003). Indeed disengagement from pain and pain related information has been suggested as a role of the DLPFC and unsurprisingly this role appears to be mediated by psychological factors. Seminowicz & Davis (2006) found that during moderately intense painful experimental stimulation in healthy subjects DLPFC activity bilaterally demonstrated a strong negative correlation with the level of pain related catastrophising, a psychological response characterised in part by difficulty disengaging with pain (Van Damme et al. 2004).

Given the prognostic role that psychological factors, notably depression and distress, have been shown to play in the development and maintenance of CLBP (see chapter 1), it is reasonable to suggest that these phenomena should be related to and reflected in the brain changes observed in this patient group. Grachev (2003) identified significant overlap in the neural regions involved in both depression and CLBP, particularly with regards the DLPFC. Imaging studies implicate prefrontal dysfunction in the pathogenesis of depression

(George et al. 1994; Liotti & Mayberg 2001) including grey matter reductions in this brain region (Brooks et al. 2009) although the precise role of the DLPFC in depression far from fully established. Recent meta-analyses of imaging studies found that while the DLPFC is commonly implicated by studies and is often found to demonstrate reduced activity at rest there is some inconsistency in the changes reported by different studies in terms of the direction of changes and their hemispheric laterality (Fitzgerald et al. 2006; Fitzgerald et al. 2008) and studies combining imaging of the DLPFC during neuropsychological tasks produce inconsistent results (Rogers et al. 2004). However Fitzgerald et al. (2008) did find consistent evidence of a failure to activate the DLPFC in response to negative emotional stimuli and suggest that dysfunction of this region might contribute to abnormal appraisal and response to negative emotional stimuli (such as pain). This conclusion is echoed by Koenigs & Grafman (2009) who emphasise the role of the DLPFC in appraisal and suppression of negative affect. If DLPFC dysfunction retards the ability to effectively appraise and suppress negative emotional stimuli, it is plausible that this might include painful stimuli. However abnormal DLPFC activity may not be specific to the processing of emotional stimuli. In their longitudinal study using fMRI Seminowicz et al. (2011) found that in CLBP patients left DLPFC activation was increased relative to healthy controls during performance a simple cognitive task with no specific emotional context. This had normalised after treatment, although this was not correlated with improvements in clinical signs and symptoms.

Together these data identify common circuitry that may underpin aspects of the CLBP experience and its associated psychological features and suggest a possible biological substrate for the clinical relationship between emotional and psychological phenomena and CLBP.

3.6 CORTICAL REORGANISATION, REPRESENTATION AND BODY PERCEPTION.

The functional and pathological relevance of cortical reorganisation to pain is currently unknown. A number of theories have been suggested one of which is altered body perception (Lotze & Moseley 2007; Swart et al. 2009; Lewis et al. 2007). It is suggested that cortical representation changes may disturb the normal perception of the body (i.e. how the body part is consciously perceived) and evidence of this has been demonstrated in phantom limb pain and CRPS patients who demonstrate reduced tactile acuity, mislocalisation of tactile stimuli and signs of distorted body image (Lotze & Moseley 2007). This concept has recently been expanded to include cortical representation of not just the

body but also the “peripersonal” space around but outside of the body (Moseley et al. 2012)

Recent behavioural evidence points to similar phenomena in CLBP. A number of studies have demonstrated deficits in tactile acuity in CLBP patients (Moseley 2008; Wand et al. 2010; Luomajoki & Moseley 2009) despite preservation of normal tactile thresholds. Wand et al. (2010) demonstrated an additional deficit in graphaesthesia (the recognition of letters traced onto the back) in CLBP patients. Together these results are suggestive of a higher-order dysfunction in the integration of sensory stimuli. CLBP patients find it difficult to delineate the outline of their back, specifically where it is painful (Moseley 2008) with some subjects reporting that they were unable to “find” their back in order to draw its outline. Subjects commonly drew the painful part of their back as disproportionately smaller. CLBP patients are also impaired on a motor imagery task that requires them to make judgements on the position of the spine from photographs, suggestive of a disruption of the trunk working body schema (Bray & Moseley 2011).

Whether proprioception is disrupted in CLBP is unclear. Studies in back pain patients, where the duration of back pain was not specified, (Gill & Callaghan 1998; Brumagne et al. 2000), and in a subgroup of CLBP patients classified clinically with flexion related “lumbar segmental instability” (O’Sullivan et al. 2003) have demonstrated a deficit compared with pain free controls. In groups of CLBP no increase in repositioning error of the lumbar spine has been found by a number of studies (Åsell et al. 2006; Descarreaux et al. 2005, Lee et al. 2010) but increases in motion detection threshold have been observed (Lee et al. 2010). Conversely Sheeran et al. (2012) demonstrated that across a range of subgroups based upon the direction of aggravating movements, CNSLBP patients demonstrated repositioning errors. Other studies have demonstrated increases in postural sway and alterations in postural strategy in response to perturbation applied to a standing footplate have been observed (della Volpe et al. 2006; Popa et al. 2007).

It is possible that the multitude of alterations in motor control and muscle recruitment strategies seen in CLBP (Hodges & Moseley 2003) may be related to altered cortical representation. Luomajoki & Moseley (2009) demonstrated a close relationship between tactile acuity performance and the ability to perform a battery of lumbo-pelvic motor control tests in CLBP patients.

3.7 ALTERED CORTICAL REPRESENTATION AND PAIN: A PROBLEM OF SENSORIMOTOR INCONGRUENCE?

It is not yet clear if or how cortical reorganisation might lead to the generation of ongoing, movement related pain by the brain. Harris (1999) suggested that altered cortical representation of somatic input may falsely signal incongruence between motor intention and movement. The generation of motor activity within the central nervous system is closely coupled to sensory feedback systems, which are monitored to detect deviation from the predicted response (Harris 1999). The theory hypothesises that where there is conflict between motor output and sensory feedback, pain is produced as a warning signal to alert the individual to abnormalities within information processing (McCabe et al. 2005).

It is possible to artificially create discordance between motor intent and the sensory feedback associated with movement using mirrors. For example, if one hand is placed in a mirror box and the other hand alongside the mirror such that its reflection appears in the space where the hidden hand should be, incongruence between motor intent, proprioception and visual feedback can be achieved by performing asynchronous bilateral wrist flexion and extension. While the intention will be to move both hands out of phase, such that while one is extending the other is flexing, visual feedback will be incongruent with this intent as the individual will see both hands flex and extend together.

Several authors have attempted to experimentally test the sensori-motor incongruence hypothesis using this methodology. McCabe et al. (2005) asked 41 healthy volunteers to perform synchronous and asynchronous limb movements with either a mirror positioned in line with the para-sagittal axis, or a non reflective whiteboard, which served to hide one moving limb from view. At the end of each of the conditions participants were asked to describe how they felt and if they were aware of any changes in either limb. Those who reported pain were then asked to verbally rate the pain intensity on a numerical rating scale. Although no formal statistical analysis was undertaken the results partly support the incongruence hypothesis as the condition of maximal incongruence – asynchronous movement with the mirror – appeared to be associated with a greater incidence of sensory changes. However, the incidence of reported pain was low (17% of participants) and of low intensity (<2/10 on a visual analogue scale) including symptoms that might not be considered painful and was very similar for both mirror conditions.

The same group repeated this protocol with a cohort of 29 fibromyalgia patients (McCabe et al. 2007), with the addition of a baseline assessment that involved synchronous and asynchronous limb movements without the mirror or whiteboard in place, to control for the confounding influence of movement induced symptoms. The data again provide partial support for the sensori-motor incongruence hypothesis as it appears that the clinical population report sensory changes more frequently than healthy volunteers during all conditions. However, in the fibromyalgia group neither the report of pain nor any other sensory symptoms appear to be greater in the condition of maximal sensori-motor incongruence. The authors suggest that this might be due to pre-existing sensori-motor conflict in the clinical population enhancing their susceptibility to any manipulation of visual feedback. An alternative interpretation was that incongruence did not exacerbate pain. In both of these studies it is difficult to assess the influence of suggestion over participants' responses.

Daenen et al. (2010) repeated the same protocol on a sample of 20 elite violin players, nine of whom presented with upper limb sensory disturbances. The methodology was somewhat strengthened by the application of statistical analyses of the data. Their results are largely in keeping with the previous research. They report significantly more sensory changes in subjects with symptoms compared to those without during the experimental conditions. In addition, there were a significantly greater number of sensory symptoms (including discomfort) reported, during the experimental conditions compared to the control conditions in which movement occurred without any manipulation of visual feedback. However, once again there was no difference in symptom report between the experimental condition in which maximal incongruence occurs and the other experimental conditions where sensori-motor incongruence is less likely.

More recently the same researchers (Daenen et al. 2012) compared a group of people with chronic whiplash to healthy controls as they undertook the same testing. In the whiplash population, sensory changes were more common when moving with a whiteboard or mirror between the arms than the control conditions. However, there was no difference between the four experimental stages, and while pain was commonly reported during the experimental conditions it is unclear from the study report if this was more common than in the control conditions as all sensory changes were analysed together. The intensity of sensory changes during the experimental stages were much lower in healthy controls and, in contrast to the patient group, healthy subjects reported significantly more sensory

changes during the stage of maximal sensori-motor incongruence than the other experimental stages. However, while healthy subjects reported such sensations as peculiarity and weight changes when moving in an environment of incongruence, in contrast to the findings of McCabe et al. (2005), no healthy subject reported pain.

Moseley et al. (2006c) used an alternative approach to inducing sensori-motor incongruence in a group of 29 healthy volunteers. In this study incongruence was induced by tendon vibration. The vibration stimulates muscle spindles, sending information to the brain that the limb is moving while simultaneous information from other proprioceptors does not corroborate this information. In comparison to sham and control conditions, vibration induced incongruence created greater feelings of peculiarity, foreignness and swelling though there was no difference in self reported pain or discomfort.

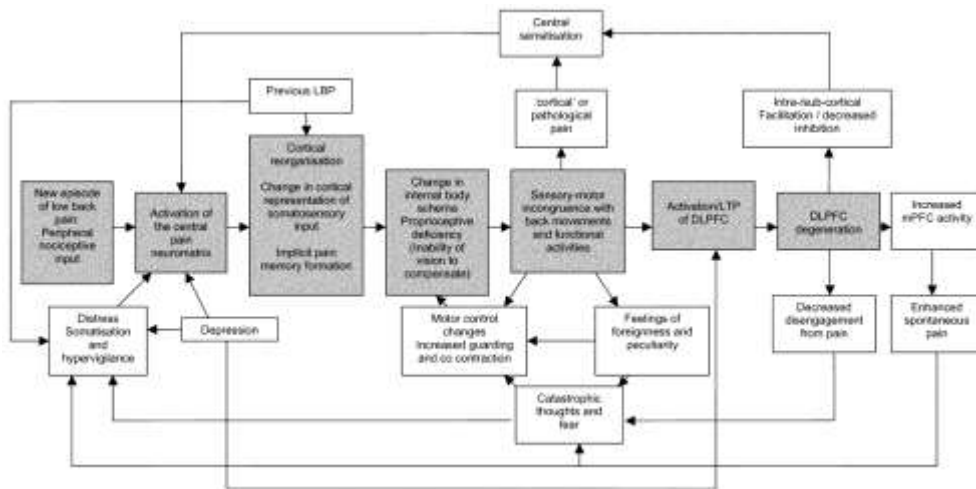
The data to date appear to suggest that an environment of sensori-motor incongruence induces various sensory changes and feeling of peculiarity, however there is little compelling evidence that incongruence induces pain effect on pain. At best this hypothesis might be considered unconfirmed.

3.8 BRAIN-CENTRED MODELS OF CHRONIC PAIN

At the time of writing two models have been proposed for the development and maintenance of low back pain that place altered brain function in a key role. Wand & O'Connell (2008) presented a speculative unified model of CLBP (see figure 1) that attempted to integrate the concepts of sensory-motor incongruence, altered proprioception, motor control and psychological factors with the observed evidence of altered cortical function.

In the model, current and previous episodes of back pain contribute to an altered cortical representation of the back. Conceivably, previous episodes of LBP may also increase distress about the problem. Alterations in proprioceptive representation, subsequent sensory-motor incongruence and pre-existing depressive mood or distress lead to over-activation and subsequent neurodegenerative change in the DLPFC. Sensory-motor incongruence may also directly produce pain, sustain altered motor control strategies and contribute to fear and catastrophic thoughts. The resulting DLPFC dysfunction contributes to central sensitization and subsequent ongoing and exaggerated pain, and also decreases the patient's ability to disengage from the pain, thus feeding back into the negative psychological influences.

Figure 3.1. A cortical dysfunction model of chronic nonspecific low back pain. (Wand & O'Connell 2008).



Similarly Apkarian et al. (2009) suggest a model of chronic pain in which a time-dependant neural reorganisation shifts the brain into a distinct state, involving atrophy and degeneration of specific regions that perpetuates chronic pain and suggest that this state may not be reversible. Both of these models were published before evidence of the apparent reversibility of structural cortical changes (Seminowicz et al. 2011; Rodriguez-raecke et al. 2009) was available. This new evidence presents a significant challenge to the notion that cortical neural degeneration is a key mechanism in chronic back pain but does not necessarily undermine the concept that altered cortical function may be an important factor in the condition.

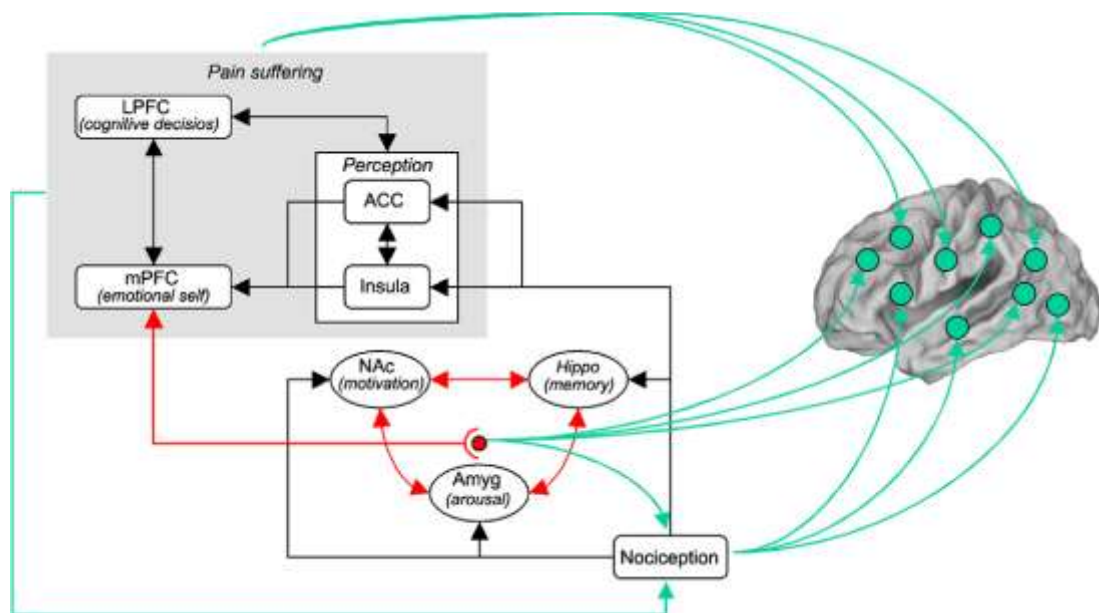
Apkarian has recently expanded on this model (Apkarian et al. 2011, Farmer et al. 2012, see figure 3.2) suggesting that the specific changes in brain function seen in chronic pain reflect a shift in pain processing from the sensory-discriminative nociceptive circuitry characteristic of the experience of acute pain to the mesolimbic circuitry associated with the emotional and affective experience of pain. In their model chronic pain is conceptualized as a form of aberrant emotional learning in which memory traces associated with pain are adversely reinforced leading to central sensitization

3.9 A CORTICAL MODEL OF CLBP? CAVEATS AND LIMITATIONS

As alluded to above, the presence of altered brain structure and function is not necessarily evidence of a causal role for these phenomena in generating chronic pain. Any or all of the above abnormalities may represent secondary manifestations of ongoing nociceptive drive from the tissues of the spine or from aberrant sub-cortical sensitivity. Conversely they may

be secondary consequences of ongoing back pain and its associated impacts on health and function, or they might simply reflect the neuroanatomical and neurophysiological substrate of ongoing pain perception. Given that the perception of pain can be considered to be an output of the brain (Moseley 2007) it is perhaps unsurprising that ongoing pain states are reflected in differences in brain function, regardless of the causal drivers.

Figure 3.2 Apkarian et al.'s (2011) brain-circuitry model of the transition from acute to chronic pain (copied from Apkarian et al. 2011)



“A model regarding brain circuitry involved in the transition from acute to chronic pain. Nociceptive information, perhaps distorted by peripheral and spinal cord sensitization processes, impinges on limbic circuitry (Hippo, hippocampus; NAc, nucleus accumbens; and Amyg, amygdala). The interaction of limbic circuitry with prefrontal processes determines the level at which a certain pain condition transitions to a more emotional state. The limbic circuitry also provides learning/modulation signals to the rest of the cortex inducing functional and anatomical distortions that reflect the suffering and coping strategies of specific chronic pain conditions. Nociceptive signals also provide the brain with modulatory signals, and are in turn controlled by the state of suffering of the individual as well as limbic changes in arousal and motivation, through descending modulatory pathways.” (Apkarian et al. 2011). ACC = anterior cingulate cortex, mPFC = medial prefrontal cortex, LPFC = lateral prefrontal cortex,

The absence of any clear relationship between the clinical course of CNSLBP and measurable spinal pathology or physical examination signs might suggest that ongoing pain may not be primarily driven from injury or disease of the tissues of the lower back. However it is possible that some as yet unidentified peripheral mechanism in the lower

back tissues may be responsible for ongoing low back pain. A cortical model of back pain does not exclude a role for ongoing nociceptive activity from the lumbar region but suggests that aberrant higher order pain processing results in pain perception and behaviour that is disproportionate to or effectively uncoupled from that input. It suggests that CLBP is not primarily a problem of the spine, but rather might be considered to be a centrally maintained somatic syndrome, distinct from but similar to fibromyalgia or CRPS. Nonetheless the evidence and models presented might be considered very “neurocentric” in that they place the brain at the centre of the problem and specifically the neuronal networks. Such a model does not account for the possible interplay of neural-immune interactions or the role of the glial system which may be critical (Watkins and Maier 2000). This omission rather reflects the limited state of knowledge of said mechanisms, not least in CNSLBP. Similarly models that overemphasize the role of the brain have recently been criticised for failing to recognise the philosophical position that pain is an emergent property of the whole person including the brain, the body and all systems therein, rather than simply an output of the brain (Thacker & Moseley 2012).

Given our incomplete understanding of cortical function and its inherent complexity it is possible to create any number of different possible models to describe how these brain changes might cause or perpetuate CLBP that all possess a degree of plausibility. However any such model will be speculative at best. Most studies of brain function in CLBP are small and cross sectional and some of the variability between findings and the relationships within the data will be the result of factors such as divergent methodology and simple lack of statistical power. What can be concluded with some confidence is that chronic pain, including CLBP, is characterised by alterations in cortical structure and function and that these alterations demonstrate relationships with the clinical manifestations of the condition. Whatever these changes represent, given the central role of the brain to the conscious experience of pain it is reasonable to suggest that therapies directed at altering brain function may potentially have the ability to mediate the symptoms of the condition. One such approach to altering brain function is through the electrical stimulation of brain tissue. The next chapter will review the literature relating to brain stimulation techniques in the treatment of pain.

CHAPTER 4 BRAIN STIMULATION IN THE TREATMENT OF CHRONIC PAIN.

4.1 INTRODUCTION

For the purposes of this thesis the term “brain stimulation” will be used to discuss methods that seek to stimulate neural tissue within the brain via the application of electrical currents. Non-electrical stimulation methods such as caloric vestibular stimulation will not be discussed. This chapter will set out a brief history of brain stimulation, with specific attention to its use as a treatment for pain, discuss the proposed mechanisms by which brain stimulation might affect pain perception and consider the evidence relating to the efficacy of brain stimulation techniques. The focus will primarily be on non-invasive brain stimulation modalities but will draw on data from both invasive and non-invasive brain stimulation studies where relevant.

4.2 THE ORIGINS OF MOTOR CORTEX ELECTRICAL STIMULATION IN THE TREATMENT OF PAIN

Brain stimulation techniques primarily seek to modulate activity in brain regions by directly altering the level of brain activity through the application of electrical currents. The basic aim of brain stimulation in the management of pain is to reduce pain by altering activity in the areas of the brain that are involved in pain processing.

Electrical stimulation of the brain is not a new concept. In a review of its historical background Priori (2003) cites the case of Scribonius Largus, court physician to the Roman emperor Claudius who observed that the application of a live torpedo fish (that emits an electrical discharge) to the scalp of a patient with headaches led to pain relief and a “sudden transient stupor”. There are examples of similar reports throughout history (Priori 2003). Outlining the history of “electrotherapeutics”, Reynolds (1971) describes a repetitive history of discovery and rediscovery, with various forms of electrical stimulation being enthusiastically advocated for a plethora of diverse conditions from sexual dysfunctions to baldness and various palsies. Nonetheless the adoption and development of modern non-piscatorial brain stimulation methods as a technique for the management of pain has been an innovation of the last 3 decades and the bulk of that related research refers to stimulation of the motor cortex.

In their review of invasive motor cortex stimulation (MCS) for central and neuropathic pain, Brown & Barbaro (2003) place the origin of the concept with the early, seminal studies of cortical somatotopy conducted by Penfield and Boldrey (1954). Stimulation over the motor

cortex of awake neurosurgical patients was found to elicit sensory responses. As a result of this Lende et al. (1971) reported the cases of 2 patients with intractable facial pain of neuropathic origin who experienced lasting pain relief following surgical resection of the post and pre central gyri where previous resection of the post central gyrus alone had not been successful. These results raised the possibility that manipulation of motor cortex function might offer a pathway to pain relief, although due to the drastic nature of the intervention this neurosurgical approach did not flourish.

Many subsequent investigations into the pathophysiology of central neuropathic pain syndromes have implicated a role for abnormal function of the thalamus, a central relay for afferent nociceptive input (Brown and Barbaro 2003). Specifically thalamic cells demonstrate abnormal bursting activity and altered somatotopic organization. Furthermore stimulation of thalamic nuclei elicited patients' own pain symptoms (Lenz et al. 1987; Gorecki et al 1989, Tasker et al. 1987). Using a cat model of thalamic deafferentation pain, Hirayama et al. (1990) demonstrated that electrical stimulation of the motor cortex effectively suppressed abnormal bursting activity in thalamic neurons. They subsequently implanted epidural electrodes into the motor cortex of seven patients diagnosed with intractable central thalamic pain syndrome, reporting good to excellent pain control from chronic electrical stimulation in all cases (Tsubokawa et al. 1991). This first clinical report of motor cortex stimulation for chronic pain triggered a host of studies and effectively launched its use as a clinical intervention for intractable chronic pain patients. It also appears to have established the motor cortex as the most popular, though not the only, target for brain stimulation approaches to chronic pain treatment.

It seems a fair observation that the motor cortex has arisen as the most common target for neurostimulation based upon models of central neuropathic pain secondary to lesions specifically affecting the thalamus. Nonetheless clinical studies have ventured beyond the use of MCS specifically for "thalamic pain", though the vast majority of studies of invasive MCS have focused on pain that is classified as neuropathic (Lima and Fregni 2008).

A recent systematic review and meta-analysis (Lima & Fregni 2008) investigated the efficacy of invasive MCS for chronic pain. They identified 22 studies including 327 participants. Since they identified no placebo-controlled trials in this area the analysis included all open label studies of invasive motor cortex stimulation that included 2 or more participants. The analysis demonstrated a responder rate of 54.6%. It is worthy of note that a "responder" was defined by each study's own definition and therefore not standardised

and these criteria were not reported within the review. The review did not account for potential risks of bias, so that even after taking into account the established biases inherent in unblinded and uncontrolled clinical studies, other potential biases were not considered systematically. Finally no data was provided regarding changes in pain scores. Together these issues make interpretation of the findings difficult.

In their own review of the evidence of MCS specifically for neuropathic pain the European Federation of Neurological Sciences (EFNS) (Cruccu et al. 2007a) concluded that there was level III evidence (characterised as evidence from controlled studies that are not randomised and do not use matched controls), that MCS is useful in 50-60% of patients with chronic post-stroke pain (CPSP) and facial neuropathic pain (of central or peripheral neuropathic origin) and rated their recommendation a level C (defined as “possibly effective”). Since then 3 small studies have utilised double-blinded within-subjects designs (in which blinded participants experience periods with the stimulator switched on and off and pain is monitored) in the treatment of Complex Regional Pain Syndrome (CRPS) (Velasco et al. 2009) and neuropathic pain (Velasco et al. 2008; Nguyen et al. 2008) and have reported encouraging results. Peyron et al. (2007) offer some arguments against the conclusion that the observed effects of MCS represent placebo responses. They point out that long term follow up indicates good to excellent pain relief over a 4 year period in around half of patients treated (Nuti et al. 2005) and cite cases of patients who reported a cessation of pain relief following equipment malfunctions that they were unaware of (Nuti et al. 2005).

While there is encouraging but limited evidence suggesting that MCS may effectively treat chronic pain there are clear drawbacks. The procedure is surgical and therefore associated with increased risk of adverse events and complications. It requires specialised neurosurgical expertise and is relatively expensive to perform. As such it is not practised widely and is used primarily as a therapeutic option when alternative approaches have failed. Nonetheless the development and application of modern non-invasive brain stimulation techniques for the treatment of pain has, at least in part, been driven by the perceived success of invasive brain stimulation. In the 1980's Merton and Morton (1980) first demonstrated that it was possible to non-invasively stimulate the human cortex in vivo using brief high voltage electrical stimuli. Since that pioneering work several non-invasive brain stimulation techniques have been developed that might represent cheaper and safer methods for stimulating the cortex.

The next section will outline the 3 most prominent forms of non-invasive brain stimulation in terms of their methods and possible physiological effects.

4.3 NON-INVASIVE BRAIN STIMULATION (NIBS) TECHNIQUES

4.3.1 REPETITIVE TRANSCRANIAL MAGNETIC STIMULATION (rTMS)

Transcranial magnetic stimulation (TMS) involves stimulation of the cerebral cortex (the outer layer of the brain) via a stimulating coil applied to the scalp. Electric fields are induced in brain tissue directly using short-duration rapidly changing magnetic fields (Barker, 2002). These electric fields produce action potentials in cortical and subcortical axons (Priori et al. 2009). While generally considered to induce a relatively focal electrical field, the induced field is variable and is affected by various factors including the geometry of both the stimulating coil and the neural architecture at the site of stimulation as well as local tissue conductivity (Barker 2002). The field is considered to be restricted to superficial regions such as the cerebral cortex and subcortical white matter (McKinley et al. 2012) In repetitive TMS (rTMS) trains of these stimuli are applied to the target region of the cortex to induce alterations in brain activity both locally and in remote brain regions (Leo 2007).

TMS stimulation has both direct and indirect effects on neural tissue and function. There is a direct action of the induced electrical current upon local neurons and secondary indirect effects on the post-synaptic targets of these local neurons (Lemon, 2002). rTMS produces alterations of cortical excitability that are specific to the frequency of stimulation and last beyond the immediate period of stimulation (Lefaucheur 2008). As a general rule it is considered that low frequency stimulation, wherein stimuli are applied in trains of a frequency of 0.2-1Hz suppresses cortical excitability whereas high frequency trains ($\geq 5\text{Hz}$), delivered in bursts result in increased local cortical excitability (Lefaucheur 2008) and it is on this basis that clinical studies have sought to apply rTMS as a treatment for pain.

Closer scrutiny of the evidence regarding the effects of rTMS on cortical function reveals a less clear picture. In their review Classen and Stefan (2008) discuss various areas where findings are variable or conflicting. For instance while studies have demonstrated a reduction in the size of motor evoked potentials in response to low frequency rTMS applied to the primary motor cortex, suggestive of a local inhibitory effect, inter-individual variability is marked with some subjects demonstrating an increase in amplitude. Additionally conflicting effects were seen across studies with regards the influence of stimulation intensity on MEP amplitude and the effects of low frequency rTMS on the excitability of the cortex contralateral to that stimulated. This inconsistency was

highlighted by Hiscock et al. (2008), in their systematic review of the effects of rTMS on corticospinal excitability. They found conflicting evidence for the effects of low frequency rTMS, with multiple studies suggesting that it either facilitated, inhibited or had no effect on MEP amplitude.

High frequency rTMS does present a somewhat clearer picture. rTMS has been demonstrated to facilitate MEPs, reduce short intra-cortical inhibition and enhance intra-cortical facilitation (Classen and Steffan 2008). Hiscock et al. (2008) found that at stimulation frequencies of ≥ 10 Hz the weight of evidence supported an excitatory effect of rTMS (as evidenced by facilitation of MEP amplitudes). While studies have suggested that the stimulation intensity may modulate the cortical response to rTMS, with stimulation of the motor cortex at stimulation intensities below the resting threshold for eliciting MEPs (resting motor threshold (RMT)) suppressing excitability and suprathreshold stimulation producing facilitation (Classen and Leffert 2008), Hiscock et al. 2008 found no influence of stimulation intensity on outcome. Importantly, methodological quality was either unclear or inadequate in most of the included studies.

4.3.2 TRANSCRANIAL DIRECT CURRENT STIMULATION (tDCS)

Transcranial direct current stimulation (tDCS) involves the safe and painless application of low intensity constant electrical currents (commonly ≤ 2 mA) to the cerebral cortex of the brain via electrodes that are placed on the scalp (Fregni et al. 2007). tDCS has been developed as a clinical tool for the modulation of brain activity in recent years and uses electrodes that are applied to the scalp over the targeted brain area to deliver a weak constant current (Lefaucheur, 2008). While rTMS might be considered a neurostimulation therapy, in that the intervention directly and indirectly induces action potentials in populations of neurons, tDCS has been characterised as a neuromodulation therapy. The distinction arises because tDCS does not directly induce action potentials, rather it polarises neurons which alters their average level of discharge (Priori et al. 2009). In a recent review Priori et al. (2009) argue that both techniques ultimately lead to the same final result: alterations of cortical excitability that outlast the period of stimulation, and it is this effect that clinical applications of both techniques seek to exploit. The induced field in tDCS is considered to be much less focal than for TMS and the path of the current is not well understood, though modeling studies suggest that brain regions remote from the electrode sites also receive a substantial amount of current and that current may concentrate around the edge of gyri, leading to a lack of homogeneity of stimulation at the stimulation site (Brunoni et al. 2011, McKinley et al 2012).

Similar to rTMS much of the evidence relating to the effect of tDCS on cortical activity has focused on its effects when applied to the motor cortex (M1) since measurement of corticospinal outputs from this area is relatively straightforward using techniques such as TMS. Early studies by Priori (1998) suggested that anodal stimulation (wherein the anode is placed over the cortical region being investigated) of M1 at an intensity of 0.5mA significantly reduced the amplitude of MEPs, whereas cathodal tDCS had no effect. This was the first study of its kind that demonstrated that such weak electrical currents cross the skull and influence cortical excitability. In his review of brain polarization research, Priori (2003) cites the subsequent study by Nitsche & Paulus (2000) as confirmatory evidence of this. While superficially it may be argued that this study confirms that DC stimulation alters cortical excitability, the authors actually found an opposite effect to Priori. Anodal DC stimulation significantly facilitated MEPs and cathodal stimulation reduced MEP size. Various explanations for this inconsistency have been suggested (Priori, 2003) including the use of a higher stimulation intensity (1mA), and other methodological differences between the studies. In a recent review of the state of the art in tDCS research (Nitsche et al. 2008) a more consistent picture arises. Anodal stimulation demonstrates effects consistent with an increase in excitability and cathodal stimulation with a decrease in the overwhelming majority of studies. These alterations last beyond the immediate period of stimulation and have been shown to remain for at least one hour if stimulation is applied for 10 minutes or more (Nitsche et al. 2008).

4.3.3 CRANIAL ELECTROTHERAPY STIMULATION (CES)

Cranial electrotherapy stimulation refers to the application of low intensity direct current, as in tDCS, but the stimulating current is applied in a pulsed format and the technique has been developed separately to that of tDCS. Much of the early work on CES (then predominantly known as “electrosleep”) was developed in the Soviet Union through the 1950’s and 60’ based upon Pavlov’s observations that an electrical conditioning stimulus elicited a sleep like state in dogs and the theory that it caused a form of cerebral inhibition (von Richthofen and Mellor 1979). Electrosleep was suggested as a treatment for a range of psychological disorders. Initially electrosleep aimed to induce a therapeutic sleep-like state and used currents of around 5mA (Brown 1975) but it was proposed by Wageneder and St Schuy (1970) that this state may have been independent of the therapeutic effect and that, rather, the benefits of the treatment were secondary to a direct effect of electrical current on the brain. They suggested the alternative title “cerebral electrotherapy” that has now commonly been replaced by “CES”.

In modern forms of CES the stimulation is commonly delivered by electrodes attached to the scalp or via clips to the earlobes, and treatment is not directed towards focal targets in the brain as with tDCS or rTMS. The stimulation remains pulsed but is delivered at lower intensities of up to 1mA, and often much lower. It has been used in the treatment of pain, addiction, anxiety, insomnia and stress (Klawansky et al. 1995, Kirsch and Smith 2000).

4.4 NEUROPHYSIOLOGIC MECHANISMS OF NIBS TECHNIQUES

4.4.1 RTMS AND TDCS

Various studies have investigated the potential synaptic mechanisms underlying the effects of tDCS and rTMS. In a recent review Stagg & Nitsche (2011) discuss that the effects of tDCS seen during stimulation are underpinned by distinct mechanisms from the after-effects of tDCS stimulation. Where the effects during stimulation appear to be due to changes in membrane potential the after effects of tDCS appear to be due to synaptic modulation.

Liebetanz et al. (2002) and Nitsche et al. (2004) demonstrated that the long lasting effects of both anodal and cathodal stimulation were suppressed by administration of an n-methyl d-aspartate (NMDA) receptor antagonist, and that pharmacological blocking of sodium channels eliminated only the excitatory effects of anodal stimulation. They conclude that the effects of anodal stimulation require depolarization of membrane potentials and that the lasting effects of stimulation are likely due to NMDA receptor mediated long term potentiation. They later confirmed that administration of an NMDA receptor agonist prolonged the excitatory effects of anodal stimulation (Nitsche et al. 2004). Similarly NMDA antagonists have been shown to block the after effects of some rTMS protocols (Huang et al. 2007).

Other neurotransmitter/receptor mechanisms have been implicated in the effects of tDCS. Nitsche et al. (2006) demonstrated that pharmacological blocking of the D2 dopamine receptor abolished the after-effects of cathodal stimulation on excitability, whereas enhancement of D2 receptors consolidated the effects, suggesting a dopaminergic mechanism underpinning the reductions of cortical excitability induced by cathodal stimulation. Similarly studies have demonstrated that manipulation of GABA, acetylcholine, catecholamine and serotonin receptors all modulate the neuroplastic changes induced by tDCS (Stagg & Nitsche 2011) although it cannot be assumed that common mechanisms also underpin TMS-induced plasticity. For example, while amphetamine has been demonstrated to extend the duration of after effects of tDCS (Nitsche et al. 2004), an earlier study

demonstrated suppression of rTMS induced plasticity by amphetamine administration (Ziemann et al. 2002).

There is evidence that non-synaptic mechanisms may also play a role in the after effects of tDCS, at least following cathodal stimulation. Ardolino et al. (2005) investigated the after effects of cathodal stimulation of the motor cortex using TMS, transcranial electrical stimulation (TES) and EEG. TES differs from TMS and tDCS in that it applies high-voltage stimulation of the brain via scalp electrodes. Unlike TMS, wherein the effects on MEPs are induced indirectly through stimulation of populations of cortical interneurons, TES modulates MEP amplitude via direct activation of corticospinal axons below the level of the cerebral cortex (Ziemann 2002). Ardolino et al. (2005) demonstrated that following cathodal stimulation MEP amplitude was reduced in response to both TMS and TES, suggesting that the after effects of tDCS did not only involve intracortical synaptic modulation but also direct changes in corticospinal axonal excitability. Decreases in the resting motor threshold were observed in addition to alterations in MEP size to cortical tDCS, which the authors interpret as reflecting an alteration of neuronal membrane excitability.

Other studies have not demonstrated changes in TES-induced MEPs following tDCS (Nitsche & Paulus 2000; Nitsche & Paulus 2001) although the effect on TMS-induced MEPs is reasonably consistent across the literature. In their recent review paper Antal et al. (2009) conclude that the evidence indicates that tDCS has a predominantly intra-cortical effect that is mediated by changes to neuronal membrane polarisation leading to alterations in NMDA receptor function.

Ardolino et al. (2005) also demonstrated alterations in the power of slow EEG rhythms reflective of a decrease of cortical activity in response to cathodal tDCS. This suggests a wider effect that extends beyond the structures directly stimulated. This suggestion is supported by the findings of a number of brain imaging studies which will now be considered.

4.4.2 THE INFLUENCE OF RTMS AND TDCS ON WIDER BRAIN FUNCTION

Brain imaging studies illustrate that non-invasive brain stimulation not only influences brain activity local to the site of stimulation but also has effects across more distributed neural networks. Using fMRI Baudewig et al. (2001) noted cathodal tDCS applied to M1 reduced local brain activity associated with a finger movement task while anodal tDCS had little effect. Using positron emission tomography (PET) to measure regional cerebral blood flow

(rCBF, an indirect measure of the level of local neural activity) in response to tDCS stimulation of M1, Lang et al. (2005) found that compared with sham stimulation, active anodal and cathodal tDCS led to significant alterations in brain activity. Both anodal and cathodal stimulation increased activity local to the site of stimulation (M1) and in the contralateral M1. Anodal stimulation led to an increase in activity across a wide network of cortical and subcortical regions compared with cathodal stimulation which resulted in widespread decreases of rCBF. These effects were stable across a 50 minute post-stimulation period. This study provides the most convincing evidence to date that tDCS can lead to lasting, widespread alterations of brain activity.

rTMS has demonstrated similar effects. Low frequency (Lee et al. 2003) and high frequency rTMS (Lee et al. 2003; Rounis et al. 2005) increased local activity at the site of stimulation during a finger movement task, despite the effects of low and high frequency stimulation on corticospinal excitability being opposite. Immediate after effects of local stimulation of M1 have been demonstrated at stimulation intensities of greater than the resting motor threshold (Bestmann et al., 2003; 2004). At subthreshold intensities this local increase in activity was not seen in these studies but both supra and sub-threshold stimulation induced increases in activation levels in remote cortical and subcortical regions such as the pre- and supplementary motor areas, the cingulate motor area, the putamen and the thalamus. Similar effects have been seen in response to rTMS applied to locations other than M1. While only suprathreshold stimulation of the dorsal pre-motor cortex led to local increases in activity, both supra- and subthreshold stimulation led to increases in activation in both cortical and subcortical networks (Bestmann et al. 2005). The absence of sham control conditions in these studies raises the question of whether the observed brain changes were the direct result of stimulation, or the correlates of the participants' expectation and experience of stimulation.

4.4.3 PHYSIOLOGICAL EFFECTS OF CES

CES has not enjoyed the same degree of investigative interest as tDCS and rTMS and as such there is little robust data regarding its potential effects on brain activity. Much of the literature discusses suggested mechanisms of effect for a variety of conditions from depression, anxiety and insomnia to pain.

In terms of direct evidence from human participants, Dymond et al. (1975) measure the induced voltage within the brain (via surgically implanted electrodes that had been placed in the temporal lobes as part of an intervention for epilepsy) during electrosleep

stimulation of between 0.1 and 1mA intensities. The current was applied via surface electrodes situated at the frontal poles and mastoid processes. They demonstrated that stimulation even at lower intensities altered voltage within brain tissue in a dose-dependent fashion. This confirmed that the induced current did reach brain tissue and therefore plausibly might induce local physiological effects.

In a recent narrative review paper discussing the use of CES in the treatment of fibromyalgia Gilula (2007) suggests a direct effect of CES on activity in the limbic system, the reticular activating system (RAS) and/or the hypothalamus. They also suggest that CES might activate descending pain modulation pathways, alter EEG rhythms, and/or alter activity in sympathetic autonomic nervous system via vagus or cranial nerve activation. Similarly De Felice (1997) suggests that the mechanism of action may be due to a direct effect on brain tissues producing cortical and subcortical inhibition. A coherent mechanism of action of CES that is underpinned by evidence is yet to be presented, in large part due to the paucity of recent research in this field.

In summary a number of methods on non-invasive brain stimulation exist and, particularly for rTMS and tDCS, there is a broad body of evidence indicating that they exert direct local effects on cortical excitability and lead to alterations in activity of neural networks remote from the site of stimulation. While this provides a potential method of altering central pain processing the research discussed to this point has not specifically related to pain.

4.5 BRAIN STIMULATION: POSSIBLE NEUROPHYSIOLOGIC MECHANISMS OF RELIEF OF CHRONIC PAIN.

4.5.1 EVIDENCE FROM MCS STUDIES

A body of evidence has emerged relating to the effects of invasive epidural MCS on brain activity in patients with chronic pain. While it cannot be assumed that invasive MCS will induce identical effects as non-invasive stimulation techniques these studies illustrate possible mechanisms of action for brain stimulation interventions.

In an exploratory study Peyron et al. (1995) investigated brain activity (via rCBF) in 2 patients with neuropathic central post-stroke pain treated with MCS. Of the two patients only one achieved substantial pain relief and demonstrated concurrent attenuation of nociceptive reflexes. Using PET neuroimaging at 3 weeks and 4 months following electrode implantation and the commencement of stimulation treatment they observed increases in rCBF in the thalamus and brainstem in the patient who experienced pain relief compared to

the patient who did not. From this limited and uncontrolled dataset they suggested that MCS may activate descending inhibitory pain control systems via thalamic/brainstem relays.

Following this study Garcia-Larrea et al. (1999) used a similar protocol in 10 patients with a mix of central and peripherally maintained chronic refractory neuropathic pain and also measured somatosensory evoked potentials (SEPs). They compared the results of scans taken pre-stimulation, twice during a period of stimulation, and then at 30 minutes post stimulation. They found no increase in activity at the site of the stimulating electrodes but significant increases in the ipsilateral ventrolateral thalamus, anterior cingulate gyrus, medial thalamus, upper brainstem and contralateral insula. Changes in the anterior cingulate cortex were not reversed when measured 30 minutes post stimulation. Since no increase was seen in the motor cortex itself the authors concluded that MCS does not modify local synaptic activity but rather exerts its effects via activation of subcortical pathways. No effect was seen on SEP's but nociceptive reflexes were reduced in three patients. Contrary to their hypothesis they found no effect of stimulation on the somatosensory cortex. The authors propose a speculative model of action for MCS in which ventrolateral thalamic activation elicits a cascade of activity in brain areas that receive afferents from the thalamus including the medial thalamus, anterior cingulate and upper brainstem.

The results and interpretations might be evaluated with some caution. Most of the named brain regions only demonstrated changes that reached significance in a low threshold statistical analysis, and when a more stringent analysis was performed which corrected for multiple comparisons the only region that demonstrated significant change was a small region of the ipsilateral lateral thalamus. The PET changes were analysed based on findings from the whole sample but of the 10 participants the degree of pain relief experienced varied and no formal correlation analysis is presented between the experience of pain relief and the results of imaging. Larger increases in ACC activity were observed in those with satisfactory pain relief but the small sample did not support formal statistical comparisons. Similarly the study did not utilise a control group and as such participants are not blinded. Given the wealth of data outlining the neurophysiologic correlates of placebo interventions, which also include increased activity in regions such as the ACC and the PAG (Price et al, 2008; Wager et al.2004) it is unclear whether the results seen are specific effects of MCS or possibly the neurological substrate of a placebo effect.

Building upon these early studies the same group (Peyron et al. 2007) used PET imaging to more closely interrogate the relationship between brain activity and pain relief in response to MCS. In a group of 19 patients with chronic neuropathic pain, imaging was performed prior to, during and 75 minutes following MCS. The study introduced an element of blinding by switching off the stimulator 4 weeks prior to the PET study and throughout this and the study period participants were not informed of the stimulation condition, although assessors were not blinded and the order of stimulation was not randomised.

No significant effect on pain was observed until the 75 minutes post stimulation period. Similarly little change was observed in brain activity between the baseline and “on” phases of the study, except for a limited activation of the contralateral pregenual ACC (pACC). At 75 minutes post stimulation participants reported varying degrees of pain relief with only 3 reporting none. At the same time-point increased activity was still observed in the contralateral pregenual ACC as well as the ipsilateral premotor cortex, the midcingulate cortex (MCC), SMA, OFC, basal ganglia the periaqueductal grey (PAG) and the pons. The majority of these rCBF changes were found to correlate with the degree of pain relief reported and functional connectivity analysis demonstrated correlation between the ACC and the PAG, pons and basal ganglia.

Again using PET this group investigated the effect of MCS upon opioid receptor binding in the brain in eight neuropathic pain sufferers (Maarrawi et al. 2007). The level of opioid receptor binding can be seen as an indirect measure of the amount of local secretion of endogenous opioids, with decreased receptor binding reflecting increased opioid level. Preoperative scans were compared with a scan taken following 7 months of chronic MCS. They found that opioid receptor binding was significantly decreased post-stimulation in the ACC, PAG, PFC and cerebellum and that the decreases observed in the ACC and PAG were significantly correlated with pain relief. The authors propose that the results suggest that MCS might activate descending top-down cortico-subcortical inhibitory pathways, that this lasting effect might underpin the latent clinical effect commonly observed following MCS and that endogenous opioids play a role in MCS induced analgesia. However no control group or condition was employed and when considering these results it should be considered that placebo effects have also been found to be associated with alterations in opioid receptor binding (Zubieta et al. 2005)

Reviewing these imaging studies Garcia-Larrea & Peyron (2007) conclude that the evidence is suggestive of at least two key potential mechanisms. The consistent finding of alteration

in activity in the pACC in response to MCS is presented as evidence for a possible modulation of the emotional appraisal of pain as oppose to a direct effect upon the sensory-discriminative intensity of pain. This interpretation is consistent with an array of evidence that suggests that pain and negative affect are integrated within the cingulate cortex (Bush et al. 2000; Devinsky et al. 1995; Shackman et al. 2011). The similarly consistent finding of modulation of PAG activity that is coupled with pACC changes and the observation of attenuated spinal nociceptive reflexes in participants who respond to the intervention is held to suggest an activation of top-down inhibitory mechanisms, since it is well established that the PAG plays a key role in descending modulatory control over nociceptive pathways (Fields et al. 2006).

This evidence is useful in considering possible analgesic mechanisms of invasive brain stimulation but it cannot be assumed that invasive and non-invasive methods would necessarily share a common mechanism of action. The next section will consider the evidence related to the possible mechanisms of analgesia from non-invasive stimulation methods.

4.5.2 EVIDENCE FROM NIBS STUDIES.

There are limited data pertaining to the possible physiological events that might underpin an analgesic effect of NIBS techniques in chronically painful conditions. Chronic CRPSI is associated with a decrease in levels of GABA-mediated intra-cortical inhibition (ICI) (Schwenkreis et al. 2006). In a trial of a single session of rTMS for chronic neuropathic pain affecting the hand Lefaucheur, (2006) demonstrated first that compared to healthy controls, patients demonstrated reduced levels of ICI in the cortex relating to their affected limb. High frequency (10Hz) rTMS applied to M1 led to an increase in ICI and the degree of increase correlated with the degree of pain relief reported, although no change was seen following low frequency (1Hz) stimulation. In contrast in a group of patients with chronic pain of mixed aetiology Antal et al. (2010) demonstrated superior effects on pain in response to anodal tDCS stimulation of M1 compared with sham stimulation with a concurrent *decrease* in ICI levels. In participants with chronic visceral pain Fregni et al. (2010) found lasting pain relief following a 10 day course of low frequency (1Hz) stimulation rTMS of the right secondary somatosensory cortex compared to sham stimulation that was sustained at 3 weeks post treatment. Using MRS scanning they demonstrated increases in levels of the excitatory neurotransmitters glutamate and n-acetyl aspartate (NAA) at the site of stimulation that correlated with pain relief. These studies suggest that stimulation might alter specific neurotransmitter levels, but the

heterogeneity in terms of stimulation parameters, location, the type of pain studied and the observed physiological effects make comparisons and the drawing of firm conclusions difficult.

4.5.3 ACUTE EXPERIMENTAL PAIN

A number of authors have investigated the influence of applying rTMS and tDCS to acute experimentally induced pain. In reviewing this evidence Lefaucheur et al. (2008) conclude that while there is plenty of data to suggest that rTMS elicits effects over acute pain perception, that data is conflicting and inconsistent in places, possibly due to the application of different stimulation parameters to different type of experimental pain. High frequency rTMS applied to the motor cortex has been demonstrated to reduce susceptibility to cold pain in both healthy subjects (Summers et al. 2004) and those with CLBP (Johnson et al. 2006). Low frequency motor cortex rTMS was demonstrated to reduce capsaicin induced C-fibre mediated acute pain, but increase laser evoked pain (Tamura et al. 2004) although the opposite effect to this latter increase was observed by Poreisz et al. (2008) in response to theta-burst stimulation of M1, in which short train 50Hz stimulations are delivered at a frequency of 5Hz (Huang et al. 2005). Summarising this literature Mylius, (2010) concluded that the majority of studies of motor cortex rTMS indicate that high and low frequency stimulation increases the perception of A-fibre mediated pain but decreases the perception of C-fibre induced experimental pain. In an update to that review they conclude that the evidence is somewhat conflicting but that the most robust effect arising from the data is that high frequency rTMS of the motor cortex reduces susceptibility to cold pain (Mylius 2012).

Inconsistencies have been seen in studies investigating targets other than M1. For example a number of studies have investigated the effect of rTMS to the MFC on acute pain perception. Kanda et al. (2003) found that paired pulse rTMS reduced pain perception in response to CO₂ laser stimuli, Mylius et al. (2006), using a similar stimulus, observed an increase in pain report and Yoo et al. (2006) using high frequency rTMS found reduced pain tolerance.

In tDCS fewer studies have been undertaken. Cathodal tDCS applied to the somatosensory and motor cortex has been found to reduce laser evoked pain perception and to attenuate components of laser evoked potentials that are thought to reflect processing elements of the perception of pain (Antal et al., 2008; Csifcsak et al., 2009; Terney et al., 2008). Bachmann et al. (2010) also demonstrated increased mechanical pain thresholds as well as

increases in non-noxious thermal and mechanical detection thresholds but observed no increase in thermal pain thresholds. They concluded that cathodal tDCS reduces sensitivity to A fibre mediated sensory input. In their recent review Mylius et al. (2012) conclude that cathodal tDCS appears to be more effective than anodal tDCS in reducing evoked pain but that the data varies significantly. In a separate review Luedtke et al. (2012) did not pool data on experimental pain due to the degree of methodological heterogeneity between studies but conclude broadly that the level of evidence relating to tDCS in experimental pain is low.

While these studies indicate that NIBS might specifically modulate the perception of acute experimental pain it is not necessarily reasonable to assume that such an effect might be responsible for its potential effects in chronic pain, particularly in light of the evidence that acute and chronic pain appear to be associated with distinct neuronal networks (Baliki et al. 2006, Wasan et al. 2011, Apkarian et al. 2011). Further, while they indicate specific effects on the processing of pain perception in response to specific types of noxious stimuli they do not provide a detailed picture of the mechanisms involved.

4.6 THE EFFICACY OF NON-INVASIVE BRAIN STIMULATION - RECENT REVIEWS.

These approaches to pain treatment are relatively novel. It is important to assess the existing literature robustly to ascertain the current level of supporting evidence and to inform future research and potential clinical use. In recent years a number of reviews have been published in this area.

The European Federation of Neurological Societies (EFNS) published guidelines on the use of neurostimulation therapy for chronic neuropathic pain in 2007 (Cruccu et al. 2007a) following a review of the existing literature. Using a narrative synthesis of the evidence they concluded that there was moderate evidence (from 2 RCTs) that high frequency rTMS (≥ 5 Hz) of the motor cortex induces significant pain relief in central post stroke pain and several other neuropathic conditions but that the effect is modest and short-lived. They did not recommend its use as a sole clinical treatment but suggest that it might be considered in the treatment of short lasting pain.

Lima and Fregni (2008) undertook a systematic review and meta-analysis of motor cortex stimulation for chronic pain. They pooled data from rTMS and tDCS studies. While the report states that data was collected on mean between-group pain scores it is not presented. The authors present the pooled data for the number of responders to

treatment across studies. They conclude that the number of responders is significantly higher following active stimulation compared with sham. In their analysis the threshold for treatment response is defined as a global response according to each studies own definition and as such it is not well standardised and is difficult to interpret.

A recent meta-analysis of individual patient data from studies of motor cortex rTMS for neuropathic pain conditions (Leung et al. 2009), restricted to studies that clearly reported the neuroanatomical origin of participants' pain, suggested an effect size of around 14% improvement in pain. Importantly neither Lima and Fregni (2008) or Leung et al.(2009) presented a clear approach to assessing the risk of bias in the included studies.

Kirsch and White (2000) reviewed studies of CES in the management of chronic pain and concluded in favour of the use of CES. The review did not report any formalised search strategy, inclusion criteria or quality assessment and discussed a number of unpublished studies that remain unpublished. Given these limitations and those of the reviews of tDCS and rTMS it is difficult to draw conclusions currently with regards the true efficacy of these various NIBS techniques.

4.7 SUMMARY AND CONCLUSIONS

There is clear and consistent physiological evidence that non-invasive brain stimulation techniques (particularly tDCS and rTMS) induce local and remote alterations in brain activity and there appears to be encouraging evidence from studies of invasive brain stimulation of alterations in brain activity that correlate with reported pain relief in chronic pain patients. This suggests that electrical stimulation of brain tissue may represent a therapeutic option in the treatment of pain, and non-invasive modalities offer a potentially safe and pragmatic means of delivery.

As discussed in the previous chapter CLBP, like other chronic pain conditions, is characterized by alterations in brain structure and function and as such might be considered a centrally maintained pain syndrome. While this is not a prerequisite to targeting the brain with a view to reducing pain it does provide a reasonably clear rationale for considering brain stimulation as a treatment option. If dysfunctional central pain processing is playing a key role in CLBP then treatments that seek to affect central pain processing directly may be worth consideration. Additionally even if the symptoms of CLBP are driven by peripheral nociceptive input from damaged lumbar spine tissues brain stimulation techniques might still induce therapeutic effects.

Nonetheless at this stage it is difficult to reliably evaluate the true efficacy of NIBS techniques from the existing literature. The first original study in this thesis aims to address this issue directly through a rigorous and systematic evaluation of the existing evidence relating to the efficacy of rTMS, tDCS and CES in the management of chronic pain.

CHAPTER 5: STUDY 1. A COCHRANE SYSTEMATIC REVIEW ON NON- INVASIVE BRAIN STIMULATION TECHNIQUES FOR THE TREATMENT OF CHRONIC PAIN.

Protocol published as: O'Connell NE, Wand BM, Marston L, Spencer S, Desouza LH (2010a) Non-invasive brain stimulation techniques for chronic pain. Cochrane Database of Systematic Reviews 10 (1) CD008208 PROTOCOL. See Appendix 1)

Full Review published as: O'Connell NE, Wand BM, Marston L, Spencer S, DeSouza LH. Non-invasive brain stimulation for chronic pain in adults Cochrane Database of Systematic Reviews 2010: 9: CD008208. See Appendix 2)

5.1 INTRODUCTION

The first study in this thesis aims to comprehensively assess the evidence for the efficacy of non-invasive brain stimulation techniques as a treatment for chronic pain. As discussed in Chapter 3 no study had reliably evaluated the efficacy of these techniques. Since the area is in its infancy and to avoid seriously limiting the amount of data that might be identified, rather than focus the review specifically to chronic low back pain it was decided to expand the review to consider all types of chronic, but not acute, pain. Following liaison with the Cochrane Collaboration's Pain, Palliative and Supportive Care (PaPaS) review group the title was registered with the Cochrane Library and the protocol was published in the Cochrane library (O'Connell et al. 2010a, Appendix 1).

5.2 STUDY OBJECTIVES

To review all randomised and quasi-randomised studies of non-invasive cortical stimulation techniques in the treatment of chronic pain. The key aims of the review were:

To critically evaluate the efficacy of non-invasive cortical stimulation techniques compared to sham controls for chronic pain.

To critically evaluate the influence of altered treatment parameters (i.e. stimulation method, parameters, dosage, site) on the efficacy of non-invasive cortical stimulation for chronic pain.

5.3 METHODS

5.3.1 CRITERIA FOR CONSIDERING STUDIES FOR THIS REVIEW

5.3.1.1 TYPES OF STUDIES

Randomised controlled trials (RCTs) and quasi-randomised trials (e.g. by order of entry or date of birth) that utilised a sham control group were included. This included parallel and cross-over study designs. Studies were included regardless of language or blinding. Observational studies or non-randomised studies were excluded since they carry a higher risk of bias. In particular a lack of randomisation leaves a study at greater risk of confounding by differences in the baseline characteristics of participants (Higgins and Green 2008). Additionally studies without a control group are unable to control for the natural history of the condition and statistical factors such as regression to the mean. A sham control group was considered essential to control for placebo effects.

5.3.1.2 TYPES OF PARTICIPANTS

Male or female participants over the age of 18 years with any chronic pain syndrome (with a duration of > 3 months) were included. It was not anticipated that any studies are likely to exist in a younger population. Migraine and other headache studies were not included due to the episodic nature of these conditions.

5.3.1.3 TYPES OF INTERVENTIONS

Studies investigating the therapeutic use of non-invasive forms of brain stimulation (tDCS, rTMS or CES) were included. Studies of electroconvulsive therapy (ECT) were not included as its mechanism of action (the artificial induction of an epileptic seizure (Stevens et al. 1996)) differs substantially from the other forms of brain stimulation. Invasive forms of brain stimulation involving the use of electrodes implanted within the brain and indirect forms of stimulation such as caloric vestibular stimulation and occipital nerve stimulation were also not included.

5.3.1.4 TYPES OF OUTCOME MEASURES

PRIMARY OUTCOMES

The primary outcome measure was change in self-reported pain using validated measures of pain intensity such as visual analogue scales (VAS), verbal rating scales (VRS) or numerical rating scales (NRS).

SECONDARY OUTCOMES

Secondary outcomes that were extracted when available include self-reported disability data, quality of life measures and the incidence/nature of adverse events.

5.3.2 SEARCH METHODS FOR IDENTIFICATION OF STUDIES

5.3.2.1 ELECTRONIC SEARCHES

For the OVID MEDLINE search, the subject search was run with the Cochrane Highly Sensitive Search Strategy for identifying randomised trials in MEDLINE: sensitivity maximising version (2008 revision) as referenced in Chapter 6 and detailed in the Cochrane Handbook for Systematic Reviews of Interventions Version 5.0.1 (Higgins and Green 2008). This filter was slightly adapted to include the term "sham" in the title or abstract. The search strategy and filter proposed for MEDLINE is presented in the appendices of the complete published review (Appendix 2) and included a combination of controlled vocabulary (MeSH) and free-text terms. All database searches were based on this strategy but were appropriately revised to suit each database.

5.3.2.2 ELECTRONIC DATABASES

To identify studies for inclusion in this review the following electronic databases to identify published articles were searched:

The Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library 2009, issue 4); The Cochrane Pain, Palliative and Supportive Care Group Trials Register (current issue); OVID MEDLINE (1950 to November Week 3 2009); OVID EMBASE (1980 to Week 47 2009); PsychINFO (1806 to November Week 4 2009); CINAHL (1982 to 11 January 2010); and LILACS (1982 to 15 December 2009).

5.3.3.3 SEARCHING OTHER RESOURCES

The reference lists of all eligible trials, key textbooks and previous systematic reviews were hand searched to identify additional relevant articles.

To identify research in progress and unpublished research the National Research Register (NRR) Archive, Health Services Research Projects in Progress (HSRProj), Current Controlled Trials register (incorporating the meta-register of controlled trials and the International Standard Randomised Controlled Trial Number (ISRCTN)) were searched.

5.3.3.4 LANGUAGE

The search attempted to identify all relevant studies irrespective of language. Non-English papers were assessed and, where necessary, translated with the assistance of a native speaker. A final list of included articles was sent to two experts in the field of therapeutic brain stimulation with a request that they review the list for possible omissions.

5.3.4 DATA COLLECTION AND ANALYSIS

5.3.4.1 SELECTION OF STUDIES

Two review authors independently checked search results and included eligible studies. Initially the titles and/or abstracts of identified studies were read by two review authors. Where it was clear from the study title or abstract that the study was not relevant or did not meet the selection criteria it was excluded. If it was unclear then the full paper was assessed, as well as all studies that appeared to meet the selection criteria. Disagreement between review authors was resolved through discussion between the two review authors. Where resolution was not achieved a third review author considered the paper(s) in question.

5.3.4.2 DATA EXTRACTION AND MANAGEMENT

Two review authors extracted data independently using a standardised form that was piloted by both authors independently on three randomised controlled trials of transcutaneous electrical nerve stimulation prior to the searches. Discrepancies were resolved by consensus. The form included the following:

- Risk of bias assessment results.
- Country of origin.
- Study design.
- Study population - condition; pain type; duration of symptoms; age range; gender split; prior management.
- Sample size - active and control groups.
- Intervention - stimulation site, parameters and dosage (including number and duration of trains of stimuli and number of pulses for rTMS studies).
- Type of sham.
- Credibility of sham (for rTMS studies - see below).
- Outcomes - mean post-intervention pain scores for the active and sham treatment groups at all follow-up points.
- Results - short-term, intermediate and long-term follow up.
- Adverse effects.

5.3.4.3 ASSESSMENT OF RISK OF BIAS IN INCLUDED STUDIES

Risk of bias of the included studies was assessed using the Cochrane 'Risk of bias' assessment tool outlined in Chapter 8 of the Cochrane Handbook for Systematic Reviews of Interventions Version 5.0.1 (Higgins 2008). This risk of bias tool is specifically based on items for which there is empirical evidence that they influence the results of clinical trials.

The criteria assessed for parallel study designs (using yes/no/unclear judgements) were: adequate sequence generation; adequate allocation concealment; adequate blinding of assessors; adequate blinding of participants; adequate assessment of incomplete outcome data; whether free of suggestion of selective outcome reporting; and whether free of other bias.

The criteria assessed for cross-over study designs (using yes/no/unclear judgements) were: adequate sequence generation; whether data were clearly free from carry-over effects; adequate blinding of assessors; adequate blinding of participants; whether free of the suggestion of selective outcome reporting; and whether free of other bias.

Two review authors independently checked risk of bias. Disagreement between review authors was resolved through discussion between the two review authors. Where resolution was not achieved the paper(s) in question were considered by a third review author.

5.3.4.4 ASSESSMENT OF SHAM CREDIBILITY

An issue regarding the credibility of sham conditions specifically for rTMS studies is whether the sham condition that is employed controls for the auditory (clicking sounds of various frequencies) and sensory stimulation that occurs during active stimulation (Lisanby et al. 2001; Loo et al. 2000). Various types of sham have been proposed including angling the coil away from the scalp (thus preserving the auditory cues but not the sensation of stimulation), using coils that mimic the auditory cues combined with gentle scalp electrical stimulation to mask the sensation and simple inert coils that reproduce neither the sound nor the sensation of active stimulation. Failure to control for such cues may impact negatively on patient blinding, particularly in cross-over design studies. Lisanby et al. (2001) and Loo et al. (2000) suggest that an ideal sham condition for rTMS should:

- not stimulate the cortex;
- be the same as active stimulation in visual terms and in terms of its position on the scalp;
- not differ from active stimulation in terms of the acoustic and afferent sensory sensations that it elicits.

Devices have been developed that meet these criteria (Borckardt et al. 2008; Rossi et al. 2007; Sommer et al. 2006). There is evidence that simply angling the coil away from the scalp at an angle of less than 90° may still result in brain stimulation and not be truly inert

(Lisanby et al.2001). This strategy is also easily detected by the recipient of stimulation. In these ways this type of sham might obscure or exaggerate a real clinical effect of active stimulation.

The type of sham used in studies of rTMS was assessed for credibility as optimal (the sham controls for the auditory and sensory characteristics of stimulation and is visually indistinguishable from real stimulation (Lisanby et al.2001; Loo et al.2000)) or sub-optimal (the sham fails to account for either the auditory and sensory characteristics of stimulation, or is visually distinguishable from the active stimulation, or fails on more than one of these criteria). A judgement of unclear was made where studies did not adequately describe the sham condition. Two independent review authors performed rating of sham credibility. Disagreement between review authors was resolved through consensus. Where resolution was not achieved the paper(s) in question were considered by a third review author. Where sham credibility was assessed as unclear or sub-optimal a judgement of 'unclear' for the criteria 'adequate blinding of participants' was made in the risk of bias assessment.

At the time this review was designed and undertaken there was evidence that sham controls in tDCS do ensure effective blinding of participants and assessors (Gandiga et al. 2006). Given that CES delivers stimulation intensities less than those of tDCS it is assumed that the same applies to sham controls of CES.

5.3.4.5 MEASURES OF TREATMENT EFFECT

The standardised mean difference (SMD) was used to express the size of treatment effect on pain intensity measured with VAS or NRS since studies used a mix of similar, but not identical pain scales. In such cases where different scales are used to measure the same construct it is less appropriate to use the simple mean difference as differences in the scales contribute to difference in the observed variability and it is not reasonable to assume that observed changes are equivocal in terms of size of these different scales (Higgins and Green 2008). However SMD is more difficult to interpret. In order to aid interpretation of the pooled effect size the SMD was back-transformed to a 0 to 100 mm VAS format on the basis of the standard deviation from a representative trial included in the analysis. The likely clinical importance of the resulting effect size was considered using the criteria proposed in the IMMPACT consensus statement (Dworkin et al. 2008). Specifically a decrease in pain of < 15% was judged as no important change, ≥ 15% as a minimally important change, 30% as a moderately important change and ≥ 50% as a substantially important change.

5.3.4.6 UNIT OF ANALYSIS ISSUES

Cross-over trials were entered into a meta-analysis where it was clear that the data were free of carry-over effects. To preserve the paired data characteristics of the cross-over studies their results were pooled with parallel studies by imputing the post-treatment between-condition correlation coefficient from an included study that presented individual patient data and using this to calculate the standard error of the standardised mean difference (SE(SMD)). This data was entered into the meta-analysis using the generic inverse-variance method as suggested in the Cochrane Handbook for Systematic Reviews of Interventions, section 16.4.6.2 (Higgins and Green, 2008).

5.3.4.7 DEALING WITH MISSING DATA

Where insufficient data were presented in the study report to enter a study into the meta-analysis, study authors were contacted to request access to the missing data.

5.3.4.8 DATA SYNTHESIS

Pooling of results was performed where adequate data supported this in RevMan 5 software (version 5.0.23) (RevMan 2008) using a random effects model. A random effects model was chosen as it was clear that differences in the dose parameters and populations make it unlikely that each study is estimating precisely the same intervention effect (Higgins and Green 2008). Separate meta-analyses were undertaken for different forms of stimulation intervention (i.e. rTMS, tDCS and CES) and for short-term (0 to < 1 week post-intervention), mid-term (≥ 1 to 6 weeks post-intervention) and long-term (≥ 6 weeks post-intervention) outcomes where adequate data were identified.

Where more than one data point was available for short-term outcomes, the first post-stimulation measure was used, where multiple treatments were given the first outcome at the end of the treatment period was used. For medium-term outcomes where more than one data point was available, the measure that fell closest to the mid-point of this time period was used.

5.3.4.9 SUBGROUP ANALYSIS AND INVESTIGATION OF HETEROGENEITY

Heterogeneity was explored using the Chi^2 test to investigate its statistical significance and the I^2 statistic to estimate the amount. Where significant heterogeneity ($p < 0.1$) was present subgroup analysis was performed. Pre-planned subgroup comparisons included site of stimulation, frequency of TMS stimulation (low ≤ 1 Hz, high ≥ 5 Hz), multiple versus single-dose studies, the type of painful condition (central neuropathic versus peripheral neuropathic versus non-neuropathic pain versus facial pain (for each stimulation type).

Central neuropathic pain included pain due to identifiable pathology of the central nervous system (e.g. stroke, spinal cord injury), peripheral neuropathic pain included injury to the nerve root or peripheral nerves, facial pain included trigeminal neuralgia and other idiopathic chronic facial pains, non-neuropathic pain included all chronic pain conditions without a clear neuropathic cause (e.g. chronic low back pain, fibromyalgia, complex regional pain syndrome type I).

5.3.4.10 SENSITIVITY ANALYSIS

When sufficient data were available, sensitivity analyses were conducted on the following study factors: risk of bias, sham credibility (for rTMS studies), and cross-over versus parallel group designs and the robustness of the data manipulation carried out for the inclusion of cross-over trials.

5.4 RESULTS

5.4.1 RESULTS OF THE SEARCH

5.4.1.1 PUBLISHED DATA

The search strategy identified 1148 citations, including 305 duplicates. Full details can be found in the Appendices of the full published Cochrane Review (Appendix 2 of this thesis). Figure 5.1 illustrates the search screening process. Screening of the 843 unique citations by title and abstract identified 39 as potentially eligible for the review. Three studies were identified from hand searching of the reference lists of included studies of which two were not retrievable in abstract or full manuscript form. The level of agreement between review authors, calculated using the kappa statistic for study eligibility based on title and abstract alone, was 0.77. Three more papers were identified by the review authors that were not picked up from the search strategy. These were also deemed to be potentially eligible for the review. One of the experts contacted to review the search results for possible omissions identified one additional study. The full-text screening of the 44 citations identified 33 eligible studies. The kappa level of agreement between authors for eligibility from full-text screening was 0.87.

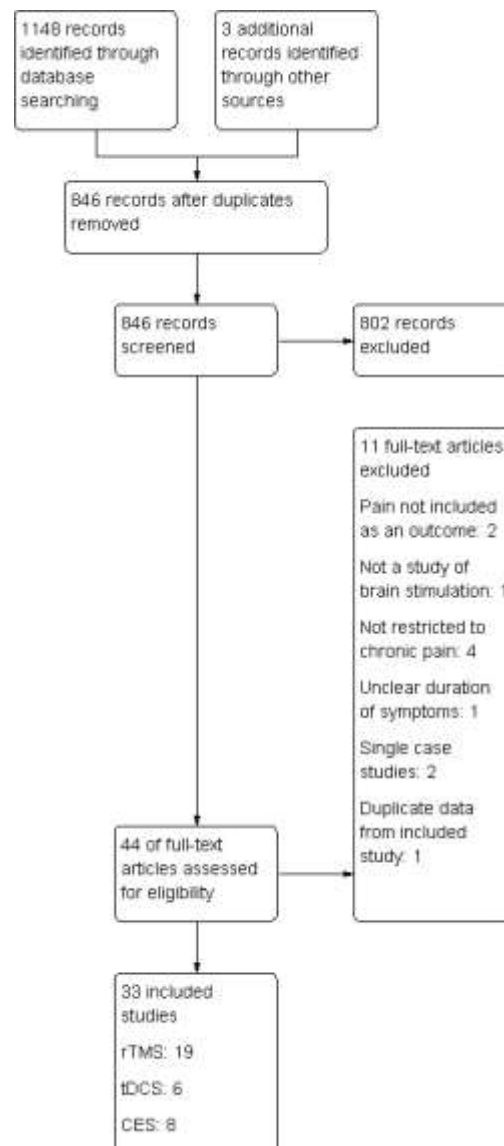
5.4.1.2 UNPUBLISHED DATA

The search strategy identified 5920 registered studies. Screening of the studies by the register records identified 23 studies that might potentially produce relevant data. Of these seven were duplicated across trials registers, leaving 16 unique registered studies. The level of agreement between review authors for eligibility from the trial register records, calculated using the kappa statistic was 0.89. The contact author for each of these studies

was contacted by post or email with a request for any relevant data that might inform the review. No data were available from any of these studies for inclusion in this review

Details of excluded studies can be found in the “Characteristics of Excluded” Studies table in the full published review (Appendix 2 of this thesis).

Figure 5.1: A flow chart of the search screening process.



5.4.2 INCLUDED STUDIES

Full details of included studies can be found in the “Characteristics of Included Studies” table in the full published review (Appendix 2 of this thesis).

5.4.2.1 COUNTRY OF ORIGIN AND LANGUAGE OF PUBLICATION

Of the 44 studies considered 33 met the eligibility criteria (André-Obadia et al. 2006; André-Obadia et al. 2008; Boggio et al. 2009; Borckardt et al. 2009; Capel et al. 2003;

Carretero et al. 2009; Cork et al. 2004; Defrin et al. 2007; Fenton et al. 2009; Fregni et al. 2005; Fregni et al. 2006a; Fregni et al. 2006b; Gabis et al. 2003; Gabis et al. 2009; Hirayama et al. 2006; Irlbacher et al. 2006; Kang et al. 2009; Katsnelson et al. 2004; Khedr et al. 2005; Lefaucheur et al. 2001; Lefaucheur et al. 2001; Lefaucheur et al. 2004; Lefaucheur et al. 2006; Lefaucheur et al. 2008; Lichtbroun et al. 2001; Mori et al. 2010; Passard et al. 2007; Pleger et al. 2004; Rollnik et al. 2002; Saitoh et al. 2007; Tan et al. 2000; Tan et al. 2006; Valle et al. 2009). All but one of the studies (Irlbacher et al. 2006) was written in English. Studies were undertaken in Brazil, Egypt, Europe (France, Germany, Italy, Spain and the UK), Israel, Japan, Russia, South Korea and the USA. Most studies were based in a laboratory or outpatient pain clinic setting.

5.4.2.2 TYPE OF STIMULATION, APPLICATION AND USE

Nineteen studies investigated rTMS (André-Obadia et al. 2006; André-Obadia et al. 2008; Borckardt et al. 2009; Carretero et al. 2009; Defrin et al. 2007; Fregni et al. 2005; Hirayama et al. 2006; Irlbacher et al. 2006; Kang et al. 2009; Khedr et al. 2005; Lefaucheur et al. 2001a; Lefaucheur et al. 2001b; Lefaucheur et al. 2004; Lefaucheur et al. 2006; Lefaucheur et al. 2008; Passard et al. 2007; Pleger et al. 2004; Rollnik et al. 2002; Saitoh et al. 2007). Eight studies investigated CES (Capel et al. 2003; Cork et al. 2004; Gabis et al. 2003; Gabis et al. 2009; Katsnelson et al. 2004; Lichtbroun et al. 2001; Tan et al. 2000; Tan et al. 2006) and six studies investigated tDCS (Boggio et al. 2009; Fenton et al. 2009; Fregni et al. 2006a; Fregni et al. 2006b; Mori et al. 2010; Valle et al. 2009).

5.4.2.3 STUDY DESIGNS

There was a mixture of parallel and cross-over study designs. For rTMS there were four parallel studies (Carretero et al.2009; Defrin et al. 2007; Khedr et al. 2005; Passard et al. 2007) and 15 cross-over studies (André-Obadia et al. 2006; André-Obadia et al. 2008; Borckardt et al. 2009; Fregni et al. 2005; Hirayama et al. 2006; Irlbacher et al. 2006; Kang et al. 2009; Lefaucheur et al. 2001a; Lefaucheur et al. 2001b; Lefaucheur et al. 2004; Lefaucheur et al. 2006; Lefaucheur et al. 2008; Pleger et al. 2004; Rollnik et al. 2002; Saitoh et al. 2007). For CES there were five parallel studies (Gabis et al. 2003; Gabis et al. 2009; Katsnelson et al. 2004; Lichtbroun et al. 2001; Tan et al. 2006) and three cross-over studies (Capel et al. 2003; Cork et al. 2004; Tan et al. 2000) of which two were considered as parallel studies, with only the opening phase of the study considered in this review because subsequent phases were unblinded (Capel et al. 2003; Cork et al. 2004). For tDCS there were four parallel studies (Fregni et al. 2006a; Fregni et al. 2006b; Mori et al. 2010; Valle et al. 2009) and two cross-over studies (Boggio et al. 2009; Fenton et al. 2009).

5.4.2.4 STUDY PARTICIPANTS

The included studies were published between 2000 and 2010. In rTMS studies sample sizes at the study outset ranged from four to 60 participants with a total of 422 participants randomised. Of these studies nine had 20 or more participants (André-Obadia et al. 2008; Carretero et al. 2009; Hirayama et al. 2006; Irlbacher et al. 2006; Khedr et al. 2005; Lefaucheur et al. 2004; Lefaucheur et al. 2006; Lefaucheur et al. 2008; Passard et al. 2007). In CES studies sample size ranged from 20 to 75 with a total of 391 randomised participants and in tDCS studies sample size ranged from seven to 32 participants with a total of 83 randomised participants. Only one study of tDCS had over 20 participants (Fregni et al. 2006b).

Studies included a variety of chronic pain conditions. Eight rTMS studies included participants with neuropathic pain of mixed origin; of these five included a mix of central, peripheral and facial neuropathic pain patients (André-Obadia et al. 2006; André-Obadia et al. 2008; Hirayama et al. 2006; Lefaucheur et al. 2004; Lefaucheur et al. 2008), two included a mix of central and peripheral neuropathic pain patients (Lefaucheur et al. 2006; Saitoh et al. 2007) of which one study (Saitoh et al. 2007) included a patient with phantom limb pain. One study included a mix of central neuropathic pain and phantom limb pain patients (Irlbacher et al. 2006). One study included a mix of central and facial neuropathic pain patients Lefaucheur et al. 2001a, two rTMS studies included only central neuropathic pain patients (Defrin et al. 2007; Kang et al. 2009), one included only peripheral neuropathic pain patients (Borckardt et al. 2009) and four studies included non-neuropathic chronic pain including fibromyalgia (Carretero et al. 2009; Passard et al. 2007), chronic pancreatitis pain (Fregni et al. 2005) and complex regional pain syndrome type I (CRPSI) (Pleger et al. 2004). Finally one study included a mix of peripheral neuropathic and non-neuropathic chronic pain (Rollnik et al. 2002) including one participant with phantom limb pain and one with osteomyelitis. The majority (13) of rTMS studies specified chronic pain that was refractory to current medical management (André-Obadia et al. 2006; André-Obadia et al. 2008, Defrin et al. 2007, Hirayama et al. 2006; Kang et al. 2009; Khedr et al. 2005; Lefaucheur et al. 2001a; Lefaucheur et al. 2001b; Lefaucheur et al. 2004; Lefaucheur et al. 2006; Lefaucheur et al. 2008; Rollnik et al. 2002; Saitoh et al. 2007). This inclusion criterion was varyingly described as intractable, resistant to medical intervention or drug management.

Of studies of CES, one study included participants with pain related to osteoarthritis of the hip and knee (Katsnelson et al. 2004), two studied chronic back and neck pain (Gabis et al.

2003; Gabis et al. 2009). Of these the later study also included participants with chronic headache but these data were not considered in this review. Two studies included participants with fibromyalgia (Cork et al. 2004; Lichtbroun et al. 2001) and two studies included participants with chronic pain following spinal cord injury (Capel et al. 2003; Tan et al. 2006), although it is unclear from these study reports whether the pain was classified as neuropathic or non-neuropathic. One study included participants with a mixture of "neuromuscular pain" excluding fibromyalgia of which back pain was reportedly the most prevalent complaint (Tan et al. 2000) although further detail was not reported on.

Of studies of tDCS one study included participants with a mixture of central, peripheral and facial neuropathic pain (Boggio et al. 2009), one study included participants with neuropathic pain secondary to multiple sclerosis (Mori et al. 2010), one included participants with central neuropathic pain following spinal cord injury (Fregni et al. 2006a) and two studies included non neuropathic pain, specifically chronic pelvic pain (Fenton et al. 2009) and fibromyalgia (Fregni et al. 2006b). Three studies of tDCS specified recruiting participants with pain that was refractory to medical management (Boggio et al. 2009; Fenton et al. 2009; Fregni et al. 2006a).

Most studies included both male and female participants except the studies of Fenton et al. (2009) (chronic pelvic pain) and Fregni et al. (2006b) (fibromyalgia). Two studies did not present data specifying the gender distribution of participants (Capel et al. 2003; Katsnelson et al. 2004).

5.4.2.5 OUTCOMES

5.4.2.5.1 PRIMARY OUTCOMES

All included studies assessed pain using self-reported pain visual analogue or numerical rating scales. There was variation in the precise measure of pain (for example, current pain intensity, average pain intensity over 24 hours) and in the anchors used particularly for the upper limit of the scale (e.g. "worst pain imaginable", "unbearable pain", "most intense pain sensation"). Several studies did not specify the anchors used.

All studies assessed pain at the short-term (< 1 week post-treatment) follow-up stage. Twelve studies reported collecting outcome data for medium-term (≥ 1 to 6 weeks post-treatment) (André-Obadia et al. 2008; Borckardt et al. 2009; Carretero et al. 2009; Defrin et al. 2007; Fenton et al. 2009; Fregni et al. 2006a; Fregni et al. 2006b; Gabis et al. 2009; Kang et al. 2009; Khedr et al. 2005; Lefaucheur et al. 2001a; Mori et al. 2010; Passard et al. 2007;

et al. Valle et al. 2009). Of these data could be extracted from four study reports (Carretero et al. 2009; Gabis et al. 2009; Kang et al. 2009) and the authors of three studies provided the data upon request (Khedr et al. 2005; Mori et al. 2010; Passard et al. 2007). Four studies reported collecting outcome data for long-term (> 6 weeks) follow up (Gabis et al. 2009; Kang et al. 2009; Passard et al. 2007; Valle et al. 2009). Of these data could be extracted from Gabis et al. (2009) and Kang et al. (2009) and the authors of Passard et al. (2007) provided the data upon request.

5.4.2.5.2 SECONDARY OUTCOMES

Only secondary outcomes that distinctly measured self-reported disability or quality of life were considered for extraction and included in the Characteristics of included studies table. Five studies used measures of disability or pain interference (Cork et al. 2004; Kang et al. 2009; Passard et al. 2007; Tan et al. 2000; Tan et al. 2006) and five studies collected measures of quality of life (Fregni et al. 2006b; Lichtbroun et al. 2001; Mori et al. 2010; Passard et al. 2007; Valle et al. 2009).

5.4.3 STUDIES OF rTMS

See Table 5.1 for a summary of stimulation characteristics utilised in rTMS studies.

5.4.3.1 STIMULATION LOCATION

The parameters for rTMS application varied significantly between studies including by site of stimulation, stimulation parameters and the number of stimulation sessions. The majority of rTMS studies targeted the primary motor cortex (M1) (André-Obadia et al. 2006; André-Obadia et al. 2008; Defrin et al. 2007; Hirayama et al. 2006; Irlbacher et al. 2006; Kang et al. 2009; Khedr et al. 2005; Lefaucheur et al. 2001a; Lefaucheur et al. 2001b; Lefaucheur et al. 2004; Lefaucheur et al. 2006; Lefaucheur et al. 2008; Passard et al. 2007; Pleger et al. 2004; Rollnik et al. 2002; Saitoh et al. 2007). Of these one study specified stimulation of the right hemisphere (Kang et al. 2009), two studies specified stimulation over the midline (Defrin et al. 2007; Pleger et al. 2004) and the remainder stimulated over the contralateral cortex to the side of dominant pain. One of these studies Hirayama et al. (2006) also investigated stimulation of the supplementary motor area (SMA), pre-motor area (PMA) and primary somatosensory cortex (S1). Two studies stimulated the pre-frontal cortex (PFC) with one study stimulating the left PFC (Borckardt et al. 2009) and one study the right dorsolateral PFC (DLPFC) (Carretero et al. 2009). One study investigated stimulation of the left and right secondary somatosensory cortex as separate treatment conditions (Fregni et al. 2005).

5.4.3.2 STIMULATION PARAMETERS

5.4.3.2.1 FREQUENCY

Eight studies investigated low-frequency (< 5Hz) rTMS (André-Obadia et al. 2006; Carretero et al. 2009; Fregni et al. 2005; Irlbacher et al. 2006; Lefaucheur et al. 2001b; Lefaucheur et al. 2006; Lefaucheur et al. 2008; Saitoh et al. 2007). Of these one study used a frequency of 0.5 Hz in one treatment condition (Lefaucheur et al. 2001b) and the rest used a frequency of 1 Hz. Eighteen studies investigated high-frequency (\geq 5 Hz) rTMS (André-Obadia et al. 2006; André-Obadia et al. 2008; Borckardt et al. 2009; Defrin et al. 2007; Fregni et al. 2005; Hirayama et al. 2006; Irlbacher et al. 2006; Kang et al. 2009; Khedr et al. 2005; Lefaucheur et al. 2001a; Lefaucheur et al. 2001b; Lefaucheur et al. 2004; Lefaucheur et al. 2006; Lefaucheur et al. 2008; Passard et al. 2007; Pleger et al. 2004; Rollnik et al. 2002; Saitoh et al. 2007). Of these three studies used 5 Hz stimulation (Defrin et al. 2007; Hirayama et al. 2006; Irlbacher et al. 2006), 10 studies used 10 Hz stimulation (Borckardt et al. 2009; Kang et al. 2009; Lefaucheur et al. 2001a; Lefaucheur et al. 2001b; Lefaucheur et al. 2004; Lefaucheur et al. 2006; Lefaucheur et al. 2008; Passard et al. 2007; Pleger et al. 2004; Saitoh et al. 2007) and four studies used 20 Hz stimulation (André-Obadia et al. 2006; André-Obadia et al. 2008; Fregni et al. 2005; Khedr et al. 2005; Rollnik et al. 2002).

5.4.3.2.2 OTHER PARAMETERS

Wide variation was observed between studies for various stimulation parameters. The overall number of rTMS pulses delivered varied from 120 to 4000. The study by Defrin et al. (2007) reported a total number of pulses of 500 although the reported stimulation parameters of 500 trains, delivered at a frequency of 5 Hz for 10 seconds would imply 25000 pulses. Six studies specified a posteroanterior orientation of the stimulating coil (André-Obadia et al. 2006; Lefaucheur et al. 2001b; Lefaucheur et al. 2004; Lefaucheur et al. 2006; Lefaucheur et al. 2008; Passard et al. 2007) one study specified a coil orientation 45° posterolateral to the midline (Kang et al. 2009), one study compared a posteroanterior coil orientation with a medial-lateral coil orientation (André-Obadia et al. 2008) and the remaining studies did not specify the orientation of the coil. Within studies that reported the information the duration and number of trains and the inter-train intervals varied. One study did not report this information (Fregni et al. 2005).

5.4.3.2.3 TYPE OF SHAM

rTMS studies employed a variety of sham controls. In nine studies the stimulating coil was angled away from the scalp to prevent significant cortical stimulation. Of these, four

Table 5.1 rTMS studies - characteristics of stimulation.

(N/S = not specified, N/A not applicable, PA = postero-anterior, ML = medial-lateral, PL= postero lateral)

Study	Location of stimulation	Coil orientation	Freq (Hz)	Intensity (% RMT)	No. of trains	Duration of trains	Inter-train interval (sec)	Total no. of pulses	Sessions per group
André-Obadia 2006	M1 contralateral to painful side	PA	20, 1	90	20Hz: 20	20Hz: 4 sec	20 Hz: 84	1600	1
					1Hz: 1	1Hz: 26 mins			
André-Obadia 2008	M1 contralateral to painful side	PA / ML	20	90	20	4 sec	84	1600	1
Borckardt 2009	Left PFC	N/S	10	100	40	10 sec	20	4000	3 over a 5-day period
Carretero 2009	Right DLPFC	N/S	1	110	20	60 sec	45	1200	Up to 20 daily
Defrin 2007	M1 midline	N/S	5	115	500	10 sec	30	? 500*	10, x 1 daily
Fregni 2005	Left and right SII	N/S	1	90	N/S	N/S	N/S	1600	1
Hirayama 2006	M1, S1, PMA, SMA	N/S	5	90	10	10 sec	50	500	1
Irlbacher 2006	M1 contralat to painful side	N/S	5, 1	95	N/S	N/S	N/S	500	1
Kang 2009	Right M1	45° PL	10	80	20	5 sec	55	1000	5, x1 daily
Khedr 2005	M1 contralat to painful side	N/S	20	80	10	10 sec	50	2000	5, x1 daily
Lefaucheur 2001a	M1 contralat to painful side	N/S	10	80	20	5 sec	55	1000	1
Lefaucheur 2001b	M1 contralat to painful side	PA	10, 0.5	80	10Hz: 20	10 Hz: 5 sec	10 Hz: 55	10 Hz: 1000	1
					0.5Hz: 1	0.5 Hz: 20 mins		0.5 Hz: 600	
Lefaucheur 2004	M1 contralat to painful side	PA	10	80	20	5 sec	55	1000	1
Lefaucheur 2006	M1 contralat to painful side	PA	10, 1	90	10 Hz: 20	10 Hz: 6 sec	10 Hz: 54	10 Hz: 1200	1
					1 Hz: 1	1 Hz: 20 mins		1 Hz: 1200	
Lefaucheur 2008	M1 contralat to painful side	PA	10, 1	90	10 Hz: 20	10 Hz: 6 sec	10Hz: 54	10Hz: 1200	1
					1 Hz: 1	1 Hz: 20 mins		1Hz: 1200	

Table 5.1 continued

Study	Location of stimulation	Coil orientation	Freq (Hz)	Intensity (% RMT)	No. of trains	Duration of trains	Inter-train interval (sec)	No. of pulses	sessions per group
Passard 2007	M1 contralateral to painful side	PA	10	80	25	8 sec	52	2000	10, x 1 daily (working days)
Pleger 2004	M1 hand area	PA	10	110	10	1.2 sec	10	120	1
Rollnik 2002	M1 midline	PA	20	80	20	2 sec	N/S	800	1
Saitoh 2007	M1 over motor representation of painful area	PA	10, 5, 1	90	10 Hz; 5	10 Hz: 10 sec	10 Hz: 50	500	1
					5 Hz: 10	5 Hz: 10 sec	5 Hz: 50		
					1 Hz: 1	1 Hz: 50 sec	N/A		

studies (André-Obadia et al. 2006; André-Obadia et al. 2008; Kang et al. 2009; Khedr et al. 2005) specified that the coil was also elevated from the scalp and five studies specified that the coil was angled 45° away from the scalp (Carretero et al. 2009; Hirayama et al. 2006; Pleger et al. 2004; Rollnik et al. 2002; Saitoh et al. 2007) of which two studies (Hirayama et al. 2006; Saitoh et al. 2007) also simultaneously electrically stimulated the skin of the scalp in both the active and sham stimulation conditions in order to mask the sensations elicited by active rTMS and thus preserve participants' blinding. The remaining 10 studies utilised sham coils. Of these, four studies specified that the sham coil made similar or identical sounds to those elicited during active stimulation (Borckardt et al. 2009; Defrin et al. 2007; Irlbacher et al. 2006; Passard et al. 2007). Six studies did not specify whether the sham coil controlled for the auditory characteristics of active stimulation (Fregni et al. 2005; Lefaucheur et al. 2001a; Lefaucheur et al. 2001b; Lefaucheur et al. 2004; Lefaucheur et al. 2006; Lefaucheur et al. 2008).

5.4.3.2.4 ADVERSE EVENT REPORTING

Thirteen studies did not report any information regarding adverse events (Borckardt et al. 2009; Cork et al. 2004; Defrin et al. 2007; Gabis et al. 2009; Kang et al. 2009; Katsnelson et al. 2004; Khedr et al. 2005; Lefaucheur et al. 2006; Lefaucheur et al. 2008; Lichtbroun et al. 2001; Pleger et al. 2004; Tan et al. 2000; Tan et al. 2006).

5.4.4 STUDIES OF CES

See Table 5.2 for a summary of stimulation characteristics utilised in CES studies.

5.4.4.1 STIMULATION DEVICE, PARAMETERS AND ELECTRODE LOCATION

Four studies of CES used the "Alpha-stim" CES device (Electromedical Products International, Inc, Mineral Wells, Texas, USA). This device uses two ear clip electrodes that attach to each of the participant's ears (Cork et al. 2004; Lichtbroun et al. 2001; Tan et al. 2000; Tan et al. 2006) these studies utilised stimulation intensities of 100 μ A with a frequency of 0.5 Hz. One study (Capel et al. 2003) used a device manufactured by Carex (Hemel Hempstead, UK) that also used earpiece electrodes and delivered a stimulus intensity of 12 μ A.

Two studies used the "Pulsatilla 1000" device (Pulse Mazor Instruments, Rehavol, Israel) (Gabis et al. 2003; Gabis et al. 2009). The electrode array for this device involved an electrode attached to each of the participant's mastoid processes and one attached to the forehead; current is passed to the mastoid electrodes. One study (Katsnelson et al. 2004) used the "Nexalin" device (Kalaco Scientific Inc, Scottsdale, AZ, USA). With this device current is applied to a forehead electrode and returned via electrodes placed behind the patient's ears. These three studies utilised significantly higher current intensities than those using ear clip electrodes with intensities of 4 mA (Gabis et al. 2003; Gabis et al. 2009) and 11 to 15 mA (Katsnelson 2004).

Table 5.2 CES studies -characteristics of stimulation (NS= not specified)

Study	Electrode placement	Frequency (Hz)	Pulse width (msec)	Waveform shape	Intensity	Duration (mins)	Treatment sessions per group
Capel 2003	Ear clip electrodes	10	2	N/S	12 μ A	53	x 2 daily for 4 days
Cork 2004	Ear clip electrodes	0.5	N/S	Modified square wave biphasic	100 μ A	60	? daily for 3 weeks
Gabis 2003	Mastoid processes & forehead	77	3.3	Biphasic asymmetric	\leq 4 mA	30	x 1 daily for 8 days
Gabis 2009	Mastoid processes & forehead	77	3.3	Biphasic asymmetric	\leq 4 mA	30	x 1 daily for 8 days
Katsnelson 2004	Mastoid processes & forehead	N/S	N/S	2 conditions: symmetric, asymmetric	11 to 15 mA	40	x 1 daily for 5 days
Lichtbroun 2001	Ear clip electrodes	0.5	N/S	Biphasic square wave	100 μ A	60	x 1 daily for 30 days
Tan 2000	Ear clip electrodes	0.5	N/S	N/S	10 to 600 μ A		12 (timing not specified)
Tan 2006	Ear clip electrodes	N/S	N/S	N/S	100 to 500 μ A	60	x 1 daily for 21 days

All CES studies gave multiple treatment sessions for each treatment group with variation between the number of treatments delivered. Capel et al. (2003) delivered treatments twice daily for four days. Cork et al. (2004) delivered treatment once daily for a three-week period. Gabis et al. (2003) and Gabis et al. (2009) delivered treatment once daily for eight days, Katsnelson et al. (2004) for five days, Lichtbroun et al. (2001) for 30 days and Tan (2006) for 21 days. Tan et al. (2000) delivered 12 treatments although the frequency of these is unclear from the study report.

5.4.4.2 TYPE OF SHAM

Five studies utilised inert sham units (Capel et al. 2003; Cork et al. 2004; Lichtbroun et al. 2001; Tan et al. 2000; Tan et al. 2006). These units were visually indistinguishable from the active devices. Stimulation at the intensities used is subsensation and as such it should not have been possible for participants to distinguish between the active and sham conditions.

Two studies (Gabis et al. 2003; Gabis et al. 2009) utilised an "active placebo" treatment unit. This sham device was visually indistinguishable and delivered a current of much lower intensity (≤ 0.75 mA) than the active stimulator to evoke a similar sensation to ensure patient blinding. Similarly Katsnelson et al. (2004) utilised a visually indistinguishable sham device that delivered brief pulses of current of < 1 mA. The placebo conditions used in these three studies delivered current at much greater intensities than those used in the active stimulation conditions of the other CES studies.

5.4.5 STUDIES OF TDCS

See Table 5.3 for a summary of stimulation characteristics utilised in tDCS studies.

5.4.5.1 STIMULATION PARAMETERS AND ELECTRODE LOCATION

Two studies of tDCS stimulated the dorsolateral prefrontal cortex in one treatment group (Fregni et al. 2006b; Valle et al. 2009). Six studies stimulated the motor cortex (Boggio et al. 2009; Fenton et al. 2009; Fregni et al. 2006a; Fregni et al. 2006b; Mori et al. 2010; Valle et al. 2009). Of these four stimulated the cortex contralateral to the side of worst pain (Boggio et al. 2009; Fregni et al. 2006a; Fregni et al. 2006b; Mori et al. 2010) of which two studies stimulated the opposite hemisphere to the dominant hand where pain did not have a unilateral dominance (Fregni et al. 2006a; Fregni et al. 2006b). One study stimulated the left hemisphere for all conditions (Valle et al. 2009). One study of chronic pelvic pain stimulated the opposite hemisphere to the dominant hand in all subjects (Fenton et al. 2009). One study specifically investigated the use of tDCS in conjunction with transcutaneous electrical nerve stimulation (TENS) therapy (Boggio et al. 2009). Data

comparing active tDCS and sham TENS with sham tDCS and sham TENS were extracted for the purposes of this review.

Three studies (Fregni et al. 2006a; Fregni et al. 2006b; Mori et al. 2010) delivered a current intensity of 2 mA for 20 minutes once a day for five days. One study (Fenton et al. 2009) applied a current intensity of 1 mA once a day for two days and one study (Boggio et al. 2009) applied one treatment per stimulation condition at an intensity of 2 mA for 30 minutes.

Table 5.3: tDCS studies -characteristics of stimulation

Study	Location of stimulation	Electrode pad size	Intensity (mA)	Anodal or cathodal	Stimulus duration (mins)	No. treatment sessions
Boggio 2009	M1 contralateral to painful side	35cm ²	2	Anodal	30	1
Fenton 2009	M1 dominant hemisphere	35cm ²	1	Anodal	20	2
Fregni 2006a	M1 contralateral to painful side or dominant hand	35cm ²	2	Anodal	20	5, x1 daily
Fregni 2006b	M1 & DLPFC contralateral to painful side or dominant hand	35cm ²	2	Anodal	20	5, x1 daily
Mori 2010	M1 contralateral to painful side	35cm ²	2	Anodal	20	5, x1 daily
Valle 2009	M1 & DLPFC contralateral to painful side or dominant hand	35cm ²	2	Anodal	20	5, x1 daily

All studies of tDCS utilised a sham condition whereby active stimulation was ceased after 30 seconds without the participants' knowledge.

5.4.6 EXCLUDED STUDIES

11 studies were excluded after consideration of the full study report. Of these one was not a study of brain stimulation (Frentzel, Kleditzsch, and Konrad 1989), two did not assess self-reported pain as an outcome (Belci et al. 2004; Johnson et al. 2006), four were not

restricted to participants with chronic pain (Evtiukhin et al. 1998; Katz and Melzack 1991; Longobardi et al. 1989; Pujol et al. 1998). One study was unclear on the duration of participants' symptoms (Avery et al. 2007), two were single case studies (Silva et al. 2007; Zaghi et al. 2009), one study presented duplicate data from a study already accepted for inclusion (Roizenblatt et al. (2007), duplicate data from Fregni et al. 2006b) and one did not employ a sham control (Evtiukhin et al. 1998).

5.4.7 RISK OF BIAS IN INCLUDED STUDIES

Full details of the risk of bias assessment for each individual study can be found in the "Characteristics of Included Studies" table in the full published review (Appendix 2 of this thesis). Risk of bias varied across studies for all of the assessment criteria. For a summary of risk of bias assessment across studies see Figure 5.2. The (kappa statistic) level of agreement between the two review authors across all risk of bias criteria was 0.73.

5.4.7.1 SEQUENCE GENERATION

For the criteria 'adequate sequence generation' cross-over trials were awarded a judgement of 'Yes' where the study report mentioned that the order of treatment conditions was randomised. Since this criteria has a greater potential to introduce bias in parallel designs a judgement of 'Yes' was only awarded where the method of randomisation was specified and adequate.

All cross-over trials were judged as having a low risk of bias for this criteria. Of the parallel trials five trials were judged as having an unclear risk of bias (Carretero et al. 2009; Cork et al. 2004; Defrin et al. 2007; Katsnelson et al. 2004; Tan et al. 2006) as they did not specify the method of randomisation used. One study was judged as having a high risk of bias for this criteria (Khedr et al. 2005) as the report suggests that patients were allocated depending on the day of the week on which they were recruited, which was not judged as being genuinely random.

5.4.7.2 ALLOCATION CONCEALMENT

The criteria 'Adequate concealment of allocation' was only considered for studies with parallel designs. Six studies did not report concealment of allocation and were judged as 'Unclear' (Carretero et al. 2009; Cork et al. 2004; Defrin et al. 2007; Katsnelson et al. 2004; Passard et al. 2007; Tan et al. 2006) and one study (Khedr et al. 2005) was judged as having a high risk of bias for this criterion since the method of randomisation employed would not have supported concealment of allocation.

Figure 5.2 Results of the risk of bias (rob) assessment for each included study. (Green circle=low, yellow circle= unclear, red circle = high ROB)

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias	Adequate blinding of assessors?	Adequate blinding of participants?	Free from carry-over effects?
André-Obadia 2006	+		?	+	+	+	?	+
André-Obadia 2008	+		+	+	+	+	?	+
Boggio 2009	+		?	+	+	+	+	+
Borckardt 2009	+		+	+	+	?	?	+
Capel 2003	+	+	+	-	+	+	+	
Carretero 2009	?	?	+	+	+	+	?	
Cork 2004	?	?	?	-	+	+	+	
Defrin 2007	?	?	+	+	+	+	?	
Fenton 2009	+		+	+	+	+	+	?
Fregni 2005	+		+	-	+	+	?	+
Fregni 2006a	+	+	+	?	+	+	+	
Fregni 2006b	+	+	+	?	+	+	+	
Gabis 2003	+	+	+	+	?	+	+	
Gabis 2009	+	+	+	+	?	+	+	
Hirayama 2006	+		+	+	+	?	?	+
Irlbacher 2006	+		-	+	+	?	?	+
Kang 2009	+		+	+	+	+	?	+
Katsnelson 2004	?	?	?	-	-	+	+	
Khedr 2005	-	-	+	+	+	+	?	
Lefaucheur 2001a	+		+	+	+	?	?	+
Lefaucheur 2001b	+		+	+	?	?	?	+
Lefaucheur 2004	+		+	+	+	?	?	+
Lefaucheur 2006	+		?	+	+	?	?	+
Lefaucheur 2008	+		+	+	+	+	?	+
Lichtbroun 2001	+	+	?	-	+	+	+	
Mori 2010	+	+	+	+	+	+	+	
Passard 2007	+	?	+	+	+	+	?	
Pleger 2004	+		+	+	+	?	?	+
Rollnik 2002	+		+	+	+	?	?	+
Saitoh 2007	+		+	+	+	?	?	+
Tan 2000	+		-	+	?	?	+	+
Tan 2006	?	?	+	+	+	+	+	
Valle 2009	+	+	+	-	+	+	+	

5.4.7.3 BLINDING OF ASSESSORS

Eleven studies did not specify whether they blinded outcome assessors (Borckardt et al. 2009; Hirayama et al. 2006; Irlbacher et al. 2006; Lefaucheur et al. 2001a; Lefaucheur et al. 2001b; Lefaucheur et al. 2004; Lefaucheur et al. 2006; Pleger et al. 2004; Rollnik et al. 2002; Saitoh et al. 2007; Tan et al. 2000). While studies used self-reported pain outcomes we considered that the complex nature of the intervention and the level of interaction this entails between participants and assessors suggests that a lack of blinding of researchers engaged in the collection of outcomes might potentially introduce bias. As such, where blinding of assessors was not clearly stated a judgement of 'Unclear' was made for this criterion.

5.4.7.4 BLINDING OF PARTICIPANTS

All studies attempted to blind participants. However, due to the difficulties involved in producing a robust sham control in rTMS studies (see Assessment of risk of bias in included studies) an assessment was made of sham credibility. Where sham coils were utilised they did not control for the sensory aspects of stimulation. Where the coil was angulated or angulated and elevated away from the scalp, this is potentially distinguishable both visually and by the sensory effects of stimulation. Two studies (Hirayama et al. 2006; Saitoh et al. 2007) simultaneously electrically stimulated the scalp during rTMS stimulation to mask the differences in sensation between conditions. However, by angulating the coil away from the scalp participants may have been able to visually distinguish between the conditions. All rTMS studies were assessed as having sub-optimal sham control conditions and were therefore assessed as having an 'Unclear' risk of bias.

All studies of tDCS and CES were assessed as having a low risk of bias for this criterion.

5.4.7.5 INCOMPLETE OUTCOME DATA (ATTRITION BIAS)

Seven studies were assessed as having an unclear risk of bias for this criterion (André-Obadia et al. 2006; Boggio et al. 2009; Cork et al. 2004; Katsnelson et al. 2004; Lefaucheur et al. 2006; Lichtbroun et al. 2001). In the study of André-Obadia et al. (2006) two participants (17% of the study cohort) did not complete the study and this was not clearly accounted for in the data analysis. This was also the case for Boggio et al. (2009) where two subjects (25% of the cohort) failed to complete the study. Four studies did not clearly report levels of drop-out (Cork et al. 2004; Katsnelson et al. 2004; Lefaucheur et al. 2006; Lichtbroun et al. 2001). Two studies were assessed as having a high risk of bias for this criterion (Irlbacher et al. 2006; Tan et al. 2000). In the study by Irlbacher et al. (2006) only

13 of the initial 27 participants completed all of the treatment conditions. In the study by Tan et al. (2000) 17 participants did not complete the study (61% of the cohort) and this was not clearly accounted for in the analysis. This level of withdrawal was considered to be a fatal flaw.

5.4.7.6 SELECTIVE REPORTING (REPORTING BIAS)

Studies were assessed as having a high risk of bias where the study report did not produce adequate data to assess the effect size for all groups/conditions, and these data were not made available upon request. Six studies (Capel et al. 2003; Cork et al. 2004; Fregni et al. 2005; Katsnelson et al. 2004; Lichtbroun et al. 2001; Valle et al. 2009) were assessed as having a high risk of bias for this criteria. Two studies were judged as being at unclear risk of bias (Fregni et al. 2006a; Fregni et al. 2006b). In the reports of these studies data were not presented in a format that could be easily interpreted. On request data were available from these two studies for the primary outcome at baseline and short-term follow up but not for other follow-up points. The remaining studies were assessed as having a low risk of bias for this criterion.

5.4.7.7 OTHER POTENTIAL SOURCES OF BIAS

5.4.7.7.1 CARRY-OVER EFFECTS IN CROSS-OVER TRIALS

One study (Fenton et al. 2009) was judged as unclear on this criterion as no pre-stimulation data were provided and no investigation of carry-over effects was discussed in the study report. In one cross-over study (Saitoh 2007) baseline differences between the sham and the 10 Hz stimulation condition were notable. A paired t-test did not show a significant difference ($P > 0.1$) and this study was judged as having a low risk of bias for carry-over effects.

5.4.7.7.2 OTHER SOURCES OF BIAS

One study of CES (Katsnelson et al. 2004) did not clearly present relevant baseline group characteristics of the included participants and was judged as being at high risk of bias for this criterion. One study of CES (Tan et al. 2000) also applied electrical stimulation to the painful body area as part of the treatment which may have affected the final outcomes. Two studies of CES (Gabis et al. 2003; Gabis et al. 2009) used an "active placebo condition" that delivered a level of cortical stimulation that was greater than that used in the active arm of other CES studies. It is possible that delivering cortical stimulation in the sham group might mask differences between the sham and active condition. Also such a large

difference in current intensity compared with other studies of CES might be a source of heterogeneity. These three studies were judged as 'Unclear'.

5.4.8 EFFECTS OF INTERVENTIONS

5.4.8.1 PRIMARY OUTCOME: PAIN. rTMS

5.4.8.1.1 rTMS FOR SHORT-TERM RELIEF OF CHRONIC PAIN

The primary meta-analysis pooled data for post treatment pain scores from all rTMS studies with low or unclear risk of bias where data were available ($n = 368$, after correction for multiple comparisons $n = 267$) including cross-over and parallel designs (André-Obadia et al. 2006; André-Obadia et al. 2008; Borckardt et al. 2009; Carretero et al. 2009; Defrin et al. 2007; Hirayama et al. 2006; Kang et al. 2009; Lefaucheur et al. 2001a; Lefaucheur et al. 2001b; Lefaucheur et al. 2004; Lefaucheur et al. 2006; Lefaucheur et al. 2008; Passard et al. 2007; Pleger et al. 2004; Pleger et al. 2004; Rollnik et al. 2002; Saitoh et al. 2007). The studies by Khedr et al. (2005), and Irlbacher et al. (2006) were excluded as they were classified as having a high risk of bias on at least one criteria.

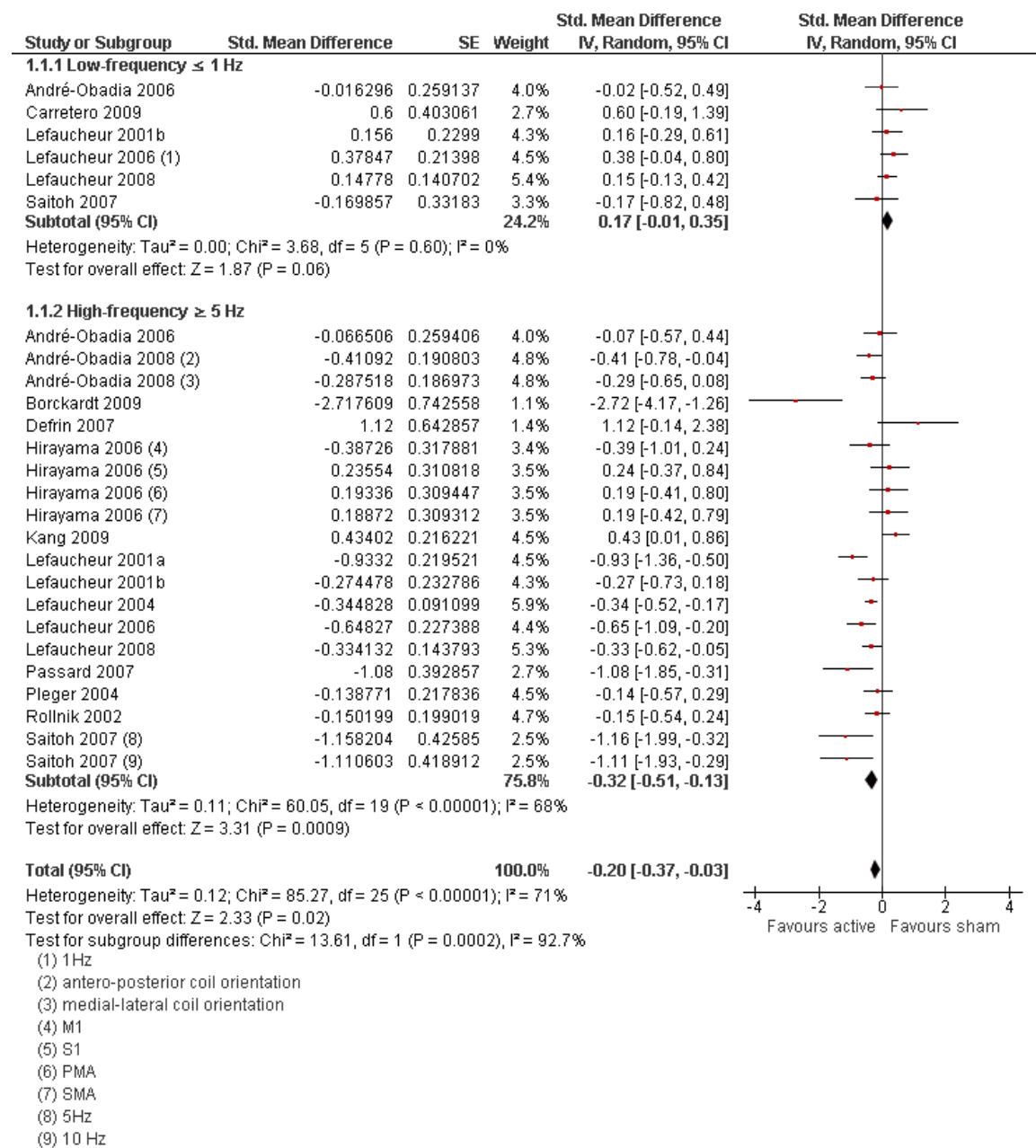
The correlation coefficient used to calculate the SE(SMD) for cross-over studies was imputed from data extracted from André-Obadia et al. (2008) (as outlined in **section 5.3.4.6 Unit of analysis issues**). The number of participants in each cross-over study was divided by the number of comparisons made by that study. For parallel studies the SEM was calculated from the 95% confidence intervals of the standardised mean difference (SMD) and both the SMD and the SEM were entered into the meta-analysis. This was then entered into the meta-analysis with the SMD using the generic inverse variance method. Figure 5.3 shows the forest plot for this analysis.

Substantial heterogeneity ($I^2 = 71\%$) was observed and was investigated using pre-planned subgroup analyses (see section 5.3.4.9). Categorising studies by high (≥ 5 Hz) or low (< 5 Hz) frequency rTMS reduced heterogeneity in the low-frequency group ($I^2 = 0\%$). In this group there was evidence of no effect of low-frequency rTMS for short-term relief of chronic pain. However, substantial heterogeneity was observed in the high-frequency group ($I^2 = 68\%$). Separating studies that deliver a single treatment per condition with those that delivered multiple treatment sessions did not reduce heterogeneity substantially in multiple-dose studies ($I^2 = 87\%$) or single-dose studies ($I^2 = 61\%$). Restricting the analysis to single-dose studies of high-frequency stimulation of the motor cortex (corrected $n = 184$) reduced heterogeneity ($I^2 = 36\%$). Figure 5.4 shows the forest plot for this subgroup analysis. In this group the pooled SMD was -0.40 (95% confidence interval (CI) -0.26 to -0.54), $P < 0.00001$.

The SMD was back transformed to a mean difference using the pooled standard deviation from the largest trial in the analysis that carried the most weight in the meta-analysis (Lefaucheur 2004).

This was then used to estimate the real percentage change on a 0 to 100 mm VAS of active stimulation compared with the sham condition in that study. This equated to a reduction of 9.3 mm (95% CI 6.2 mm to 12.5 mm), or a percentage change of 15% (95% CI 10% to 20%) of the control group outcome.

Figure 5.3 Forest plot: rTMS, outcome: Pain short-term, all studies



This estimate just reaches the pre-established criteria for a minimally clinically important difference (>15%) although the confidence intervals do not clearly fall above this threshold. Of the included studies in this subgroup eight did not clearly report blinding of assessors and were awarded a judgement of 'Unclear' risk of bias for this criteria (Hirayama et al. 2006; Lefaucheur et al. 2001a; Lefaucheur et al. 2001b; Lefaucheur et al. 2004; Lefaucheur et al. 2006; Pleger et al. 2004; Rollnik et al. 2002; Saitoh et al. 2007). Sensitivity analysis removing these studies reduced heterogeneity to $I^2 = 0\%$ although only three studies (André-Obadia et al. 2006; André-Obadia et al. 2008; Lefaucheur et al. 2008) were preserved in the analysis. There remained a statistically significant difference between sham and active stimulation although the SMD reduced to -0.31 (95% CI -0.13 to -0.49). This equates to a pain reduction of 7 mm (95% CI 3 mm to 11 mm) on a 0 to 100 mm VAS pain scale or a percentage change of 12% (95% CI 9% to 18%) in comparison with sham stimulation. For multiple-dose studies of high-frequency motor cortex stimulation heterogeneity was high ($I^2 = 86\%$).

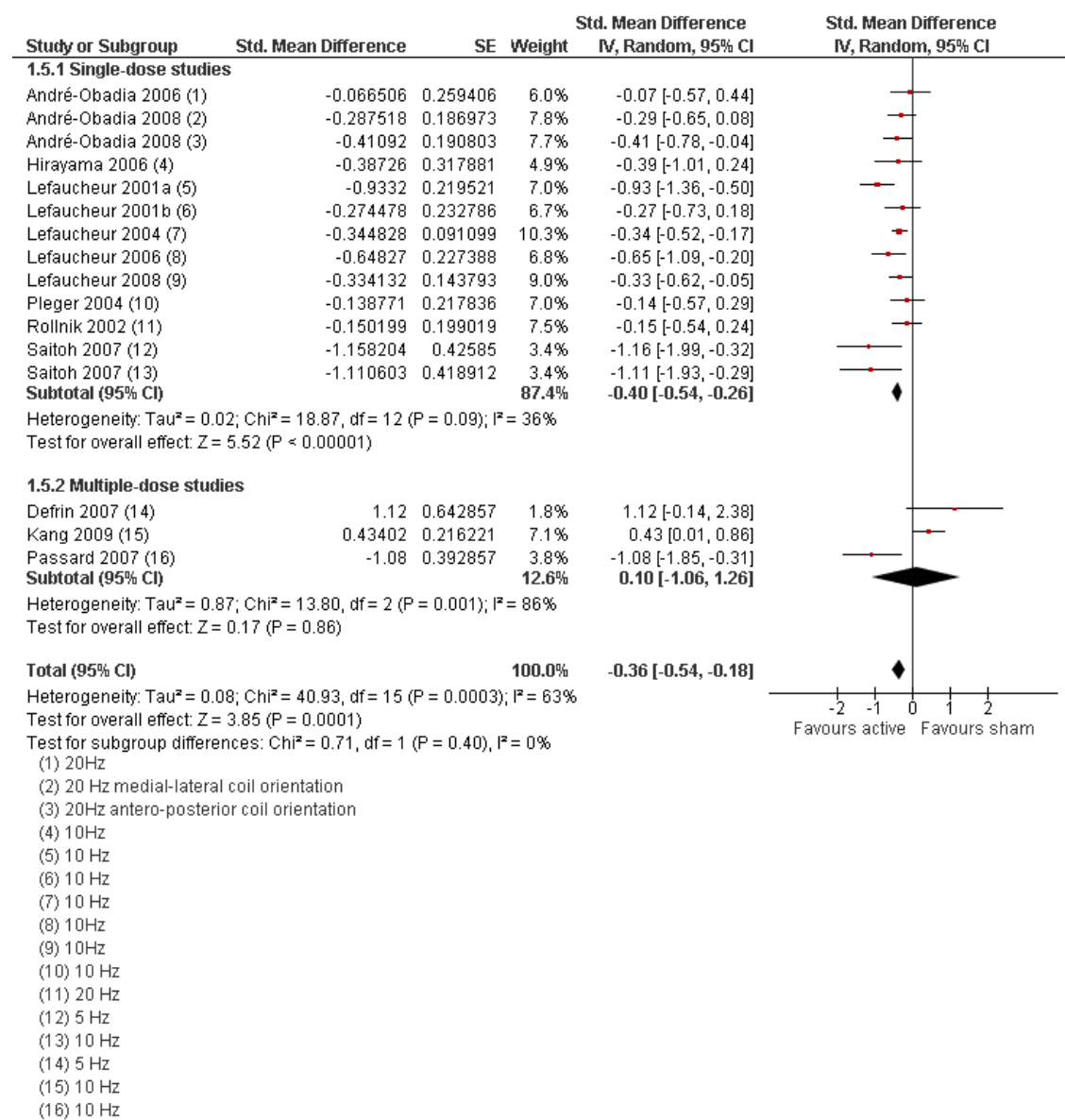
There were insufficient data to support the planned subgroup analysis by the type of painful condition as planned. However, when the analysis was restricted to studies including only well-defined neuropathic pain populations (excluding Carretero et al. 2009; Passard et al. 2007; Pleger et al. 2004; Rollnik et al. 2002) there was little impact on heterogeneity ($I^2 = 71\%$). When the analysis was restricted to studies of single-dose high-frequency motor cortex stimulation in well-defined neuropathic pain populations (excluding data from Pleger et al. 2004; Rollnik et al. 2002) there was little effect on the pooled estimate (SMD -0.45, 95% CI -0.60 to -0.29) or heterogeneity ($I^2 = 37\%$). However, when the same process was applied to multiple-dose studies of high-frequency motor cortex stimulation (excluding data from Passard et al. 2007) heterogeneity was reduced to a negligible level ($I^2 = 2\%$) and the results suggest a significant benefit of sham over active therapy (SMD 0.5, 95% CI 0.09 to 0.93, $P = 0.02$).

5.4.8.1.2 SENSITIVITY ANALYSIS

To assess whether the imputation of standard errors for cross-over studies was robust the analysis was repeated with the correlation coefficient reduced to 0.65 and increased to 0.85. This had no marked effect on the overall analysis. The same process was applied to the subgroup analysis of single-dose studies of high-frequency motor cortex stimulation. This had a negligible impact on the effect size or the statistical significance of this subgroup but a large impact on heterogeneity (increased correlation coefficient $I^2 = 59\%$, correlation decreased $I^2 = 5\%$).

To assess the impact of excluding the studies of Irlbacher et al. (2006) and Khedr et al. (2005), the analysis was performed with data from these studies included. While this produced a modest increase in the SMD it increased heterogeneity from 71% to 73%. Inclusion of the Khedr et al. (2005) study to the multiple-dose studies of high-frequency motor cortex stimulation subgroup increased heterogeneity ($I^2 = 92\%$). Inclusion of the Irlbacher (2006) study to the single-dose studies of high-frequency motor cortex stimulation subgroup also increased heterogeneity ($I^2 = 46\%$).

Figure 5.4 Forest plot: rTMS, Pain short-term, subgroup analysis: motor cortex studies only (low-frequency studies excluded).



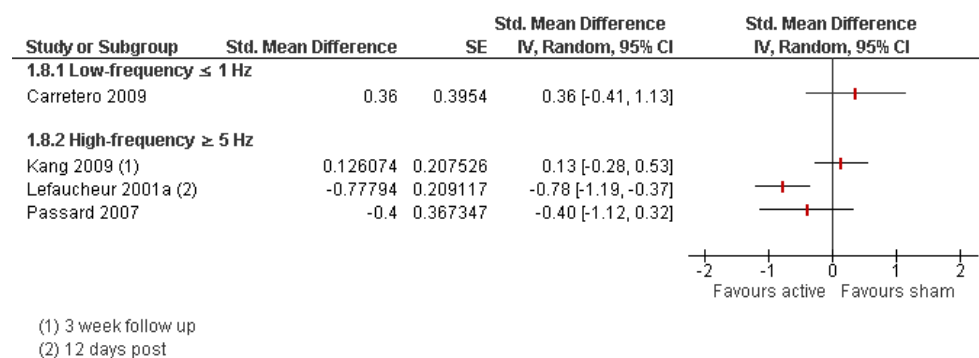
5.4.8.1.3 SMALL STUDY EFFECTS/PUBLICATION BIAS

Small study effects were investigated using Egger's test. The results are not suggestive of a significant influence of small study effects ($P = 0.570$).

5.4.8.1.4 RTMS FOR MEDIUM-TERM RELIEF OF CHRONIC PAIN (< 6 WEEKS POST-TREATMENT)

Three studies provided data on medium-term pain outcomes (Carretero et al. 2009; Lefaucheur et al. 2001a; Kang et al. 2009; Khedr et al. 2005; Passard et al. 2007). Of these the study by Khedr et al. (2005) was excluded as it was classified as having a high risk of bias. The analysis included 42 participants (see Figure 5.5). Overall heterogeneity was high ($I^2 = 75\%$). A sensitivity analysis was conducted to assess the impact of excluding the study by Khedr et al. (2005). Including this study did not reduce heterogeneity ($I^2 = 81\%$). There was insufficient data from which to draw any firm conclusions and the existing data are conflicting.

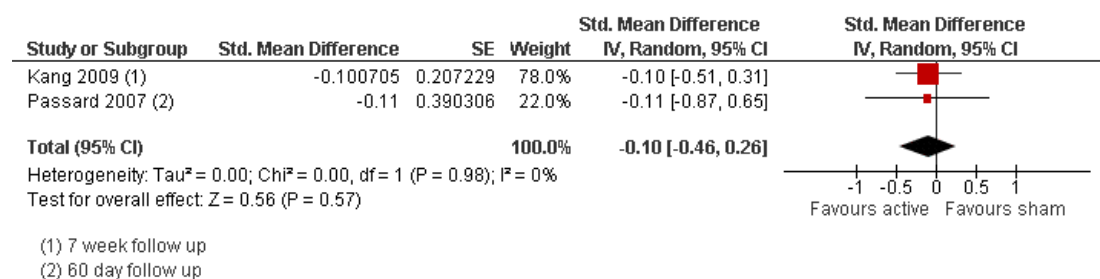
Figure 5.5 Forest plot of comparison: rTMS, outcome: Pain: medium-term follow up.



5.4.8.1.5 RTMS FOR LONG-TERM RELIEF OF CHRONIC PAIN (≥ 6 WEEKS POST-TREATMENT)

Only two studies provided data for long-term pain relief (Kang et al. 2009; Passard et al. 2007) (see Figure 5.6). The analysis included 37 participants. There was no heterogeneity ($I^2 = 0\%$).

Figure 5.6. Forest plot: rTMS, outcome: Pain, long-term follow up.



There was insufficient evidence from which to draw firm conclusions for this comparison but the available data are not suggestive of a long-term effect of rTMS on chronic pain (P = 0.57).

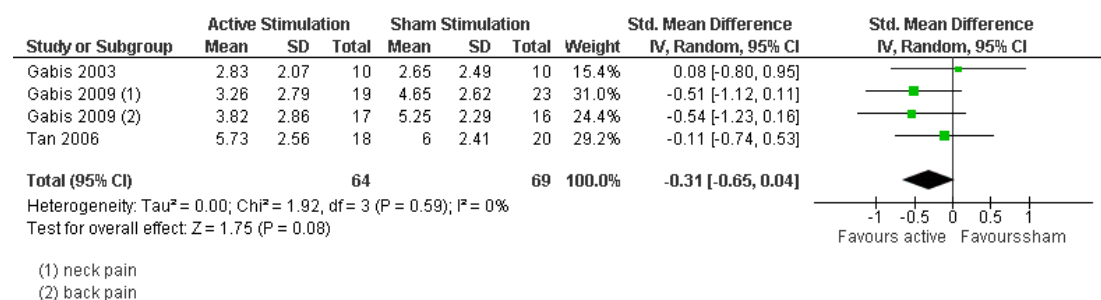
5.4.8.1.6 ADVERSE EVENTS

Of the rTMS studies that reported adverse events eight studies reported none (André-Obadia et al. 2006; André-Obadia et al. 2008; Fregni et al. 2005; Hirayama et al. 2006; Lefaucheur et al. 2001a; Lefaucheur et al. 2001b; Lefaucheur et al. 2004; Saitoh et al. 2007). Carretero et al. (2009) reported neck pain or headache symptoms in six out of 14 participants in the active stimulation group compared with two out of 12 in the sham group. One participant in the active stimulation group reported worsening depression and four participants in the sham group reported symptoms of nausea and tiredness. Passard et al. (2007) reported incidence of headaches (four out of 15 participants in the active group versus five out of 15 in the sham group), feelings of nausea (one participant in the active group), tinnitus (two participants in the sham group) and dizziness (one participant in the sham group). Rollnik et al. (2002) reported that one participant experienced headache but it is unclear in the report whether this was following active or sham stimulation.

5.4.8.2 PRIMARY OUTCOME: PAIN. CES FOR SHORT-TERM PAIN RELIEF

Three studies (Gabis et al. 2003; Gabis et al. 2009; Tan et al. 2006) provided data for this analysis. All studies utilised a parallel group design and so a standard inverse variance meta-analysis using SMD was used. Four studies did not provide the necessary data to enter into the analysis (Capel et al. 2003; Cork et al. 2004; Katsnelson et al. 2004; Lichtbroun et al. 2001) and two studies were classified as being at high risk of bias on criteria other than 'free of selective outcome reporting' (Katsnelson et al. 2004; Tan et al. 2000). See Figure 5.7 for the forest plot of this analysis.

Figure 5.7 Forest plot of comparison: CES, outcome: Pain: short-term follow up.



The studies by Gabis et al. (2003) and Gabis et al. (2009) differ substantially to that of Tan et al. (2006) on the location of electrodes and the intensity of the current provided. Despite this there was no heterogeneity ($I^2=0\%$). No individual study in this analysis demonstrates superiority of active stimulation over sham and the results of the meta-analysis do not demonstrate statistical significance though there is a trend in this direction ($P = 0.08$).

There were insufficient data to perform a meta-analysis for medium or long-term pain outcomes for CES.

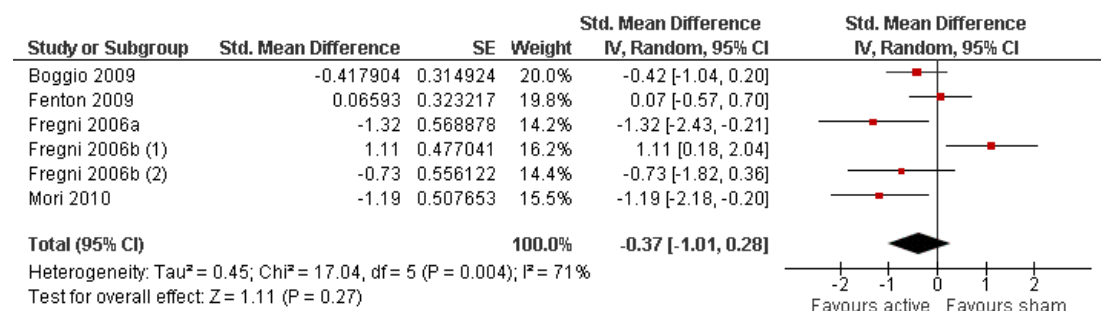
5.4.8.2.1 ADVERSE EVENTS

Only two studies of CES reported the incidence of adverse events (Capel et al. 2003; Gabis et al. 2003). In these studies no adverse events were reported.

5.4.8.3 PRIMARY OUTCOME: PAIN. TDCS FOR SHORT-TERM PAIN RELIEF

Adequate data were available from five studies (Boggio et al. 2009; Fenton et al. 2009; Fregni et al. 2006a; Fregni et al. 2006b; Mori et al. 2010) for this analysis ($n=83$). The correlation coefficient used to calculate the SE(SMD) for cross-over studies was imputed from data extracted from Boggio et al. (2009). One study (Fregni et al. 2006b) compared two distinct active stimulation conditions to one sham condition. Combining the treatment conditions was considered inappropriate as each involved stimulation of different locations and combination would hinder subgroup analysis. Instead both comparisons were included separately with the number of participants in the sham control group divided by the number of comparisons (corrected $n = 73$). The overall meta-analysis (Figure 5.8) did not demonstrate a significant effect of active stimulation ($P=0.37$) but heterogeneity was substantial ($I^2= 71\%$).

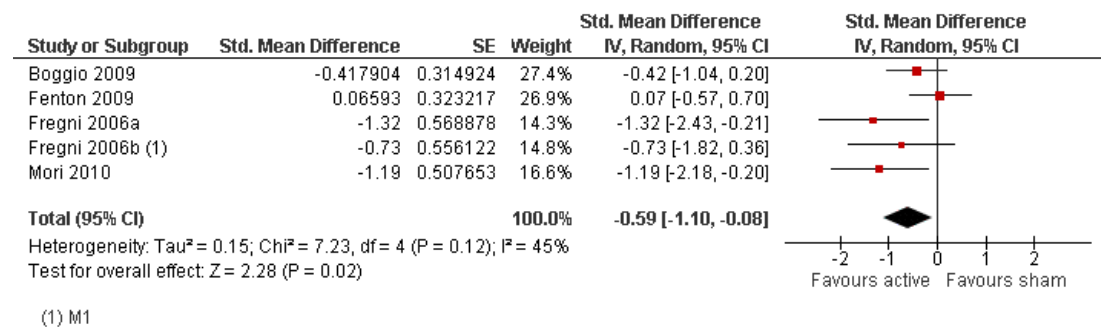
Figure 5.8. Forest plot: tDCS, outcome: Pain short-term follow up.



(1) DLPFC
 (2) M1

Subgroup analysis restricted to comparisons of active motor cortex stimulation (Figure 5.9) (excluding one group from Fregni et al. 2006b) reduced heterogeneity to a level of non-statistical significance ($I^2 = 45\%$) and suggests superiority of active over sham stimulation (SMD -0.59, 95% CI -1.10 to -0.08, $P = 0.02$). Given the wide confidence interval it was considered inappropriate to back transform the SMD to a VAS as the resulting estimate would be difficult to interpret.

Figure 5.9. Forest plot: tDCS, Pain short-term follow up, subgroup analysis: motor cortex studies only.



5.4.8.3.1 SENSITIVITY ANALYSIS

To assess whether the imputation of standard errors for cross-over studies was robust the analysis was repeated with the imputed correlation coefficient reduced and increased by a value of 0.1. This had little impact on the overall meta-analysis but when the correlation was increased in the subgroup analysis of motor cortex studies the level of heterogeneity reached statistical significance ($I^2 = 51\%$).

5.4.8.3.2 SMALL STUDY EFFECTS/PUBLICATION BIAS

Small study effects were investigated using Egger's test. The results are not suggestive of a significant influence of small study effects for the overall analysis ($P = 0.528$) or for the motor cortex subgroup analysis ($P = 0.075$).

5.4.8.3.3 ADVERSE EVENTS

All studies of tDCS reported the incidence of adverse events. Of these two studies reported none (Fregni et al. 2006a; Mori et al. 2010). Boggio et al. (2009) reported that one participant experienced headache with active stimulation. Fenton et al. (2009) reported three cases of headache, two of neck ache, one of scalp pain and five of a burning sensation over the scalp in the active stimulation group versus one case of headache in the sham stimulation group. Fregni et al. (2006b) reported one case of sleepiness and one of headache in response to active stimulation of the DLPFC, three cases of sleepiness and

three of headache with active stimulation of M1 and one case of sleepiness and two of headache in response to sham stimulation. Valle et al. (2009) reported "minor and uncommon" side effects such as skin redness and tingling which were equally distributed between active and sham stimulation. Four studies monitored for possible effects on cognitive function using the Mini Mental State Examination questionnaire (Boggio et al. 2009; Fregni et al. 2006a; Fregni et al. 2006b; Valle et al. 2009) and three of these also used a battery of cognitive tests including the digit-span memory test and the Stroop word-colour test (Boggio et al. 2009; Fregni et al. 2006a; Fregni et al. 2006b) and simple reaction time tasks (Fregni et al. 2006a). No studies demonstrated any negative influence of stimulation on these outcomes. No studies of tDCS reported severe or lasting side effects.

5.4.8.4 SECONDARY OUTCOMES: DISABILITY AND QUALITY OF LIFE

There were insufficient data from which to draw reliable conclusions for any secondary outcome measure for any stimulation type. There were not sufficient data to allow pooling for either disability or quality of life for any timepoint. That data that was extracted can be found within the data analyses section of the full published Cochrane review (for link see Appendix 2).

5.5 DISCUSSION

5.5.1 SUMMARY OF MAIN RESULTS

5.5.1.1 REPETITIVE TRANSCRANIAL MAGNETIC STIMULATION (RTMS) FOR CHRONIC PAIN

Meta-analysis of all rTMS studies in chronic pain demonstrated significant heterogeneity. Predetermined subgroup analysis suggests a beneficial short-term effect of single-dose high-frequency rTMS applied to the motor cortex. This effect is small and does not conclusively exceed the threshold of minimal clinical significance. The limited evidence from multiple-dose studies of rTMS demonstrates conflicting results with substantial heterogeneity both overall and when the analysis is confined to high-frequency motor cortex studies. Low-frequency rTMS does not appear to be effective. There is insufficient and conflicting evidence at medium-term follow-up points to allow firm conclusions to be drawn and at long-term follow-up points there is limited evidence suggesting no benefit of active stimulation over sham.

5.5.1.2 CRANIAL ELECTROTHERAPY STIMULATION (CES) FOR CHRONIC PAIN

There is insufficient evidence from which to draw firm conclusions regarding the efficacy of CES. However, the evidence from trials where it is possible to extract data is not suggestive of a significant beneficial effect. While there are substantial differences within the trials in

terms of the populations studied and the stimulation parameters used, there is no measurable heterogeneity and no trial shows a clear benefit of active CES over sham stimulation.

5.5.1.3 TRANSCRANIAL DIRECT CURRENT STIMULATION (TDCS) FOR CHRONIC PAIN

There is insufficient evidence from which to draw firm conclusions regarding the efficacy of tDCS. The existing evidence demonstrates substantial heterogeneity. Subgroup analysis suggests superiority of active over sham stimulation of the motor cortex for short-term pain relief but the confidence intervals are too wide for the purposes of estimating the effect size.

5.5.1.4 ADVERSE EFFECTS

Across all stimulation modalities there is no evidence of serious or lasting adverse effects of non-invasive brain stimulation. rTMS, tDCS and sham stimulation are associated with transient adverse effects such as headache, scalp irritation and dizziness but reporting of adverse effects was inconsistent and did not allow for a detailed analysis.

5.5.1.5 SECONDARY OUTCOME MEASURES

There were insufficient data from which to draw any reliable conclusions regarding the effect of any stimulation type on disability or quality of life.

5.5.2 OVERALL COMPLETENESS AND APPLICABILITY OF EVIDENCE

The evidence for rTMS in this review is relatively complete. We were unable to extract data from one study (Fregni et al. 2005) but this included five subjects and so we consider it unlikely that this would have affected the results of the analysis significantly. We are aware of no missing data that might have affected the subgroup analysis of high-frequency motor cortex stimulation.

We were unable to extract data from four out of seven studies of CES and these data were not available upon request. This may have impacted upon the results of our meta-analysis although one of those studies (Katsnelson et al. 2004) would have been excluded from the meta-analysis as it was judged as being at a risk of bias on criteria other than selective outcome reporting.

We were unable to extract data from one study of tDCS (Valle et al. 2009) and these data were not available upon request. These data would have significantly contributed to the power of the meta-analysis by the introduction of a further 41 participants. Therefore our

meta-analyses of tDCS and CES should be considered an incomplete summary of the evidence.

5.5.3 QUALITY OF THE EVIDENCE

No study of rTMS could be judged as having a low risk of bias across all criteria. The predominant reason for this was the use of sub-optimal sham controls that were unable to control for all possible sensory cues associated with active stimulation. A number of studies did not clearly report blinding of assessors and sensitivity analysis excluding those studies that did not report assessor blinding reduced both heterogeneity and the pooled effect size. A recent meta-epidemiological study has provided empirical evidence that incomplete blinding in controlled trials that measure subjective outcomes may exaggerate the observed effect size by 25% (Wood et al. 2008). It is therefore reasonable to expect that incomplete blinding may have exaggerated the effect size seen in the current analysis of rTMS. It could be reasonably argued that the presence of a subgroup of single-dose studies of high-frequency stimulation specific to the motor cortex that does demonstrate superiority over sham with acceptable levels of heterogeneity is evidence for a specific clinical effect of rTMS. It should be considered, however, that high-frequency rTMS is associated with more intense sensory and auditory cues that might plausibly elicit a larger placebo response, and the included studies were unable to control conclusively for these factors. Additionally there are insufficient data relating to stimulation of cortical regions other than the motor cortex from which to draw reliable comparisons. The effect size for the high-frequency studies of motor cortex rTMS approaches our predetermined threshold for clinical significance but the lower 95% confidence intervals do not meet this threshold. This estimate is based solely on single-dose studies and the evidence for multiple-dose studies is currently both limited and conflicting.

No study of CES could be judged as having a low risk of bias across all criteria. Despite this, no study from which data were available demonstrated a clear advantage of active over sham stimulation. There was substantial variation in the stimulation parameters used between studies. Notably three studies (Gabis et al. 2003; Gabis et al. 2009; Katsnelson et al. 2004) utilised an "active placebo" control in which stimulating current was delivered but at much lower intensities. These intensities well exceed those employed in the active stimulation condition of other studies of CES devices and as such it could be hypothesised that they might induce a therapeutic effect themselves. This could possibly disadvantage

the active stimulation group in these studies. However, the data available in the meta-analysis does not suggest such a trend and statistical heterogeneity between studies entered into the analysis was low.

One study of tDCS was judged as having a low risk of bias on all criteria (Mori 2010). However, the one study (Valle et al. 2009) that we could not enter into the meta-analysis would have been judged at low risk of bias had this data been available. There is evidence that the sham control used in tDCS does achieve effective blinding of participants (Gandiga et al. 2006) and studies were judged as being at low risk of bias if they reported formally blinding the participants. However, while this form of blinding is validated for stimulation intensities of 1mA all of the studies identified in this review used stimulation intensities of 2mA which may be more likely to elicit sensation. One study report (Mori 2010) alludes in the discussion to experiencing difficulties with blinding at 2 mA. This suggests a possible source of bias within the existing evidence base in favour of active stimulation but no systematic evaluation of the integrity of tDCS sham controls at this stimulation intensity exists and no strong evidence was identified indicating that successful blinding was not achieved in these studies.

All of the 33 studies may be considered to be small in terms of sample size. Given the trend seen in tDCS studies of the motor cortex towards a beneficial effect on short-term pain outcomes it is possible that the existing analysis lacks adequate power and that further large studies may demonstrate therapeutic benefit. However the predominance of small studies raises the possibility of publication bias and small study effects. It is recognised that small study effects and publication bias may influence the evidence base for new treatments such as tDCS with a propensity for negative studies to not reach full publication. As smaller studies tend to also be less rigorous this bias potentially leads to an evidence base that systematically exaggerates the efficacy of interventions (Hopewell et al. 2009; Nuesch et al. 2010).

An attempt to investigate this was made by the use of Eggers test. However this approach and others lack sensitivity (Moore et al. 2008). An examination of 12 different methods for detecting publication bias found that all had serious limitations (Thornton & Lee 2000). In the current review the lack of large trials suggests that there would be insufficient range in sample sizes between studies to provide adequate sensitivity to detect an effect. Therefore while there is no direct empirical evidence of small study effects it would be premature to conclude that they are not relevant.

5.5.4 POTENTIAL BIASES IN THE REVIEW PROCESS

There is substantial variation between the included studies of rTMS and tDCS. Studies varied in terms of the clinical populations included, the stimulation parameters and location, the number of treatment sessions delivered and in the length of follow up employed. This heterogeneity is reflected in the I^2 statistic for the overall rTMS and tDCS meta-analyses. However, subgroup investigation significantly reduced this heterogeneity. While the subgroup analyses used in this review were prespecified in the review protocol they should be considered as observational rather than randomised data and thus the evidence from them is less robust.

The majority of rTMS and tDCS studies specifically recruited participants whose symptoms were resistant to current clinical management and most rTMS studies specifically recruited participants with neuropathic pain. As such it is important to recognise that this analysis in large part reflects the efficacy of rTMS and tDCS for refractory chronic pain conditions and may not be as accurate a reflection of their efficacy across all chronic pain conditions.

One study included in the analysis of rTMS studies (Defrin et al. 2007) demonstrated a difference in pain levels between the two groups at baseline that exceeded the size of the difference observed at follow up. Specifically the group that received sham stimulation reported less pain at baseline than those in the active stimulation group. The use in the current analysis of a between-groups rather than a change from baseline comparison is likely to have affected the results although the study contributes only 1.5% weight to the overall meta-analysis and the study itself reported no difference in the degree of pain reduction between the active and sham stimulation groups.

The analysis of tDCS for short-term pain included a combination of studies that delivered a varied number of treatments but there were insufficient data to support a subgroup analysis specific to this variable. This analysis is also affected by one study that does not demonstrate a trend toward superiority of active over sham stimulation (Fenton et al. 2009). This study delivered fewer treatment sessions compared with some others in the analysis. Additionally the authors of this study concluded in favour of active stimulation by comparing the average pain outcome over a one-week period, whereas in the current analysis post-stimulation data from the day of the final treatment session was used. However, this study fulfils the criteria for inclusion into the analysis and post-hoc sensitivity analysis excluding this study was considered inappropriate.

The method used to back transform the pooled SMD to a visual analogue scale and subsequent calculation of the effect as a percentage improvement does rest upon the assumption that the standard deviation and the pain levels in the study used (Lefaucheur et al. 2004) are representative of the wider body of evidence. The study was chosen as it was the largest study and contributed the most weight to the analysis. Review of both the standard deviation and the control group pain scores in Lefaucheur et al. (2004) suggests that they fall around the middle of distributed values. However, the results of this back transformation should be considered an estimate.

5.5.5 AGREEMENTS AND DISAGREEMENTS WITH OTHER STUDIES OR REVIEWS

Our results broadly concur with the European Federation of Neurological Societies (EFNS) guidelines which similarly concluded that there was moderate evidence (two randomised controlled trials) that high-frequency rTMS (≥ 5 Hz) of the motor cortex induces significant pain relief in central post-stroke pain and several other neuropathic conditions but that the effect is modest and short-lived.

In their review Leung et al. (2009) suggested a similar effect size to the current review (a 13.7% improvement in pain, excluding the study of Khedr et al. 2005). The authors also investigated the influence of the neuro-anatomical origins of pain upon the effect size. They noted a trend suggestive of a larger treatment effect in central compared with peripheral neuropathic pain states although this did not reach statistical significance. While the data in the current review were not considered sufficient to support a detailed subgroup analysis by neuro-anatomical origin of pain, the exclusion of studies that did not specifically investigate neuropathic pain did not significantly alter the results and the two multiple-dose studies of motor cortex rTMS for central neuropathic pain that were included (Defrin et al. 2007; Kang et al. 2009) both failed to demonstrate superiority of active over sham stimulation.

All but one of the included studies in the review by Leung et al. (2009) delivered high-frequency (≥ 5 Hz) rTMS and no clear influence of frequency variations was observed within this group. Leung et al. suggest that the number of doses delivered may be more crucial to the therapeutic response than the frequency (within the high-frequency group) based on the larger therapeutic response seen in the study of Khedr et al. (2005), the study that was excluded from the current analysis due to high risk of bias. Leung et al.'s review preceded the studies by Defrin et al. (2007) and Kang et al. (2009) which did not demonstrate superiority of active over sham stimulation. While there are limited data to test this

proposition robustly the results, in this review, of the subgroup analysis of multiple-dose studies of high-frequency motor cortex rTMS in neuropathic pain do not support this proposition.

Lima & Fregni (2008) undertook meta-analyses of motor cortex stimulation for chronic pain pooling data from rTMS and tDCS studies. They concluded that the number of responders is significantly higher following active stimulation compared with sham (risk ratio 2.64, 95% CI 1.63 to 4.30) though, as discussed in the previous chapter, the threshold for treatment response was defined as a global response according to each study's own definition may not be well-standardised. They also noted a larger response to multiple doses of stimulation, an observation that is not reliably reflected in the current review. Additionally they also included the study of Khedr et al. (2005) and Canavero et al. (2002) (excluded from this review as it is not a randomised or quasi-randomised study). The current review includes a number of motor cortex rTMS studies published since that review (André-Obadia et al. 2008; Defrin et al. 2007; Kang et al. 2009; Lefaucheur et al. 2006; Lefaucheur et al. 2008; Passard et al. 2007; Saitoh et al. 2007). Since completing our review a separate systematic review has been published relating to tDCS in the treatment of pain (Luedtke et al. 2012) Unlike our review they excluded the studies by Fenton et al. (2009) as it was judged to be at high risk of bias on the grounds of unclear randomization procedure and due a lack of clarity of participant withdrawal, and Boggio et al. (2009) due to the level of dropout. They also included one trial that was published after the searches for our review (Soler et al. 2010). The results of their meta-analysis are broadly consistent with those presented here and similarly conclude that the evidence is insufficient to allow definite conclusions but that there is low level evidence that tDCS may be effective for chronic pain.

While the current review also suggests a statistically significant short-term benefit of high-frequency motor cortex rTMS in the treatment of chronic pain the effect is small, appears short-term and although the pooled estimate approaches the threshold of minimal clinical significance it is possible that it might be inflated by methodological biases in the included studies.

Unlike this review, Kirsch & Smith (2000) concluded in favour of the use of CES. As discussed in the previous chapter that review demonstrated multiple methodological limitations including a lack of formalised search strategy, inclusion criteria or quality assessment process. It also discussed a number of unpublished studies that remain unpublished at the time of the current review. Using a more systematic methodology and

including papers published since that review we found that the data that were available for meta-analysis do not suggest a statistically or clinically important benefit of active CES over sham.

5.5.6 CONCLUSIONS

5.5.6.1 IMPLICATIONS FOR PRACTICE

There is evidence that low-frequency rTMS is not clinically effective in the treatment of chronic pain. Subgroup analysis suggests that single doses of high-frequency rTMS of the motor cortex have small short-term effects on chronic pain although the limited evidence from multiple-dose studies of high-frequency rTMS to the motor cortex is conflicting. As such it is not currently clear whether rTMS represents a useful clinical tool and more evidence is needed. There is insufficient evidence from which to draw firm conclusions regarding the efficacy of tDCS or CES for the treatment of chronic pain.

5.5.6.2 IMPLICATIONS FOR RESEARCH

The existing evidence across all forms of non-invasive brain stimulation is dominated by small studies with unclear risk of bias and there is a need for larger rigorously controlled trials. Studies should endeavour to report primary outcomes clearly in a format that facilitates data extraction so that an inclusive meta-analysis might be possible, particularly in studies of CES and tDCS. All studies of non-invasive brain stimulation techniques should measure, record and clearly report adverse events to both active and sham stimulation.

In rTMS the evidence base is dominated by studies of intractable neuropathic pain and there is little evidence from which to draw conclusions regarding other types of chronic pain. All of the included rTMS studies are affected by the use of sub-optimal sham conditions that may adversely impact upon blinding. Future rTMS research should consider employing recently developed sham coils that control for all of the sensory aspects of stimulation. Such coil systems should be robustly validated as reliable and valid sham controls. The current results suggest that any future trial of rTMS in chronic pain should utilise high-frequency stimulation parameters. The influence of other stimulation parameters on efficacy is currently unclear. The results suggest that the motor cortex is the most promising site for stimulation, however this may be a function of the small number of studies that stimulated other cortical regions. There is a particular need for more multiple-dose studies of rTMS that measure both short and long-term clinical outcomes to determine whether the effect seen in this review can be considered clinically useful.

Further studies of tDCS should give consideration to the integrity of participant blinding, particularly when utilising stimulation intensities that exceed 1 mA. In terms of this thesis, no studies of rTMS or tDCS had directly investigated the effect specifically in a CLBP population. As such there was a case for an exploratory clinical study in this area. The existing data regarding tDCS suggest that the motor cortex holds promise as a stimulation target. Therefore for the second study in this thesis a clinical pilot study was planned to investigate the possible efficacy of tDCS to the motor cortex in the treatment of CNSLBP. The following chapter describes that study and its findings.

CHAPTER 6. STUDY 2. TRANSCRANIAL DIRECT CURRENT STIMULATION OF THE MOTOR CORTEX IN THE TREATMENT OF CHRONIC NON-SPECIFIC LOW BACK PAIN. A RANDOMISED, DOUBLE-BLIND EXPLORATORY STUDY.

Study published as: O'Connell NE, Cossar J, Marston L, Wand BM, Bunce D, DeSouza LH, Maskill DW, Sharp A, Moseley GL. Transcranial direct current stimulation of the motor cortex in the treatment of chronic non-specific low back pain. A randomised, double-blind exploratory study. *Clinical Journal of Pain*. See Appendix 5)

6.1 INTRODUCTION

As discussed in the previous chapter our Cochrane review into the efficacy non-invasive brain stimulation methods for chronic pain found preliminary evidence of efficacy for active tDCS applied to the motor cortex (O'Connell et al. 2010b). However due to significant clinical and statistical heterogeneity it was not possible to accurately estimate the effect size. Since that review was completed and while this exploratory study was underway one small cross-over study (Antal et al. 2010) has investigated the efficacy of 5 days of 1mA intensity tDCS in a mixed group of 12 chronic pain patients that included 8 with chronic back pain and found a reduction in pain after 5 daily active stimulation sessions with a concurrent reduction in intra-cortical inhibition. The data suggested a trend towards greater efficacy in joint arthritic pain than chronic back pain, though the study lacked sufficient power to detect this. As was the case for many of the studies included in the systematic review insufficient data was reported for the reader to ascertain the effect size though in the sham condition 4 participants achieved a reduction in pain >30% , compared with 8 in the active stimulation condition. However of 23 participants only 13 were entered into the cross-over stage of the study and it is not clear why this was the case or how that 13 were selected.

The aim of this exploratory study was to test whether daily treatments of active anodal tDCS applied to the motor cortex reduces pain significantly more than sham stimulation in a group of participants with chronic non-specific low back pain. Given that previous studies had used an arbitrary fixed dosage in terms of the number of days of stimulation the current study aimed to vary the number of days of stimulation to explore whether this had any apparent effect on outcome with an overall view to producing proof of the principle that tDCS might reduce pain in CNSLBP and to inform the dose parameters for a possible larger RCT.

6.2 MATERIALS AND METHODS

6.2.1 ETHICAL APPROVAL AND INFORMED CONSENT.

This study had full approval from the School of Health Sciences and Social Care Research Ethics Committee, Brunel University, the NHS Research Ethics Service (reference number 07/H0808/172) and the Hillingdon Hospitals NHS Trust Research and Development Office. All participants gave informed consent to take part in the study. See Appendix 3 for the participant information sheet, consent form and ethical approval documentation pertaining to this study.

A sham-controlled, interrupted time series design was utilised with randomised multiple baselines. This design is considered advantageous to a parallel or cross-over randomised controlled trial in studies with small samples as it enhances statistical power whilst still providing a degree of control over non-specific treatment effects and other biases (Cook and Campbell 1979) and is therefore suited to this kind of exploratory study. Particularly where an appropriate statistical analysis is employed interrupted time series designs facilitate a level of control for the effects of change over time, alterations in the duration of the intervention, random fluctuations and autocorrelation (Ramsay et al. 2003). Additionally the design was chosen to allow for exploration of the effect of varying the number of stimulation sessions, which no study to date has addressed. To reduce bias both the subjects and the assessor were blinded to the intervention status (i.e. sham or active stimulation).

6.2.2 PARTICIPANTS

A convenience sample of patients with back pain was recruited from the physiotherapy department and spinal diagnostic clinic of a general hospital in west London, UK. Patients referred to this department who met the inclusion criteria were invited to take part in the study by local physiotherapists or posters displayed in the physiotherapy department. Posters were also displayed across the campus of Brunel University. The inclusion criteria were as follows: aged over 18 years, proficient in written and spoken English, and a history of non specific low back pain (as defined by the European guidelines on low back pain (Airaksinen et al. 2006)) of greater than 6 months duration. The exclusion criteria were: evidence of specific spinal pathology (fractures, neoplasm, deformity, Scheuermann's disease, spinal infections, spondylolisthesis/lysis, radiculopathy), a history of spinal surgery within the year prior to commencing the study, known neurological disease, identifiable psychotic illness or other mental illness, pregnancy, or involvement in any other ongoing research project relating to their low back pain.

6.2.3 TDCS STIMULATION

tDCS was delivered using a battery driven CX-6650 ramp controlled DC stimulator (Rolf Schneider Electronics , Germany). Current was delivered by electrodes encased in sponge pads soaked with 0.9% (155 mMol) saline solution. The machine was kept behind the participant and out of their view at all times. For both the active and sham conditions, the anode was placed over the motor cortex of the subject and the cathode was placed over the contralateral supraorbital region. Electrodes were secured using soft elastic straps. For participants whose pain was predominantly on one side of their back, the contra-lateral hemisphere was stimulated. For participants whose pain was not predominantly on one side, the hemisphere contralateral to the participant's self-nominated dominant hand was stimulated. This approach is consistent with previous clinical studies (e.g. Fregni, et al. 2006; Fregni, et al. 2006; Mori et al. 2010). The location of the motor cortex was estimated using the international 10-20 EEG system and placing the centre of the electrode pad at a point 1 cm anterior and 4 cm lateral to the vertex. This location has been identified as the motor cortex representation of the lumbar paravertebral muscles in a transcranial magnetic stimulation (TMS) mapping study (O'Connell et al. 2007).

In the active stimulation condition a constant current of 2mA intensity was applied for 20 minutes with a 5 second ramp phase at the beginning. In the sham stimulation condition the machine was activated for 30 seconds using identical parameters but was then switched off, without the participant's knowledge. This sham control is commonly employed (Fregni, et al. 2006; Fregni, et al. 2006; Mori et al. 2010; Valle et al. 2009; Boggio et al. 2009) because over the initial 30 seconds of stimulation, an initial sensation of tingling under the electrode fades away. Participants are less likely to distinguish active from sham conditions if the initial period of tingling is present in both.

6.2.4 OUTCOME MEASURES

6.2.4.1 PRIMARY OUTCOMES

The primary outcomes were average self-reported pain intensity and unpleasantness over the last 24 hours. Both were measured on separate 10cm visual analogue scales (VAS). For intensity, the left anchor was "no pain" and the right anchor was "worst pain imaginable". For unpleasantness, the left anchor was "not bad at all" and the right anchor was "the most unpleasant feeling imaginable". Both measures were taken once daily during the baseline period; prior to stimulation on each day of the experimental phase; and once at each follow up point. Visual analogue scales for pain are widely used, easy to administer reliable and

correlate well with alternative scales (Hawker et al. 2011). They are also recommended for use in chronic pain studies by the IMMPACT consensus group (Turk et al. 2008).

6.2.4.2 SECONDARY OUTCOMES

To investigate any immediate effect of brain stimulation on pain, intensity or unpleasantness, both were assessed using the same VAS, but in response to the question “How would you rate your pain (intensity/unpleasantness) at the moment?”, immediately before and after each session.

Self-reported disability was measured using the 24 item Roland and Morris Disability Questionnaire (RMDQ) (Roland and Morris 1983) and anxiety and depression using the Hospital Anxiety and Depression Scale (HADS) (Zigmond and Snaith 1983). The RMDQ is the most commonly used disability index in back pain research and has been subjected to the most comprehensive evaluations. It is simple to complete, has acceptable to good psychometric properties (Smeets et al. 2011) and appears to be more responsive to change than an alternative tool, the Oswestry Disability Index (Grotle et al. 2004; Grotle et al 2005). Given that the primary goal in this study was to detect change, and to reduce the testing burden for participants the RMDQ was considered a reasonable choice. Similarly the HADS is widely used as a measure of anxiety and depression and is a reliable and valid measure of emotional distress (Julian 2011, Smarr and Keefer 2011). It is also sensitive to change in relation to medical interventions (Herrmann 1997).

These were collected daily during the baseline and follow up periods and every 5th day during the experimental phase. The success of participant blinding was investigated (i.e.) whether the sham condition was distinguishable from active stimulation) using a 0-10cm VAS with the left anchor 0cm = “100% sure the machine was switched on” and the right anchor “100% sure the machine was switched off”. This was measured immediately following each stimulation session.

6.2.4.3 ADVERSE EVENTS

To measure the incidence and nature of adverse events participants were asked, at the start of each day of the stimulation period and immediately following each stimulation session whether they experienced any adverse events or noticed any unexpected sensations and to describe the event. Participants were asked daily to report their analgesic medication.

6.2.4.4 COGNITIVE FUNCTION MONITORING

To assess for any unwanted effects of stimulation on cognitive function, a battery of cognitive tests was employed to monitor performance over a range of cognitive domains. These were taken daily during the baseline and follow up period and pre- and post-stimulation on each day of the experimental period. These tests were performed by the participants on a laptop computer using E-Prime software (©Psychology Software Tools, Sharpsburg USA). The tests are similar to those used for the same purpose in previous tDCS studies (Fregni et al. 2006a, Fregni et al. 2006b). The following tests were undertaken:

6.2.4.4.1 STROOP COLOUR-WORD TASK

Participants were required to respond to the ink colour (red, blue, yellow, or green) of the printed words “Red”, “Blue”, “Yellow”, and “Green” presented on a monitor using the appropriate keyboard key. Sixteen practice trials were administered, followed by 96 pseudo-randomized test trials, half of which were congruent (word-colour matched), and half incongruent (word-colour not matched). Measures of mean reaction time and accuracy (proportion of errors) were computed for this task.

6.2.4.4.2 WORD RECOGNITION TASK FOR EPISODIC MEMORY

A list of 40 semantically unrelated nouns was created. Twenty target words were presented at a rate of 5 seconds per word on a monitor. Following a distracter reaction time task, the 20 target words were randomly intermixed with 20 distracter words, and individually presented on a monitor for 5 seconds each. Participants were instructed to respond ‘Yes’ for target words and ‘No’ for distracter words using designated keyboard keys. On any given testing day one of eight possible lists of nouns was used to minimise the risk of participants learning the words over the course of the study. Mean reaction time and accuracy (proportion of correct responses) were analysed.

6.2.4.4.3 TWO CHOICE AND FOUR CHOICE REACTION TIME TASKS

In the 2 choice version of the task, a black disc was presented on a monitor either left or right of a central fixation cross in a pseudo-random order. In the 4 choice version of the task, the black disc was presented in one of four locations (lower or upper left or right). Participants were required to press designated keyboard keys that mapped spatially onto the position of the disc on the screen as quickly but as accurately as possible. In each condition, 20 practice trials were administered prior to 48 test trials. On each testing day one of these tasks was used as the distracter for the word memory recognition test. Mean reaction time and accuracy (proportion of errors) were analysed.

6.2.5 PROCEDURE

Participants gave their informed consent. The study included a 3 day baseline period, followed by a 15 day stimulation period during which participants received either real or sham stimulation, then a 3 day follow up period. Outcomes were assessed again, 3 weeks later. Figure 6.1 shows a flow chart of the study process. All testing and stimulation was carried out in a laboratory on a University campus.

Following consent, each participant attended for 3 days (the 'baseline period'). All outcome measures were completed daily but no interventions were given. The participant was then randomly allocated a specific day, which was not revealed to them, within the following 15 day period (the 'experimental period') during which active stimulation would commence. The 15 days of the experimental period were Mondays to Fridays for 3 consecutive weeks. Each participant received sham stimulation daily until the day randomly allocated for active stimulation to commence. Active stimulation was then given daily for the remaining days of the experimental period.

6.2.6 RANDOMISATION, ALLOCATION CONCEALMENT AND BLINDING

The day for commencing active stimulation was randomised using a computer generated random numbers list that avoided replication (i.e. no 2 subjects could be randomised to commence active stimulation on the same day). The treatment allocation for each participant were generated and sealed in an opaque envelope. This process was completed by an independent administrator prior to recruitment of the first participant. The treatment schedule was revealed to the researcher who applied the stimulation on the first day of the stimulation period but was not revealed to the participants or any other member of the research team including the researcher who oversaw all outcome assessments. Blinding was maintained until all data for all participants had been collected for all participants and extracted and entered into a spreadsheet for analysis.

6.2.7 DATA ANALYSIS

Data analysis was not performed under blinded conditions. Blinding was broken at the end of the data collection phase. Overall summary statistics were calculated, as were summary statistics by stimulation condition. Outcomes were modelled using generalised estimating equations (Zeger and Liang 1986) to determine whether there was a difference in outcome by condition (active versus sham). These allow for the two level structure (participants being tested at multiple time points) to be modelled and results are given as coefficients and 95% confidence intervals. These give marginal estimates (population average), which

can be interpreted as the effect for the average person. The correlation structure was set to exchangeable (equal correlation within subjects, but independence between subjects). For 24 hour average pain score the model controlled for the participant's perception score regarding the mode of stimulation from the previous day of testing. For the post-stimulation scores across all other outcomes the model controlled for the pre-test score for that particular day. Bonferroni correction for multiple comparisons was not used due to the exploratory nature of the study and because we wished to minimise the likelihood of not detecting an effect that was actually there (type I error). All analyses were performed using Stata version 11 (Statacorp LP, USA).

6.3 RESULTS

6.3.1 PARTICIPANTS

Eleven participants volunteered for the study but three were excluded at the recruitment stage, two because they had undergone back surgery within the last year and one because of a marked congenital structural deformity of the spine. Table 6.1 shows the demographic characteristics of participants and details of the stimulation that they received and figure 6.1 illustrates the flow of participants through the study. The mean age was 45 (SD 10) years. Seven of the 8 participants were female. All participants completed the study including the 3 week follow-up although in addition to weekends, some gaps (maximum 6 days for 1 participant) were experienced during the study process due to uncontrollable circumstances including: heavy snow (3 participants), other illness (unrelated to back pain) (1 participant), family bereavement (1 participant) car breakdown (1 participant) and a national election in which 1 participant had a supervisory role and was unable to attend. Where days were missed for any reason (including weekends) the stimulation period was continued where possible from the same point when the participant returned. Three participants missed one day each of the 15 day experimental period. The minimum number of active stimulation sessions that a participant received was three and the maximum was 14 (mean 9 (SD 4)).

Table 6.2 gives the summary statistics across all variables by treatment condition. Table 6.3 shows the coefficients with 95% confidence intervals (CI) for the active treatment compared with the sham with p values.

6.3.2 THE EFFECT OF TDCS ON BACK PAIN

Active tDCS had no effect on average 24 hour back pain intensity (coefficient -0.070, 95% CI -0.682, 0.541, $p=0.821$) nor on pain unpleasantness (coefficient -0.026, 95%CI -0.683,

0.630, $p=0.937$, number of included test occasions ($n=109$). Active tDCS provided no more pain relief pre-post sessions than sham tDCS (intensity: coefficient 0.008, 95% CI -0.314, 0.331, $p=0.959$; unpleasantness: coefficient 0.061, 95%CI -0.290, 0.411, $p=0.735$, $n=117$).

Figure 6.1. A flow chart illustrating the study process and participant flow.

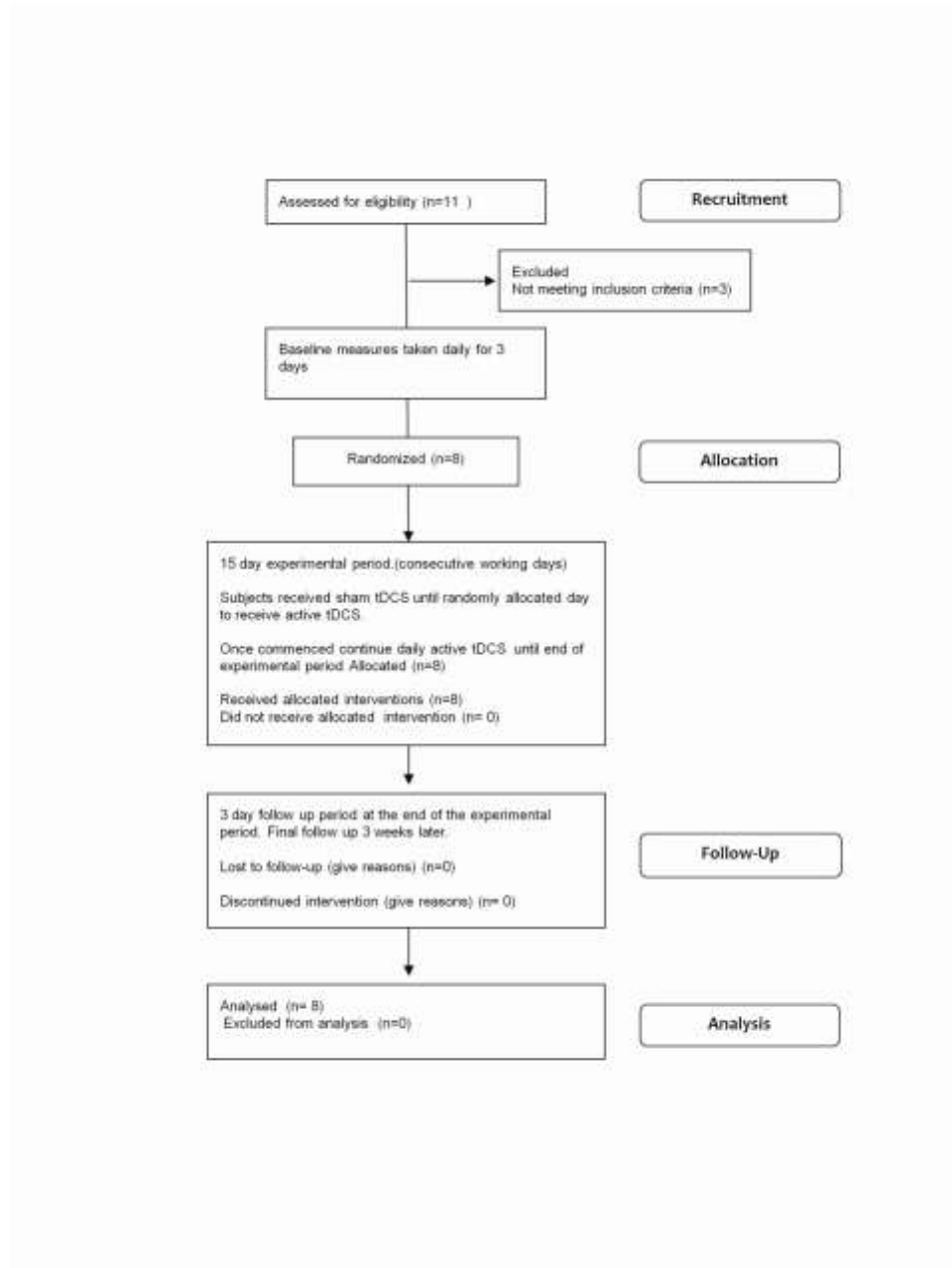


Figure 6.2 illustrates the change in pain intensity for each subject across the course of the study. Analysis of individual participants' pain intensity scores demonstrated that at the end of the last active stimulation no participants had experienced a reduction in pain of $\geq 20\%$ of their mean pain score following sham stimulation sessions

6.3.3 SECONDARY OUTCOME VARIABLES

Anxiety and depression scores were not entered into the analysis as there were insufficient data from each condition.

Table 6.1 Demographic characteristics participants and details of the stimulation received

Subject	Gender	Age (years)	Duration of pain (years)	Location of pain	Prior Clinical Management	Pain Medication	Hemisphere stimulated	Day of experimental period active stimulation commenced (1-15)	No. of days active stimulations received
1	F	34	5	Lumbar spine left side dominant, bilateral legs to below knee	Physiotherapy, analgesics	Ibuprofen as required	Right	2	14
2	F	39	3	Lumbar spine bilateral, no dominant side	Physiotherapy, analgesics Facet joint injections	None	Left	6	10
3	F	43	5	Lumbar spine left side dominant and left leg to below knee	Physiotherapy, analgesics, Facet joint injections, epidural.	Citalopram (20md/day) Co-dydramol as required	Right	9	6
4	F	48	>20	Lumbar spine, right side dominant	Chiropractic, analgesics	Ibuprofen, Co-dydramol as required	Left	4	12
5	F	61	>20	Lumbar spine, right side dominant	Spinal fusion (1994), physiotherapy, analgesics	Paracetamol as required	Left	11	5
6	F	57	13	Lumbar spine, right side dominant and right leg to below knee	Physiotherapy, pain management programme, analgesics	Ibuprofen as required	Left	12	3
7	M	42	>20	Lumbar spine bilateral, no dominant side	Physiotherapy, analgesics	None	Left	8	7
8	F	35	1-4	Lumbar spine, left sided dominance, left leg to below knee	Physiotherapy, facet joint injections, epidural, ultrasound, TENS, acupuncture	Ibuprofen, Paracetamol, Co-codamol, diclofenac as required	Right	5	11

Table 6.2: Summary statistics by treatment condition

Variable	Baseline		Sham		Active		Follow Up	
	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)
24hr average pain intensity (VAS, 0-10 cm)	5.25	(2.16)	5.19	(2.05)	5.03	(1.85)	4.57	(2.26)
24hr average pain unpleasantness (VAS, 0-10 cm)	5.33	(2.08)	5.29	(2.22)	5.16	(1.91)	4.63	(2.50)
Current pain intensity pre-stimulation (VAS, 0-10 cm)	4.35	(2.42)	4.53	(2.45)	4.27	(2.08)	3.97	(2.43)
Current pain unpleasantness pre-stimulation (VAS, 0-10 cm)	4.26	(2.65)	4.52	(2.57)	4.34	(2.14)	3.98	(2.43)
Current pain intensity post-stimulation (VAS, 0-10 cm)			4.02	(2.13)	3.88	(2.20)		
Current pain unpleasantness post-stimulation (VAS, 0-10 cm)			3.97	(2.26)	3.88	(2.27)		
Participants' judgement as to whether active or sham stimulation (VAS, 0-10 cm)			5.24	(2.54)	6.47	(1.22)		
Disability (RMDQ) (Score 0-24)	10.7	(4.5)	10.2	(4.2)	9.0	(5.2)	7.8	(4.8)
Anxiety (HADS-A) (Score 0-18)	7.2	(3.4)	6.4	(3.7)	6.1	(4.0)	5.0	(4.1)
Depression (HADS -D) (Score 0-18)	4.5	(2.7)	4.1	(3.0)	3.4	(2.9)	3.6	(2.9)
Stroop test accuracy pre-stimulation *	0.01	(0.02)	0.02	(0.02)	0.02	(0.02)	0.02	(0.02)
Stroop test accuracy post-stimulation *			0.02	(0.05)	0.02	(0.02)		
Stroop test reaction time pre-stimulation (msec)	771.05	(110.97)	665.12	(68.87)	648.20	(69.76)	648.79	(91.07)
Stroop test reaction time post-stimulation (msec)			660.19	(68.08)	645.02	(71.01)		
Word memory test accuracy pre-stimulation †	0.86	(0.07)	0.87	(0.08)	0.88	(0.08)	0.92	(0.09)
Word memory test accuracy post-stimulation †			0.86	(0.11)	0.89	(0.09)		
Word memory test reaction time pre-stimulation (msec)	858.16	(102.78)	752.69	(65.36)	744.48	(61.38)	720.57	(56.00)
Word memory test reaction time post-stimulation (msec)			747.56	(81.56)	730.12	(52.62)		
4 choice reaction time accuracy pre-stimulation *	0.05	(0.06)	0.03	(0.02)	0.03	(0.02)	0.03	(0.02)
4 choice reaction time accuracy post-stimulation *			0.03	(0.03)	0.03	(0.02)		
4 choice reaction time , reaction time, pre-stimulation (msec)	449.67	(110.30)	399.55	(73.88)	380.50	(68.63)	377.56	(81.52)
4 choice reaction time , reaction time, post-stimulation (msec)			397.33	(77.87)	378.72	(72.75)		
2 choice reaction time accuracy pre-stimulation *	0.02	(0.02)	0.02	(0.01)	0.04	(0.05)	0.02	(0.02)
2 choice reaction time accuracy post-stimulation *			0.03	(0.02)	0.02	(0.02)		
2 choice reaction time , reaction time, pre-stimulation (msec)	297.02	(44.67)	283.18	(36.72)	280.87	(33.14)	283.83	(32.48)
2 choice reaction time , reaction time, post-stimulation (msec)			280.75	(34.52)	280.83	(30.57)		
Voltage when stimulator initially turned on (volts)			9	(4)	10	(4)		

* Outcome is proportion of incorrect responses/ † Outcome is proportion correct responses

Table 6.3: Coefficients (95% confidence interval) for active treatment (compared to sham) – time not included

Outcome	Coefficient	95% CI	p-value
24hr average pain intensity*	-0.070	-0.682, 0.541	0.821
24hr average pain unpleasantness*	-0.026	-0.683, 0.630	0.937
Current pain intensity post-stimulation †	0.008	-0.314, 0.331	0.959
Current pain unpleasantness post-stimulation †	0.061	-0.290, 0.411	0.735
Participants' judgement as to whether active or sham stimulation §	0.935	0.068, 1.802	0.035
Stroop test accuracy †¥	-0.016	-0.046, 0.014	0.302
Stroop test reaction time†	-7.445	-19.611, 4.720	0.230
Word memory test accuracy †‡	0.026	0.001, 0.051	0.042
Word memory test reaction time†	-28.497	-58.171, 1.178	0.060
4 choice reaction time accuracy †¥	-0.004	-0.013, 0.006	0.455
4 choice reaction time, reaction time †	-12.554	-24.289, -0.819	0.036
2 choice reaction time accuracy †¥	-0.001	-0.011, 0.010	0.892
2choice reaction time, reaction time†	-2.666	-10.299, 4.968	0.494

Key: *Controlling for the participants' perception from the previous day of whether they are receiving active treatment or sham on a 0-10 VAS/ †Controlling for pre test score of the given variable/ § Controlling for the voltage when the stimulator is initially switched on/ ‡Outcome is proportion correct/ ¥Outcome is proportion incorrect

6.3.4 HOW EFFECTIVELY DID THE SHAM CONDITION MIMIC ACTIVE STIMULATION?

Participants scored higher on their perception of whether they had received active or sham treatment following active stimulation (mean (SD) active stimulation 6.47(1.22), sham stimulation 5.24(2.54), coefficient 0.935, 95% CI 0.068, 1.802, p=0.035) (n=117). This may indicate that the difference between the active and sham conditions was detectable.

6.3.5 COGNITIVE TESTS

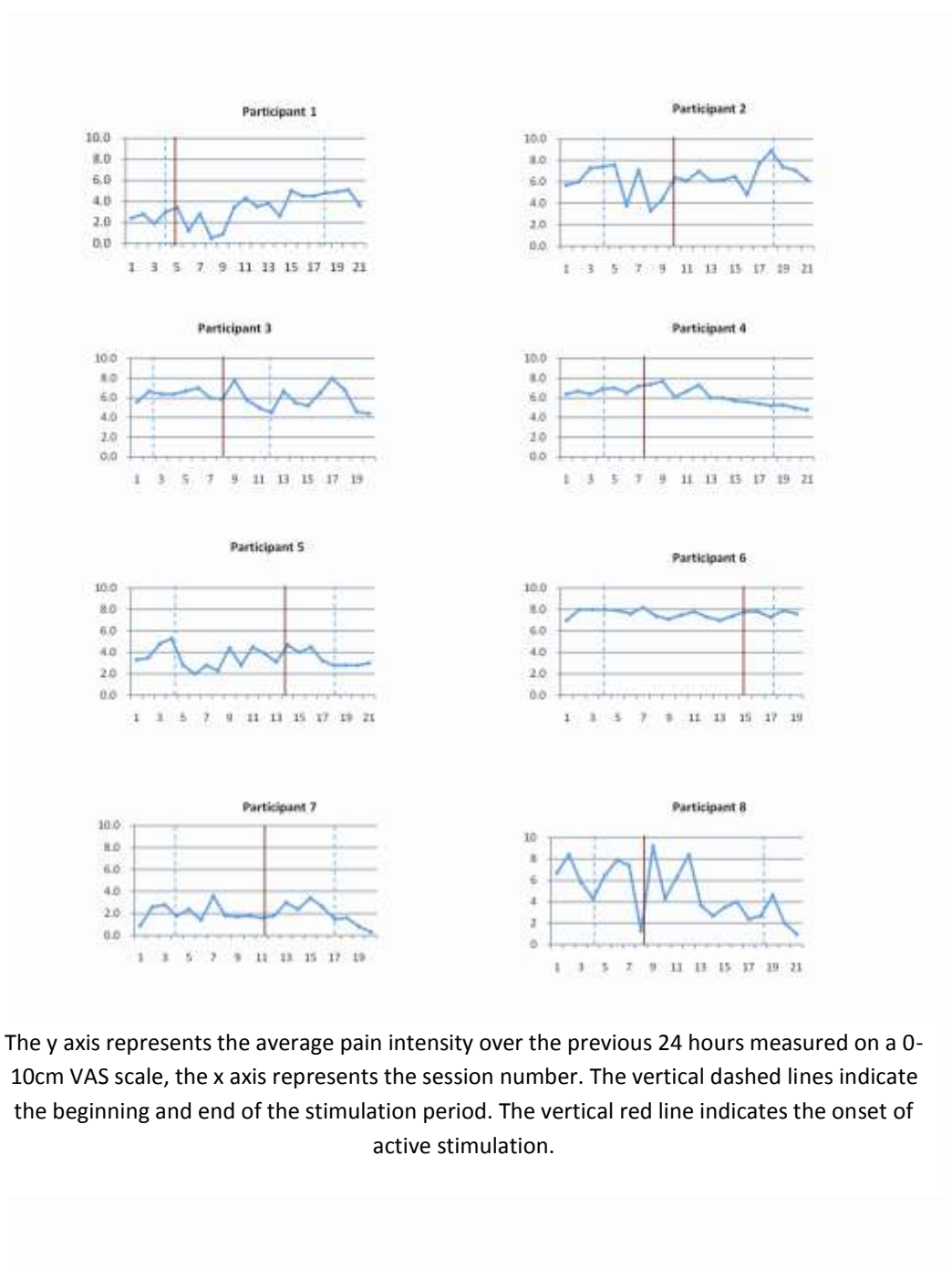
No deterioration was seen in participants' performance on any of the cognitive tests (n=117). Accuracy in the word recognition task improved after active stimulation compared to sham (coefficient 0.026, 95%CI 0.001, 0.051, p =0.042).

6.3.6 SENSITIVITY ANALYSIS

The models for pain outcomes were re-analysed without controlling for participants' perceptions of the treatment condition and then, separately, with time (entered as the day of the stimulation period 1-15) included as a controlling variable. This made no difference

to the outcome of the analyses. The model for participants' judgement as to the treatment condition was reanalysed controlling for time and initial voltage. Once time and initial voltage were controlled for there was no significant relationship between participants' judgements and the stimulation condition. (coefficient 1.090, 09% CI -0.173, 2.353, $p=0.091$).

Figure 6.2 The change in pain intensity through the course of the study for each participant.



The y axis represents the average pain intensity over the previous 24 hours measured on a 0-10cm VAS scale, the x axis represents the session number. The vertical dashed lines indicate the beginning and end of the stimulation period. The vertical red line indicates the onset of active stimulation.

6.3.7 ADVERSE EVENTS

One participant reported dizziness, which lasted for a few minutes, immediately following stimulation. This was reported on five consecutive stimulation days and always after sham stimulation. Four participants on one occasion each reported headache following the stimulation. Two of the headaches were reported following sham stimulation and two following active stimulation. One participant noted headaches on five separate days during the stimulation period, one following sham stimulation and four following active stimulation. That participant also reported a long history of regular headaches. One participant on one occasion reported an increase in a pre-existing earache pain after active stimulation. Through the course of the study one participant reported that she had notably fewer cravings for high-fat content foods.

6.3.8 POWER ANALYSIS

A post hoc power analysis based on a simple paired pre-test post-test study design suggests that to detect a moderately clinically important difference (a 30% change from baseline (20) in average 24 hour back pain intensity, with 80% power at a significance level of $p < 0.05$ would require a sample size of 15 participants. However in the current study design additional power is conferred by the collection of multiple data points per participant.

6.4 DISCUSSION

The aim of this study was to explore whether anodal tDCS applied to the motor cortex has analgesic effects in participants with chronic low back pain. The results do not provide evidence to that effect. In fact the overall change in pain and other clinical outcomes throughout the course of the study, while generally demonstrating a trend towards improvement, is minimal. Little change was observed in participants' clinical symptoms under either stimulation condition, indicating negligible placebo and non-specific effects. Indeed the mean reduction in average 24 hour pain intensity was less than 1cm on a 10cm VAS across both the active and sham stimulation conditions.

These findings are not consistent with those of existing studies of tDCS in other chronic pain conditions (Fregni, et al. 2006; Fregni, et al. 2006; Valle et al. 2009; Fregni et al. 2010; Mori et al. 2010; Antal et al. 2010). All previous published studies have concluded in favour of tDCS over sham. Notably these studies gave treatment courses of up to five stimulation sessions. In the current study all but one participant received five or more active stimulation sessions and four participants received ten or more active stimulations. The

results also demonstrate no significant change in current pain scores immediately following active stimulation.

What might explain the difference between these results and the existing literature? The small sample size raises legitimate concerns regarding the lack of statistical power to detect an effect of active tDCS over sham. This concern is reinforced by the post hoc power calculation. Nonetheless whilst small in terms of participant numbers this study was rigorously controlled with comparable statistical power to some existing studies and utilised a recommended statistical approach for this type of data (Zeger and Liang 1986) and the data demonstrate no clear trend to suggest that a larger group would have returned a different outcome. A previous study by Boggio et al. (2009) reported a significant effect in 8 participants with neuropathic pain who only received a single stimulation session.

The use of a small convenience sample significantly limits the generalizability of the findings. This was a pragmatic decision common to many clinical studies, indeed the high time requirements that the study design placed on participants made even this recruitment strategy a difficult process. As a result of convenience sampling it is plausible that through chance we may have recruited a group of participants who belong to a specific but as yet unidentified subgroup of non-responders to tDCS or that a different population may have demonstrated an effect.

Another possible explanation for these contrasting findings is that the effects of tDCS might be specific to certain types of painful conditions. A meta-analysis of individual patient data from studies of rTMS for chronic neuropathic pain (Leung et al. 2009) reported a trend towards greater efficacy in patients with centrally maintained compared to peripherally maintained pain states. However since this trend did not reach significance, it cannot be confidently concluded that rTMS is selectively effective in this way. Currently there are insufficient data related to tDCS for a similar analysis to be performed. Fregni et al. (2006) demonstrated significant improvements in pain in patients with fibromyalgia, a chronic pain syndrome that, like CLBP, is characterised by ongoing pain without a clear structural diagnosis or specific neuropathic origin, but that is associated with alterations in brain structure and function (Kuchinad et al. 2007; Nebel & Gracely 2009). However, Antal et al. (2010) noted a trend towards a smaller effect of tDCS on back pain than on pain associated with arthrosis, but the small sample size used (n=21) did not support a formal analysis of efficacy between diagnostic subgroups. As such the data regarding the specificity of

treatment effects from non-invasive brain stimulation for different conditions are inconclusive. While it is possible that tDCS might be specifically ineffective for CLBP, it is not clear what factors might underpin such an interpretation.

One further possible explanation might be that the existing evidence base is affected by a source of systematic bias. As demonstrated and discussed in the preceding chapter the existing trial literature in tDCS is dominated by small studies investigating and the risk of bias in these studies is frequently difficult to assess. It is possible that these individual study biases and a publication/ small study bias within the broader evidence base may exaggerate estimates of effect.

The analysis suggests that at least some participants may have been able to distinguish between the active and sham conditions. The use of a cross-over design and multiple daily concurrent stimulation sessions, where participants experience both conditions and can therefore make comparisons between the experience of the two may have had an influence on this outcome. Also as the stimulation period progressed participants who had a stronger grasp of the study design may have recognized that they were more likely to be receiving active stimulation. Sensitivity tests factoring time into the analysis removed the effect of stimulation condition on participants' judgements regarding the treatment condition ($p=0.091$). Consequently while it is not clearly established from these results that participant blinding was inadequate, the trend observed in this small sample indicates that a more rigorous assessment of the validity of sham tDCS at intensities of 2mA or greater is justified.

This finding also raises the question of whether the blinding of participants used in existing clinical studies can be considered robust. Validation of the sham condition at intensities of 1mA has been achieved (Gandiga et al 2006; Ambrus et al. 2012). In the current study and all existing clinical studies of tDCS except two (Fenton et al. 2009; Antal et al. 2010) for the treatment of pain, intensities of 2mA have been applied. If the blinding of participants is not truly robust this might have led some studies to exaggerate the efficacy of tDCS. One might expect blinding to be more of an issue in studies that utilise cross-over designs where participants have a direct comparison between active and sham stimulation conditions. Nonetheless in the report of the recent parallel trial by Mori et al. (16) the authors allude to having difficulties with blinding at intensities of 2mA, although, unfortunately, they do not specify what they were and no other studies have reported a formal assessment of blinding success. This issue will be considered in more detail in the next chapter.

We observed no serious or lasting adverse effects and no negative influence across a range of cognitive tests, which is consistent with previous studies. Transient headaches and nausea were reported under both active and sham conditions by a number of participants, which means at least some of them can be considered to be incidental or possible nocebo responses. In addition no deterioration was seen in performance of any of the cognitive tests and these results add to the growing body of evidence indicating that tDCS delivered with these stimulation parameters is a safe intervention.

6.4.1 STUDY LIMITATIONS

The main limitation of the current study is its small non-consecutive sample size, which has been discussed above. Another possible confounder is that the basic order of delivery of treatment condition was uniform across subjects (i.e. sham followed by active). Given that participants may have deduced that as the study progressed the probability of receiving active stimulation increased this factor might be predicted to have artificially advantaged the active stimulation condition. Nonetheless the study still returned a negative outcome which would suggest that it had little to no impact on outcome.

We estimated the location of the motor cortex without assistance from neuroimaging techniques. This is a limitation of all of the published studies of tDCS for chronic pain. This method is less accurate than fMRI based stereotactic guidance (Sparing et al. 2008) but the common use of large electrodes such as those employed in the current study makes it unlikely that this would have significantly affected our results or those of previous studies. Furthermore more sophisticated neuro-navigation techniques are unlikely to be available or affordable in standard clinical practice and would likely make this intervention unfeasible for general clinical use.

Throughout the course of the study a number of participants missed treatment sessions due to unavoidable events (in addition to weekends) and where this interrupted treatment on consecutive days it may arguably have detracted from the clinical efficacy of stimulation. This reflects the common reality of day to day clinical practice and participants who did not miss sessions did not demonstrate a better response to those who did.

The VAS used to investigate the adequacy of participant blinding was novel and has not been validated for this purpose in any participant group. As such it is possible that it lacked sensitivity and validity in this regard. Similarly we utilized a range of cognitive tests in an attempt to more sensitively investigate unexpected or unwanted affects on brain function. This was additional to specifically asking about adverse events. The tests used were chosen

to broadly investigate cognitive function but they have not been specifically validated as markers of cognitive deterioration. Finally the data analysis process was not performed under blinded conditions. This introduces a potential source of bias as it is possible that this may have affected the analysis process.

6.4.2 CONCLUSIONS

The results of this exploratory study do not provide evidence that tDCS to M1 is effective in reducing chronic low back pain. This is the first study to investigate this treatment modality in CLBP and the results are not consistent with existing studies of tDCS for chronic pain conditions. The use of a small convenience sample limits the generalizability of these findings and precludes definitive conclusions. A secondary purpose of this study was to explore which parameters of stimulation might be optimal for use in a future randomized controlled trial. However the lack of an apparent effect gives no useful information in this regard and does not suggest that the results of such a trial might favour tDCS for CLBP. There is some preliminary evidence that the sham controls regularly employed in clinical trials of tDCS may not be optimal in terms of participant blinding. It follows that in order to be able to confidently interpret the findings of clinical studies using 2mA tDCS a full and thorough investigation into the validity of blinding in these studies is of critical importance. The next chapter describes a study designed and conducted to achieve this.

CHAPTER 7. STUDY 3. IS BLINDING TO THE STIMULATION CONDITION MAINTAINED IN TRIALS COMPARING 2MA tDCS WITH SHAM STIMULATION? A CROSS-OVER STUDY.

(Study published as: O'Connell NE, Cossar J, Marston L, Wand BM, Bunce D, Moseley GL, De Souza LH (2012) Rethinking clinical trials of transcranial direct current stimulation: Participant and assessor blinding is inadequate at intensities of 2mA. PLoS One. 7 (10) e47514. See Appendix 6)

7.1 INTRODUCTION.

As discussed in previous chapters one of the stated key benefits of tDCS over other non-invasive brain stimulation methods is the ease at which the stimulation condition can be blinded through the use of a sham stimulation condition (Priori et al. 2009). Sham tDCS involves an identical process to active stimulation but, without the knowledge of the participant, the stimulator is switched off after around 30 seconds. This brief stimulation period is not considered to elicit any significant effect on brain activity (Nitsche et al. 2008).

As mentioned in the previous chapter, Gandiga et al. (2006) reviewed the results of two cross-over studies involving participants undergoing tDCS at 1mA intensity or sham stimulation to assess whether adequate blinding was achieved. They found that the duration of sensations and amount of discomfort was comparable between stimulation conditions and that active stimulation could not be distinguished from sham by either participants or blinded investigators. This study offers some empirical evidence that sham controlled studies of tDCS at 1mA intensity are successfully blinded, although the study does have limitations that should be considered. As the study was a secondary analysis of two studies with differing aims it was not specifically designed or powered to test the integrity of blinding. Nonetheless 24 healthy volunteers and 23 stroke patients could not distinguish between the stimulation conditions. Gandiga et al. (2006) also report that investigators could not distinguish the condition either. However there is no description of the methods by which this was established and no data are presented to substantiate this in the study report. It is therefore difficult to judge the veracity of this claim. Recently Ambrus et al. (2012) conducted a primary study to establish whether this sham control ensures adequate blinding at 1mA. Their results suggest that in both naïve participants and those with previous experience of tDCS there was no significant difference between the strength of the perceived stimulation under active or sham conditions. Interestingly under both conditions participants often reported experiencing ongoing subjective sensations

even when, under the sham condition, the stimulation had ceased. It is important to state that while Gandiga et al. (2006) ramped the initial increase at the onset of stimulation over 10 seconds, Ambrus et al. (2012) ramped the current increase over a longer timeframe (20 seconds) and ramped the final decrease over 10 seconds, which may have reduced the intensity of perceived sensations.

Problems with study blinding at higher stimulation intensities may arise due to the increased frequency and intensity of sensations elicited (Brunoni et al. 2011). Out of six trials of tDCS for chronic pain identified in the Cochrane review reported in chapter 5, five used stimulation intensities of 2mA (Fregni et al. 2006; Fregni et al. 2006; Boggio et al. 2009; Valle et al. 2009; Mori et al. 2010). Only one of these studies (Mori et al. 2010) reported difficulties with participant blinding but did not discuss the specific details of the problems. The remaining studies did not report a formal assessment of participant or assessor blinding.

Conversely two parallel trials of 2mA tDCS for treating depression reported that effective treatment masking was maintained (Loo et al. 2010, Loo et al. 2012) though it is worth noting that neither trial would have been designed with adequate power to test the blinding thoroughly. As described in chapter 6 the results from the preceding study in this thesis suggest potential problems with participant blinding. In that study all participants received both active and sham stimulation. The use of a cross-over design might be particularly problematic because exposure of participants to both active stimulation and sham increases the likelihood that they will distinguish one as more credible than the other. However the finding of inadequate participant blinding in that study was no longer apparent in a sensitivity analysis so it is not clearly established that participant blinding is inadequate at this intensity.

In addition to concerns over blinding of participants, assessor blinding may also be threatened in tDCS studies. Stimulation can result in noticeable temporary skin redness at the electrode sites, predominantly the reference electrode commonly placed on the forehead, that might reveal the stimulation condition to an assessor (Brunoni et al. 2011). In the previous study this skin redness was not measured or recorded although anecdotally in some participants on some days it was noticeable. While Gandiga et al. (2006) offer an assertion, unsupported by reported data, that investigator blinding was maintained at 1mA intensity they did not mention whether skin redness occurred or presented a challenge to blinding. Given that this redness may last for a short period post stimulation, if it only

occurs under the active stimulation condition it must be considered to offer a potential cue to assessors and participants regarding the stimulation condition. This has not been systematically evaluated to date at any stimulation intensity.

No studies to date have directly tested the validity of sham tDCS at intensities of 2mA. This question is pressing given that tDCS is being investigated as a potential clinical tool. A recent review of challenges for tDCS research identified the need for such studies (Brunoni et al. 2011). The aim of this study was to examine the validity of double blinding under these conditions. To adequately assess whether existing clinical studies might be regarded as effectively blinded the study was designed to replicate the most commonly reported approach to sham stimulation reported in clinical trials of tDCS

7.1.2 RESEARCH QUESTION AND HYPOTHESES

The primary research questions were “At stimulation intensities of 2mA do people correctly judge the true stimulation condition more than would be expected by chance and is this judgement influenced by previous exposure to sham or real stimulation?” and “at stimulation intensities of 2mA is skin redness at the visible electrode site more visible to the blinded assessor following active stimulation compared with sham?”.

7.1.2.1 STUDY HYPOTHESES

The hypotheses were as follows:

PARTICIPANT BLINDING

Participants will correctly judge the stimulation condition more frequently than would be expected by chance.

ASSESSOR BLINDING

The assessor will report visible skin redness under the electrode site significantly more frequently after active stimulation than after sham.

7.2 METHODS

7.2.1 ETHICAL APPROVAL AND INFORMED CONSENT

This study had full approval from the School of Health Sciences and Social Care Research Ethics Committee, Brunel University and conformed to the Helsinki declaration. All participants gave written informed consent. See Appendix 4 for the participant information sheet, consent form and ethical approval documentation pertaining to this study

7.2.2 DESIGN

This study used a double blind randomised cross-over design. The cross-over design was chosen as it would allow for the adequacy of study blinding to be tested for both parallel designs (by analyzing only the first stimulation session) and cross-over designs.

7.2.3 PARTICIPANTS

Healthy individuals, aged over 18 were recruited from staff and students at Brunel University and their family and friends. Participants must have had no prior experience of tDCS stimulation. Exclusion criteria were prior / existing history of neurological disease, psychiatric disorder, dyslexia, diabetes, epilepsy, head injury, musculoskeletal or neurological injury to the limb, dermatological condition affecting the scalp, poor understanding of written English or any other communication impairment.

7.2.4 RECRUITMENT

Participants were recruited from staff and students at Brunel University through the use of posters, online advertisements and group emails. To establish conditions that best reflected what might occur in clinical trials of tDCS participants were misdirected regarding the true research question. We misinformed participants that the study aimed to investigate the potential effects of tDCS on a word memory recognition task. The purpose of this deception was to reduce the likelihood that participants would afford more attention to distinguishing between the active stimulation and sham conditions than they might during a clinical trial of tDCS. However in the event that blinding was found to be adequate we planned to perform a formal analysis of the effect of tDCS on performance of this task. Participants were informed that the study would involve both real and sham stimulation but they were not informed about the true research question. We made this deception clear in our application for ethical approval and received approval (see Appendix 4) to proceed in this way.

7.2.5 OUTCOMES

Since the primary aim was to assess the adequacy of blinding the primary outcome was participant's judgments as to the type of stimulation that they had just received. This was measured using a YES/ NO answer to the following question:

“Do you feel that you have just received the real brain stimulation?”

It is possible that differences in the experience between active and sham stimulation may not be sufficient to influence participant's overall judgement but may affect their confidence in that judgement, and thereby influence the magnitude of a placebo effect. To

try to capture this possible effect participant's confidence in their judgement of the stimulation condition was measured using a 10cm Visual Analogue Scale (VAS) of the participant's confidence in that judgement worded as follows:

"Please place a mark on the line below that best represents your level of confidence in that judgement."

The left anchor was labelled "not confident at all" and the right anchor was labelled "completely confident".

To answer the second research question the blinded assessor documented every occasion that the participant had noticeable skin redness at the visible electrode site(s) following stimulation. This was documented as a simple YES/NO response. No formal threshold of skin redness was used as we wished to simply note when the assessor might be aware of noticeable redness in a clinical trial.

Participants were not questioned further regarding their perceptions or sensations during or after the stimulation to avoid making this the focus of their attention during the study, which might encourage a level of scrutiny of the stimulation condition and its associated sensations that is greater than would be expected in a clinical trial.

7.2.6 PROCEDURE

7.2.6.1 RANDOMISATION, ALLOCATION CONCEALMENT AND BLINDING

All eligible participants were randomised to an order of stimulation (active followed by sham, or vice versa). The randomisation schedule for all participants was established prior to recruitment by an independent administrator using a computer generated random numbers sequence (<http://www.randomizer.org/>). A randomly generated list of numbers 1 and 2 was generated (1= active stimulation first, 2= sham stimulation first) and each of these numbers was sealed in an opaque envelope with a corresponding participant number. The corresponding envelope was accessed for each consecutive participant on the day of the first stimulation session by the sole unblinded researcher who delivered the stimulation and who had no involvement in the recruitment or assessment process. Neither the participant nor the assessor were informed of the stimulation order and the blinding code was maintained until all participants had completed the study.

Participants visited the laboratory twice with a minimum 2 week washout period between visits. At each visit participants completed the word memory task, and then received their

stimulation (active or sham). Participants were then asked to report any adverse events and this was followed by a repeat of the word memory task. Following this the participants were asked to complete the form concerning their judgement of the stimulation condition. Although this was the primary research question this was undertaken at the end of the visit to appear secondary. The question and the participant's response were discussed in no more detail than that required for successful completion.

7.2.6.2 TDCS STIMULATION.

tDCS was delivered using a battery driven CX-6650 ramp controlled DC stimulator (Rolf Schneider Electronics, Germany). Current was delivered by electrodes encased in sponge pads (35cm² soaked with 0.9% (155mMol) saline solution. The machine was kept behind the participant and out of their view, and out of the blinded assessor's view for the entire stimulation period. For both the active and sham conditions, the anode was placed over the left motor cortex of the subject and the cathode was placed over the contralateral supraorbital region. Electrodes were secured using soft elastic straps. The location of the motor cortex was estimated using the international 10-20 EEG system, with the centre of the electrode pad located 1cm anterior and 4cm lateral to the vertex.

In the active stimulation condition a constant current of 2mA intensity (current density 0.057 mA/cm²) was applied for 20 minutes with a 5 second ramping phase at the beginning and end of stimulation. In the sham stimulation condition the machine was activated using identical parameters but was switched off without the participant's knowledge after 30 seconds. The researcher who applied the stimulation recorded the voltage levels 30 seconds after the onset of stimulation.

7.2.6.3 THE MEMORY TASK

In order to maintain the impression that the study aimed to test the effects of tDCS on memory a standard word recognition test of episodic memory performed by the participants on a laptop computer using E-Prime software (©Psychology Software Tools, Sharpsburg USA) was used. This was the same memory task used in the previous study (see Chapter 6), using the 4-choice reaction time task also described there as a distracter.

7.2.7. DATA ANALYSIS

For the primary analysis, the data from each session were analysed separately to answer the research question for parallel and cross-over study designs. Analyses were performed using IBM SPSS version 18 statistical software. Blinding was broken at the end of the data collection phase and, as such, data analysis was not blinded.

The Kappa measure of agreement (κ) was used to test whether participants successfully judged the stimulation condition more than would be expected by chance and to test whether the assessor noticed a visible redness following stimulation on the skin under the electrode sites more commonly after active stimulation than they did after sham. This was, in almost all cases, observed under the reference electrode (cathode). This test is more appropriate than a simple measure of agreement as it factors in the degree of agreement expected by chance alone (Altman 1991). Cut-offs for characterizing the level of agreement were <0.2 poor, 0.21-0.4 Fair, 0.41-0.6 Moderate, 0.61-0.8 Good, 0.81-1 very good (Altman 1991).

As the data were not normally distributed, differences in participants' confidence in their judgements were investigated using the appropriate non-parametric test with the following factors: stimulation condition (active/sham; Mann Whitney-U test), participant's judgements regarding whether they had received active stimulation (yes/no; Mann Whitney U test) and the session number (first/second; Wilcoxon Signed Rank test). We accepted statistical significance for all tests at $\alpha < 0.05$.

7.3 RESULTS

7.3.1 SAMPLE SIZE

No data were available on which to base a sample size calculation for dichotomised YES/NO judgements. Therefore a sample size calculation was calculated to provide adequate power to detect a change of the size seen on the VAS tool used to measure participant blinding described in Chapter 6, section 6.2.4.2. It should be acknowledged that this tool is different from that used to measure participants' confidence regarding their judgement of stimulation condition in this study (see section 7.2.5).

From this data the standardized difference was calculated as recommended by Whitley and Ball (2002) as 0.578. Using the Altman (1991) nomogram to detect a change of 0.9mm on that 100mm scale with 80% power at $p < 0.05$ would require a sample size of around 92. This was rounded up to 100 to account for drop out. It should be considered that this sample size is likely to be conservative since participants in that study received many repeated stimulations on a daily basis which over time is likely to have dulled the contrast between active and sham stimulation. If this sample size is insufficient to detect a difference it is unlikely that inadequate blinding represents a substantial source of bias in existing trials of tDCS, all of which have smaller sample sizes.

7.3.2 PARTICIPANTS

Figure 7.1 shows a flow diagram of participant flow through the study. Of 102 participants considered for eligibility, 100 were recruited into the study of which 75 were female and 89 were right handed. The mean (SD) age was 24(8.3), range 18-62. One female participant from the group randomised to receive sham stimulation first withdrew in the first session as they could not tolerate the stimulation. The remaining 99 participants completed the first stimulation session in full of whom 54 were randomised to active followed by sham. Three further participants (2 female) did not attend for a second session, one from the group allocated to receive sham first and 2 from the group allocated to receive active stimulation first. Two stated that they were too busy to participate further and one did not respond to correspondence. All withdrawals were participants randomised to receive sham stimulation followed by active stimulation. We obtained complete datasets from 96 participants.

7.3.3 METHODOLOGICAL CHECKS

Participants' confidence ratings and the initial stimulation voltage were not normally distributed. Therefore we used the nearest equivalent non-parametric statistical tests to analyse this data.

7.3.4 PARTICIPANT BLINDING

Table 7.1 presents the data for participant's judgements of the stimulation condition.

7.3.4.1 SESSION ONE

72% of participants who received active stimulation, and 56% of participants who received the sham, correctly judged the stimulation condition. Overall, 65% of participants correctly judged the stimulation condition they received which represents a "fair" level of agreement ($\kappa=0.28$, 95% confidence interval (CI) 0.09 to 0.47 $p=0.005$).

7.3.4.2 SESSION TWO

89% of participants who received active stimulation and 88% of participants who received sham judged correctly, which represents a "good" level of agreement ($\kappa= 0.77$, 95%CI 0.64 to 0.90), $p<0.001$).

Figure 7.1 Chart illustrating participant flow through the study.

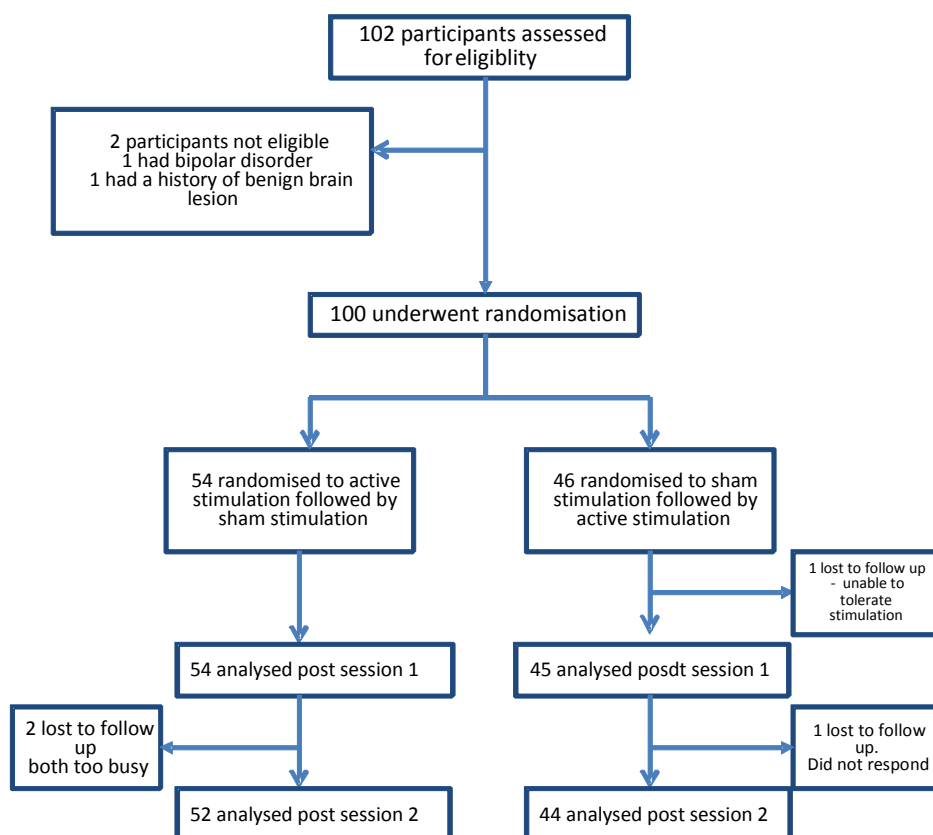


Table 7.1. Participant’s judgements of the stimulation condition, for each session. (“Yes” reflects a judgement of active stimulation, “No” reflects a judgement of sham stimulation.)

Participants Judgements		Stimulation condition		Totals
		Active Stimulation	Sham Stimulation	
Session 1	Judged “yes”	39	20	59
	Judged “no”	15	25	40
	Totals	54	45	99
Session 2	Judged “yes”	39	6	45
	Judged “no”	5	46	51
	Totals	44	52	96

7.3.4.3 PARTICIPANT CONFIDENCE

Table 7.2 presents the median participant confidence and the initial voltage for both stimulation sessions. Participants' confidence in their judgement of the stimulation condition was significantly higher in the second stimulation session (median (IQR) 6.55 (1.85 to 7.3) than it was the first stimulation session (5.6 (3.77 to 8.48)) (Wilcoxon signed rank test, $p < 0.001$). Confidence was higher where participants judged that they received active stimulation in the first session (median (IQR) judged "Yes" 6.4 (2.3 to 7.9), judged "No" 3.050 (1.65 to 6.65), Mann Whitney U test $p = 0.028$) but not in the second stimulation session (judged "Yes" 7 (5.25 to 8.8), judged "No" 6 (2.7 to 8), $p = 0.173$).

Table 7.2 Median (IQR) values for participant confidence and initial stimulation voltage for both sessions and actual and perceived stimulation conditions.

	Session 1		Session 2	
Actual stimulation condition	Active	Sham	Active	Sham
Initial voltage	9.2 (7.6 to 12.6)	9.4 (7.7 to 11.5)	9.3 (8 to 12.5)	9.3 (8 to 12.3)
Participant confidence	5.5 (2.4 to 7.6)	5.8 (1.7 to 7.3)	6.7 (4.7 to 8.6)	6.3 (2.8 to 8.4)
Participant's judgement of stimulation condition	Active	Sham	Active	Sham
Participant confidence	6.4(2.3 to 7.9)	3.05 (1.65 to 6.65)	7 (5.25 to 8.8)	6 (2.7 to 8)

7.3.5 ASSESSOR BLINDING

Table 7.3. presents the data for assessors judgements of noticeable skin redness at electrode sites post-stimulation.

The assessor noticed skin redness at the electrode site(s) following stimulation significantly more often following active stimulation than following sham stimulation in both the first session, with a "moderate" level of agreement ($\kappa = 0.512$, 95%CI 0.363 to 0.66, $p < 0.001$), and in the second session ($\kappa = 0.677$, 95%CI 0.534 to 0.82, $p < 0.001$). Skin redness was noted after 60% of active stimulation sessions and after 1% of sham stimulation sessions.

7.3.6 STIMULATION VOLTAGE

The median voltage (IQR) at the start of stimulation was 9.2 (7.7 to 11.8). To test whether the initial voltage may have influenced our results the initial stimulation voltage was compared between stimulation conditions (active versus sham) and between participants' judgements (judged "yes" or "no" to whether they thought they had received active stimulation). No significant difference in voltage was observed for either comparison (Kruskal-Wallis test, by stimulation condition $p=0.693$, by participants' judgement $p=0.377$)

7.3.7 MISSING DATA/SENSITIVITY ANALYSIS

To test whether the missing data may have significantly influenced our findings we reanalyzed the data on participants' judgements substituting all correct responses for the missing values, and then substituting all incorrect responses for the missing values. We did this separately for each stimulation session. The results remained significant, for both the first and second sessions, with both approaches (all incorrect session 1, $\kappa = 0.268$, 95% CI 0.088 to 0.456; session 2 $\kappa = 0.699$ 95%CI 0.559 to 0.839. all correct session 1 $\kappa=0.29$ (95%CI 0.102 to 0.47; session 2 $\kappa=0.779$, 95%CI 0.659 to 0.902).

Table 7.3. Assessors' judgements of skin redness at the electrode site, for each stimulation condition and each session.

Assessors Judgements		Stimulation condition		Totals
		Active Stimulation	Sham Stimulation	
Session 1	Skin redness noticeable	30	1	31
	No skin redness noticeable	24	44	68
	Totals	54	45	99
Session 2	Skin redness noticeable	29	0	29
	No skin redness noticeable	15	52	67
	Totals	44	52	96

7.3.8 ADVERSE EVENTS

There were no serious adverse events. When the first session was active stimulation, four participants reported an itch that was perceptible throughout the duration of stimulation.

One of these participants reported a strong tingling that persisted for the first 2 minutes of stimulation. One participant reported a strong tingling sensation throughout the stimulation and one reported feeling dizzy and drowsy during the stimulation. When the first session was sham, one participant reported mild dizziness during and immediately after, one was unable to tolerate stimulation in the initial 30 second “on” phase due to dizziness and withdrew from the study, although these symptoms had resolved five minutes post stimulation. In the second stimulation session, one participant reported mild dizziness during sham stimulation and one reported feeling drowsy during and immediately after active stimulation.

7.3.9 MEMORY TASK DATA

The memory task was used primarily to distract participants from the true aim of the study. Given that the results have demonstrated that blinding of participants is imperfect it would be problematic to confidently attribute any observed effect to the effects of stimulation, or indeed to the placebo effect. As such this data was not analysed further.

7.4 DISCUSSION

Our results indicate that this approach to sham stimulation does not ensure adequate blinding of participants. For a proportion of tDCS naïve participants blinding is maintained, but the probability of a participant correctly identifying the stimulation condition is greater than would be expected by chance. Given the relatively low agreement in the first session it is unlikely that this would have impacted upon the results of parallel studies in a substantial way but the threat to participant blinding is substantially worse for cross-over trials. Participants were more confident in their judgement where they judged that they were receiving active stimulation after the first session, though this difference diminished by the second stimulation.

It is highly likely that the increased sensory correlates of active stimulation were responsible for compromising participant blinding. Familiarity with the experience of active or sham stimulation and the ability to compare between sessions amplified this effect at the second stimulation session. Reports of persistent itch or tingling during stimulation in response to the adverse events question are suggestive of this. While only a minority reported these sensations, most participants probably did not consider them relevant when asked about adverse effects and to avoid giving clues to the real purpose of the study specific questioning regarding the sensory experience of stimulation was avoided. Assessor blinding was also compromised in a substantial proportion (60%) of active stimulations

across both sessions. This represents an important potential source of bias regardless of study design.

These results require a re-appraisal of some of the existing literature relating to tDCS. Focusing on clinical studies, almost all trials in chronic pain have used 2mA intensity (Fregni, et al. 2006a; Fregni, et al. 2006b; Valle et al. 2009; Fregni et al. 2010; Mori et al. 2010) and similar electrode montages. But this issue does not just extend to clinical trials in pain, as tDCS has been investigated and promoted for a range of clinical conditions, such as depression, stroke and cravings. A 2009 review reported that the majority of sham controlled trials in depression used this intensity (Nitsche et al. 2009), as have more recent depression trials (Loo et al. 2009; Loo et al. 2012) and the same applies for all trials of tDCS for reducing cravings (Boggio et al. 2008; Fregni et al. 2008; Goldman et al. 2011; Montenegro et al. 2012). All of these studies have reported superior efficacy of active stimulation over sham. While we cannot accurately predict the degree of influence that inadequate blinding may have had in these studies, there is robust meta-epidemiological evidence that incomplete blinding leads to exaggerated effects in clinical studies with subjective outcomes such as pain or depression (Wood et al. 2008) and non-specific effects of interventions such as placebo effects are known to be important in such clinical conditions (Hróbjartsson & Gøtzsche 2010; Brunoni et al. 2009). A Cochrane review suggests that placebo effects are larger with physical interventions (Hróbjartsson & Gøtzsche 2010) such as tDCS. Combined these factors require that the results of studies of 2mA tDCS be interpreted with caution. Such caution is particularly recommended given the developmental stage of clinical research in tDCS where, as discussed in previous chapters, small study effects and publication bias may also influence the evidence base with a propensity for negative studies to not reach full publication (Hopewell et al. 2009; Nuesch et al. 2010).

How might blinding of tDCS at this intensity be improved? In this study the recommended and commonly used strategies of ramping the initial increase and the final decrease of the current to reduce the contrast in sensations between the on and off position (Brunoni et al. 2011), and the soaking of electrode pads in saline solution of a concentration associated with reduced sensation and increase comfort (Dundas et al. 2007) were employed. It is possible that longer ramping times at the beginning and end of stimulation may improve participant blinding. There is some evidence for such an approach at intensities of 1mA, though only in naïve participants (Ambrus et al. 2012) but this may not be sufficient where

participants are aware of sensations throughout the stimulation period. McFadden et al. (2011) demonstrated that the pre-application of topical anaesthetics to electrode sites substantially reduced, but did not abolish the sensations associated with stimulation, although the same process would be difficult at more posterior locations in participants with substantial amounts of hair at the location of the anode. This may not present a major issue as studies have demonstrated that, at least at intensities of 1mA, the anterior electrode is the most frequent location that sensations are felt, possibly due to the greater skin sensibility in this region (Ambrus et al. 2012; Dundas et al. 2007).

Assessor blinding might be ensured by having the participant wear headgear which conceals the area under the electrodes. However the persistence of noticeable skin redness beyond the immediate post-stimulation period represents a further challenge to participant blinding. Arguably it suggests that our results may underestimate the scale of the problem in trials where stimulation is applied on multiple occasions. It is difficult to think of a clear solution to that issue, particularly as Brunoni et al. (2011) suggest that the redness can in some instances persist for several days post stimulation. Misinforming participants that the skin redness is a normal reaction to the damp electrodes rather than a reaction to stimulation itself might mitigate this to some degree. Future studies of tDCS may benefit from other methods to optimise blinding, for example de facto masking (Berger 2012), in which the treatment is not blinded but both treatments are presented as the active one. De facto masking might be more problematic if a non-stimulation sham is used that carries less credibility with participants but would seem very possible if the "sham" condition used is active tDCS over a distinct brain area that is not hypothesized to elicit specific treatment effects. The use of assessors who are themselves naive to tDCS and less sensitive to the possible cues that indicate the stimulation condition might improve the rigour of blinding. In addition the collection of outcome measures at timepoints beyond the duration of skin redness would also solve this problem although this would impair the ability of a study to investigate any immediate short-term effects.

Novel forms of DC stimulation are emerging that might also improve participant blinding. Transcranial Random Noise Stimulation (tRNS) delivers a current intensity that is randomly oscillated at high frequency. Similar to tDCS, weak tRNS applied for 10 minutes increases cortical excitability for up to 1 hour (Terney et al. 2008). A study of the cutaneous perception thresholds for stimulation found that tRNS had a higher threshold (Ambrus et al 2010). The threshold intensity for 50% of participants to detect sensations was 1.2mA for

tRNS compared with 0.4mA for tDCS. While this is still below the 2mA used in most clinical studies it seems reasonable to suggest that this method might achieve more adequate participant blinding as the degree of sensations is diminished. Finally it appears that varying the shape of the electrode pads does not make a meaningful difference to the perception of tDCS and so does not offer the potential for improved blinding (Ambrus et al. 2011). Any modified sham protocol will require rigorous testing to ensure adequate blinding and ensuring adequate blinding with modified sham protocols should be a research priority in this field.

It is not clear that this higher stimulation intensity is necessary to ensure clinical efficacy. The underlying rationale for tDCS are its effects on cortical excitability which have been clearly demonstrated at intensities of 1mA (Nitsche et al. 2008) and there is evidence to suggest that successful participant blinding is achievable under these conditions (Gandiga et al. 2007, Ambrus et al. 2012). Antal et al. (2010) reported a positive effect of 1mA tDCS applied to M1 on chronic pain. Using intensities of 1mA in future research may represent a more methodologically sound option, though it is plausible that reducing the intensity may impact upon potential efficacy. Whether the presence of skin redness presents a challenge to blinding at this lower intensity is unclear. As discussed Gandiga et al (2006) report adequate assessor blinding but reported no specific methodology and presented no data to this effect.

This study has some limitations. The perceptual correlates of stimulation were not examined in any detail. This decision was taken to minimise the risk that participants would over-scrutinize the experience of tDCS, which was felt would not accurately reflect the conditions of the average clinical trial. As such it is not possible to tell with confidence which factors most impacted on blinding. The VAS scale that we used to measure participant's confidence in their judgements has not been specifically validated for that task and may have lacked sensitivity and validity. The use of specific cut-offs to define the kappa level of agreement is arbitrary and recommended cut-offs do vary between sources, with little to guide a decision on which is most valid. The "fair" level of agreement seen in session one on participant's judgements could have been judged "poor" using different criteria. As such it is more informative to look at the actual percentage agreement across stimulation conditions to establish the size of the difference. The data analysis process was not performed under blinded conditions. This introduces a potential source of bias as it is possible that this may have affected the analysis process.

Finally retrospectively it may have been useful to take the assessor's view on whether they felt that the participants had received active or sham stimulation. While documenting when the assessor noticed skin redness after stimulation acts as a surrogate measure of this, through interaction with participants for whom blinding was imperfect it is plausible that verbal and non-verbal cues might influence assessor blinding. Using a similar tool to that used by participants may have added value. As discussed above the use of an assessor who was not naïve to the process of tDCS and the possible cues to the stimulation condition may have compromised assessor blinding to a larger extent, though this is likely to have been the case in most existing tDCS clinical studies.

In conclusion this is the first study to formally assess the validity of this sham procedure and provides evidence of inadequate blinding. This has important implications for the interpretation of studies which have utilised this approach and subsequently for the conclusions of the Cochrane review in this thesis. It also presents a significant challenge for the design of future tDCS studies.

CHAPTER 8 DISCUSSION

8.1 INTRODUCTION

Through a critical review of the existing literature this thesis identified the need to develop more effective therapies for CNSLBP and CLBP generally. It has outlined the growing evidence to support the role of altered CNS processing in CLBP, thereby establishing the CNS, and the brain particularly, as a potential target for new therapeutic approaches. The theory behind and physiological evidence underpinning the use of brain stimulation in the treatment of pain is described and leads to the question of whether brain stimulation might be an effective treatment option for chronic pain broadly and CNSLBP specifically. This question has led to three novel research projects which contribute substantially to knowledge in this field. Together these studies have rigorously and systematically assessed the strength of the existing evidence regarding the efficacy of NIBS techniques for treating chronic pain, provided the first well controlled exploratory study into the use of tDCS for the treatment of CNSLBP and the first rigorous assessment of study blinding in tDCS at 2mA. While in depth discussions of each study have been provided in chapters 5, 6 and 7, this chapter will summarise the new knowledge that arises from these studies, consider the implications of this knowledge for our understanding of brain stimulation as a treatment for chronic pain and CNSLBP and identify important avenues for further research.

8.2 DOES THE EXISTING EVIDENCE INDICATE THAT NIBS TECHNIQUES ARE EFFECTIVE FOR TREATING CHRONIC PAIN?

This was the first systematic review to meet the requirements of the Cochrane collaboration, whereas previous reviews had failed to apply a rigorous approach to data synthesis or to assessing the methodological quality and risk of bias within the existing evidence base. As such it can be argued that this is the first genuinely reliable and systematic comprehensive review in this field and the conclusions of this review are subsequently more circumspect than those of previous narrative and systematic reviews. The results of the review suggest that high frequency rTMS applied to the motor cortex may have a small short term effect on pain intensity but that blinding of participants is likely to have been suboptimal in these studies and may have resulted in exaggerated effect sizes. Despite this the observed effects do not clearly meet the threshold for a clinically important difference. This may be because the effect arises from the pooling of studies that only delivered a single dose of stimulation. The limited data available from multiple dose studies is less clear, and does not consistently demonstrate benefit. More

evidence is clearly needed but the lack of a clear dose-response relationship in terms of the number of stimulation sessions applied cannot be considered to be a positive indicator.

There are numerous potential explanations for this, including continued uncertainty about the optimal stimulation parameters and heterogeneity, both of the stimulation parameters utilised and the clinical characteristics of the participants in these trials. In fact, most studies recruited participants with neuropathic pain that had proven refractory to all previous interventions and this might bias against rTMS, which might have performed better in a less severe or intractable patient population. Conversely the observed positive effects may have simply resulted from study and reporting biases rather than a specific effect of rTMS. In previous chapters we have considered that in addition to internal study biases, the evidence base and pooled estimates of effect may be affected by small study biases.

While limited data suggest that CES is ineffective, a few small trials suggest a positive effect of tDCS applied to the motor cortex, though the estimate of effect size is imprecise. These studies investigated tDCS for a variety of conditions, but at the time of the review and the undertaking of the exploratory study, none had specifically tested tDCS as a treatment for chronic low back pain. Since then one study has been published (Antal et al. 2010, discussed in chapter 6) that investigated the use of tDCS for a mixed diagnostic group including some participants with CLBP but no other study has investigated CLBP exclusively and this gap, in conjunction with the positive exploratory evidence identified in the systematic review led to the development of the clinical exploratory study.

8.3 DOES TDCS APPLIED TO THE MOTOR CORTEX OF PATIENTS WITH CNSLBP REDUCE PAIN COMPARED WITH SHAM STIMULATION?

The exploratory study undertaken here (O'Connell et al. 2012a) was the first and remains the only study to date to specifically investigate the use of this modality in CLBP. The dosage of tDCS in existing studies seems to have been selected rather arbitrarily, and no theoretical or evidence-based rationale has been presented for this. Most studies delivered 20 minutes of 2mA intensity stimulation for 5 days, probably because the first published clinical trial (Fregni et al. 2006a) reported this to be effective. The current study was the first to explore the possible effect of varying dosage on the efficacy of tDCS and incorporated the rigour offered by randomisation, allocation concealment and efforts towards double-blinding. No effect of tDCS was observed over sham stimulation. This puts our findings at odds with those of existing published trials. It is possible that our study

simply lacked sufficient power, or that by chance a sample of non-responders were recruited into the study. Lack of power is an issue with most exploratory studies and at an overall group level is a serious limitation. However the choice of design using multiple time-points and a recommended statistical approach maximised the within-participant power to detect a change.

These results from the current study do not suggest that tDCS is effective for CNSLBP but given the limitations acknowledged above they do not offer conclusive evidence against such an effect. The study was planned in part to provide exploratory data upon which to choose the optimal stimulation parameters to inform the design of an RCT. The lack of any observable effect makes that process difficult. The observation that blinding may be inadequate strongly suggested that there was a more urgent need to interrogate the assumptions that trials of tDCS at 2mA achieve effective blinding. Were this not the case then a significant risk of bias in existing studies and a challenge to the design of future studies will have been identified. To proceed with a larger RCT of 2mA tDCS without confirming the adequacy of study blinding risked producing data of questionable reliability.

8.4 DO CLINICAL STUDIES OF 2MA TDCS ACHIEVE EFFECTIVE BLINDING TO THE STIMULATION CONDITION?

The data from the exploratory study suggested the possibility that blinding may not be maintained at stimulation intensities of 2mA. Remarkably clinical trials in tDCS have largely adopted this stimulation intensity under the assumption that it is associated with effective blinding of participants and assessors and yet evidence only exists that blinding is adequate at a stimulation intensity of 1mA, which is associated with less sensation. Without rigorous assessment of the validity of this assumption some doubt must remain over trials of 2mA tDCS, as blinding is widely recognised as fundamental to the internal validity of clinical trials (Higgins and Green 2008). On this basis the third and final study in this thesis (O'Connell et al. 2012b) aimed to carry out such an assessment. In an adequately powered and rigorously controlled study, in which steps were taken to mimic the conditions of a clinical trial of tDCS we found that participant blinding was imperfect, particularly in studies with a cross-over design, and that assessor blinding was also compromised. This study has fundamental importance to the field of tDCS clinical research as it represents the first time that the integrity of study blinding has been formally investigated and the findings demand a reappraisal of many published trials of tDCS in chronic pain and for a number of other conditions.

The findings of this study also have direct implications for the conclusions of the Cochrane review presented in this thesis. The trials of tDCS included in that review were assessed as having a low risk of bias for participant and assessor blinding based on the assumption of adequate blinding. Cochrane reviews are updated every few years with the addition of newly published studies. However in addition to that exercise there is a strong case for revising the risk of bias assessment of the existing tDCS trials that used 2mA stimulation as being at unclear or high risk of bias on the criteria of participant and assessor blinding. It follows that there is also a case for moderating the conclusions of the review. Specifically the knowledge that existing trials of tDCS cannot be confidently considered to be effectively blinded would require an explicit statement to the effect that not only is the evidence for tDCS limited to a small number of small studies and the estimate of effect too imprecise from which to draw firm conclusions but inadequate blinding introduces a further risk of bias that might have exaggerated the observed effect of all of the studies that applied a stimulation intensity of 2mA.

8.5 THE IMPLICATIONS OF THESE FINDINGS AND RECOMMENDATIONS FOR FUTURE RESEARCH

There are a number of reasons to be circumspect regarding the evidence base for NIBS as a treatment for chronic pain. While there is exploratory evidence that rTMS and tDCS might reduce pain intensity, it is not clear that such an effect reflects a clinically important change and due to a number of sources of potential bias within individual studies and the evidence base as a whole, the observed effects themselves should be interpreted with caution. As arguably the most reliable assessment of the evidence to date our review has already achieved a substantive impact having been cited by and used to inform the development of the South African guidelines for the management of neuropathic pain (Chetty et al. 2012) and the French guidelines for the use of rTMS (Lefaucheur et al. 2011).

It follows from the findings of this review that it would be premature to approve the widespread use of any NIBS method for the treatment of chronic pain related to any condition at this time. While evidence exists that non-invasive brain stimulation may have potential as a treatment modality for chronic pain, direct evidence was lacking in CLBP. The exploratory evidence presented herein is unsupportive, though not conclusively so, but as the first, albeit small, negative study of tDCS for chronic pain to be published to date it makes an important contribution to a field at risk from publication and small study biases. In addition the study is the first in the field of pain to clearly raise concerns regarding the

validity of much of the existing data, and these concerns have been confirmed in the final study of this thesis.

There remains a need to conduct further research in this field. This thesis provides no conclusive evidence that these methods are ineffective; rather it provides grounds for a more cautious approach to interpreting the current data. In tDCS improved blinding of participants might be achieved in a number of ways such as lowering the stimulation intensity, the use of tRNS, in which the threshold for detecting active stimulation is higher, the use of local anaesthetic creams, or by applying an active control condition. Nonetheless it is not certain that these strategies will achieve effective blinding and the challenge to both participant and assessor blinding presented by lasting skin redness following active stimulation is less easy to solve. Any modified sham procedure will require a full and robust validation of blinding in order for the results of future trials to be interpreted with confidence.

Beyond ensuring adequate blinding there is a need to test whether the findings of existing positive studies can be replicated in similar groups of participants and in wider diagnostic groups of pain patients with long term follow up. If such a confirmation is successful then there is a strong case for further studies that seek to establish the optimal dosage of stimulation in terms of the specific stimulation parameters and cortical targets, and the number of doses given. For example it seems reasonable to suggest that a change of priorities for rTMS clinical research in chronic pain is required. The case remains for exploring alternative stimulation targets and parameters, but there is a more urgent need to examine robustly the more promising findings within the existing data through large, rigorous, adequately blinded trials that deliver a reasonable dose and investigate effects over a meaningful timescale. A data-led approach derived from this review suggests that high frequency stimulation of the motor cortex is a logical focus for this effort. We have subsequently presented these arguments in an invited commentary in *Pain* (O'Connell and Wand 2011, see Appendix 7).

If these findings are found to be robust and if NIBS techniques can be demonstrated to deliver clinically meaningful improvements in CNSLBP or other chronic pain conditions in comparison with sham then the next stage of research will be to conduct trials to establish whether NIBS techniques demonstrate superiority or at least non-inferiority over existing treatments. This will require rigorous controlled trials and evaluations should give close attention to the incidence of adverse events in relation to stimulation and include thorough

cost-benefit analyses. Given the gauntlet of marginally effective, or ineffective treatment options that chronic pain and CLBP patients are faced with, these future studies should be considered an essential prerequisite to the recommendation of NIBS for chronic pain. However for all NIBS techniques, if the existing positive results are not replicated under these conditions then much of the existing rationale for ongoing research is undermined and it may be reasonable to abandon this avenue of enquiry. The case has also been made that tDCS might be used as an adjunct to enhance other therapeutic approaches via cumulative effects or by acting synergistically through enhancing excitability and therein neural plasticity. One exploratory study reports that active tDCS increased pain relief associated with a perceptual illusion, designed to evoke the illusion of normal walking legs in patients with pain following spinal cord injury (Soler et al. 2010) and a protocol has been published recently describing a sham controlled RCT of tDCS in addition to cognitive behavioural therapy for CLBP (Luedtke et al. 2011). Such studies should meet the criteria to be included in future updates of the Cochrane review.

The potential validity of a model of CNSLBP which incorporates altered CNS function is not affected directly by the success or failure of brain stimulation as a therapy. It does not necessarily follow logically that the success or failure of a given treatment approach invalidates the proposed underlying pathological mechanisms. As discussed in chapter 3 while the growing evidence of abnormal CNS function in CLBP offer some compelling possibilities for our understanding of chronic pain, the evidence is limited and incomplete and current models are speculative at best. Further research is needed to deepen our understanding of the observed brain changes in chronic pain and CNSLBP and to more clearly explore their relevance. This will require a broad spectrum of approaches, from neurophysiological research to better understand the mechanisms at play to more detailed imaging and clinical studies in larger populations. In order to illuminate the interaction between the course of these changes and clinical presentation there is a pressing need for further longitudinal studies in this area. Recruiting patients in the acute phase of their first episode of low back pain and studying the neurophysiological correlates of the natural course of the condition would go some way to clarifying the order of events and the possible role of these changes, or lack thereof, in the progression to chronicity. While the first such studies have begun to emerge (Baliki et al 2012) and produce the interesting results (discussed in section 3.3) there is a need for further rigorous studies. Ideally this would start in a broad general population without back pain but the population size required by such a study is likely to be pragmatically prohibitive in terms of both cost and

time. As knowledge develops and our understanding of these changes develops the chances for identifying effective therapies that target the CNS should improve.

Brain stimulation is not the only possible approach to addressing brain changes in chronic pain. As discussed above psychological and behavioural therapies essentially target the brain, though are more frequently aimed at improving function through better pain management than reducing pain, and, in the case of CLBP do not appear to be very effective (Henschke et al. 2010). A better understanding of the neurophysiological mechanisms of chronic pain may well identify potential targets for novel pharmacological approaches. Novel non-pharmacological strategies have been developed with the theoretical aim of normalising altered cortical representation and retraining inhibition using a variety of strategies. In CRPS and a group with a mix of neuropathic pain conditions a graded motor imagery programme has demonstrated preliminary evidence of effectiveness in small clinical trials (Moseley 2004; Moseley 2006) and positive effects have been found in small exploratory studies for tactile discrimination training CRPS (Moseley et al. 2008; Moseley & Wiech, 2009) and phantom limb pain (Flor et al. 2001). Interestingly the clinical improvements seen in phantom limb pain with tactile discrimination training have been found to be correlated with reversal of cortical reorganization (Flor et al. 2001). More recently a small case series suggested that a graded programme of sensorimotor retraining incorporating patient education, tactile discrimination training, motor imagery and actual movement may improve pain and disability in CNSLBP (Wand et al. 2011), and evidence is emerging that altering the perception of back movement through the addition of visual feedback modulates movement related back pain (Wand et al. 2012). Nonetheless these approaches are exploratory and have yet to be reproduced under the rigorous conditions of a clinical trial. These various approaches offer some promise and represent an interesting avenue for future clinical research.

The case for a new model of CNSLBP was established in Chapter 2 and arises directly from the failure of existing models to adequately explain the variability of clinical presentation or outcomes and the failure of existing therapies to demonstrate high levels of effectiveness. Nonetheless to confidently move to a predominantly “neurocentric” view of CNSLBP might be considered premature. The debate continues regarding the potential benefits of subgrouping patients with CNSLBP, and there is still the potential that better targeting of treatments to specific groups of patients might enhance treatment outcomes. In addition some spinal researchers have recently called for a renewed focus on the “bio” in the

biopsychosocial model and suggest that, rather than reflecting a lack of spinal structural pathology underpinning the presentation of CNSLBP, the lack of observed associations between spinal pathology and clinical presentation might simply reflect the flaws and insufficiencies in the existing literature (Hancock et al. 2011). Further research will be needed to test which of these interpretations is the more accurate. Similarly while abnormal CNS processing may play a role, it is not necessarily the driving role in explaining the persistence of back pain. A useful parallel can be drawn from the condition CRPS. The findings of a variety of alterations in brain activity and function in CRPS raised the possibility that the condition had its origin in the CNS, and yet a recent expert review presents a picture which incorporates peripheral and central nervous system malfunction with an aberrant inflammatory response (Marinus et al. 2011). It is important that when considering CLBP we continue to maintain a broad perspective regarding potential mechanisms.

Any emergent therapy for CLBP faces a significant challenge. CLBP can be defined as a condition that fails to respond to a variety of treatments. This might be considered unsurprising as evidence for a modern rise of disability in relation to low back pain (Waddell 2004, Waxman et al 2000) suggests that, at least in part, there is a socially constructed element to the phenomena rather than a purely biological basis. Regardless a significant proportion of people continue to suffer the burden of this condition and continue to seek effective treatment. Given the likely sociocultural influences on the clinical presentation of CLBP and its resulting disability it may be argued that no treatment taken out of the emotional, social, cultural and political context in which the patient resides is likely to be a panacea and that a primarily biological explanation, based either on a model of spinal or central nervous system dysfunction may not be adequate. In addition it is not a given that more treatment will necessarily produce better outcomes and it is possible that the continued promotion of various treatments of dubious or limited benefit may perpetuate the problem. In recent years some eminent back pain researchers have suggested that a fresh approach to conceptualising low back pain may be required. The epidemiologist Heine Raspe reflected :

“It is a promising hypothesis that de-medicalization of non-specific back pain may eventually lead to less overall suffering, chronification and social disability than all of the medical, both diagnostic and therapeutic, interventions that are currently employed”. (Raspe 2002)

On a similar note Buchbinder et al. (2010) suggested in a recent editorial that in relation to CLBP:

“The major challenge facing clinicians today may now be how to avoid unhelpful and potentially harmful treatment rather than selecting the optimal approach.”

If it remains the case that existing treatments and potential future approaches do not clearly demonstrate adequate efficacy these statements may offer clues to an alternative approach to this difficult condition. Nonetheless given the personal and social burden that the condition represents, the withdrawal of treatments of limited worth would leave a gap in care that most would consider unacceptable and would fail to adequately support sufferers. The need remains for research to continue to focus on trying to find better answers to both our understanding of the condition and possible avenues to better management. But before new approaches are rolled out into common clinical practice high-level clinical evidence should have been clearly established.

8.6 OVERALL CONCLUSIONS

This thesis has outlined the rationale for non-invasive brain stimulation as a treatment for CLBP, explored the efficacy of tDCS as such a treatment, and investigated some of the methodological challenges to reliably establishing the efficacy of such approaches. While the evidence presented does not represent promising evidence for the effectiveness of NIBS techniques for treating this condition it clearly highlights important limitations within the existing evidence base, demonstrates the need for improved controls in clinical trials of these techniques and provides suggestions and priorities for future research. While new, more effective approaches to managing CLBP are in urgent demand, further research in this field must ensure that attention is paid to development and use of rigorous controls to ensure that, if positive results are produced, we can be confident that they represent a genuinely beneficial treatment option for CLBP patients.

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APPENDIX 1

PUBLISHED COCHRANE PROTOCOL

NON-INVASIVE BRAIN STIMULATION TECHNIQUES FOR CHRONIC PAIN IN

ADULTS (PROTOCOL) (O'CONNELL ET AL. 2010A)

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APPENDIX 2

FULL PUBLISHED COCHRANE REVIEW (O'CONNELL ET AL. 2010B)

NON-INVASIVE BRAIN STIMULATION TECHNIQUES FOR CHRONIC PAIN IN

ADULTS (REVIEW)

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APPENDIX 3

STUDY 2: BRUNEL REC AND NRES ETHICAL APPROVAL, NHS RESEARCH &
DEVELOPMENT APPROVAL, PARTICIPANT INFORMATION SHEET, CONSENT FORM

School of Health Sciences and
Social Care

Research Ethics Committee

School of Health Sciences and
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Brunel University,
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Middlesex UB8 3PH
Telephone: +44 (0)1895 274000
Web www.brunel.ac.uk

25 October 2007

Proposer: Neil O'Connell

Title: Transcranial Direct Current Stimulation in the Treatment of Chronic Non Specific Low Back Pain - A randomised double-blinded interrupted time-series investigation

Reference: 07/06/STF/16

Letter of Approval

The School Research Ethics Committee has considered the amendments recently submitted by you in response to the Committee's earlier review of the above application

The Chair, acting under delegated authority, is satisfied that the amendments accord with the decision of the Committee and has agreed that there is no objection on ethical grounds to the proposed study. Approval is given on the understanding that the conditions of approval set out below are followed:

- *The agreed protocol must be followed. Any changes to the protocol will require prior approval from the Committee.*

NB:

- Research participant information sheets and (where relevant) flyers, posters and consent forms, should include a clear statement that research ethics approval has been obtained from the School of Health Sciences and Social Care Research Ethics Committee.
- Approval to proceed with the study is granted subject to receipt by the Committee of satisfactory responses to any conditions that may appear above, in addition to any subsequent changes to the protocol.



David Anderson-Ford
Chair, Research Ethics Committee
School of Health Sciences and Social Care

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25 October 2007

STATEMENT OF SPONSORSHIP/INDEMNITY

Proposer: Neil O'Connell
Title: Transcranial Direct Current Stimulation in the Treatment of Chronic Non Specific Low Back Pain - A randomised double-blinded interrupted time-series investigation
Reference: 07/06/STF/16

This is to confirm that the above named research project utilises human participants, their organs, tissue and/or data as defined under the sponsorship requirements of the Research Governance Framework for Health and Social Care 2005, incorporating the Medicines for Human Use (Clinical Trials) Regulations 2004.

On behalf of the School of Health Sciences and Social Care, Brunel University, we undertake to act as the identified Research Sponsor for this project.

This letter confirms:

- The research proposal has been discussed, assessed and registered with the Research Ethics Committee of the School of Health Sciences and Social Care, Brunel University and, following internal scrutiny and approval in accordance with Brunel University Research Ethics Standard Operating Procedures, provisional sponsor approval is granted.
- The Chief Investigator has undergone a process of scientific critique commensurate with the scale of the project.
- Indemnity and insurance arrangements have been put in place to cover the project
- Resources and support are available to the researcher(s) to aid delivery of the research as proposed.
- The School of Health Sciences and Social Care will undertake and enforce those sponsor duties set out in the NHS Research Governance Framework for Health and Social Care.

Sponsorship is conditional on the project receiving applicable ethical and regulatory approval for all research-related aspects of its conduct. A copy of the ethics approval letter **must** be sent to the Chair of the School Research Ethics Committee prior to the study commencing.

(Where relevant) sponsorship is dependant on obtaining R& D Office approval for all NHS sites where the research is being conducted.

Yours sincerely,



David Anderson-Ford
Chair, Research Ethics Committee
School of Health Sciences and Social Care



National Research Ethics Service
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19 December 2007

Mr Neil E O'Connell
Lecturer in Physiotherapy
Brunel University
School of Health Sciences and Social Care
Mary Seacole Building
Uxbridge
UB8 3PH

Dear Mr O'Connell

Full title of study: Transcranial Direct Current Simulation in the Treatment of Chronic Non Specific Low Back Pain vT A randomised, double-blinded interrupted time-series investigation.
REC reference number: 07/H0808/172

Thank you for your letter of 11th December 2007, responding to the Committee's request for further information on the above research and submitting revised documentation.

The further information has been considered on behalf of the Committee by the Chair.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised.

Ethical review of research sites

The Committee has not yet been notified of the outcome of any site-specific assessment (SSA) for the research site(s) taking part in this study. The favourable opinion does not therefore apply to any site at present. We will write to you again as soon as one Research Ethics Committee has notified the outcome of a SSA. In the meantime no study procedures should be initiated at sites requiring SSA.

As you have submitted a new application form you will now have to create new SSI forms from the latest version of the application. This must in turn be sent to the relevant RECs.

Conditions of approval

The favourable opinion is given provided that you comply with the conditions set out in the attached document. You are advised to study the conditions carefully.

Approved documents

This Research Ethics Committee is an advisory committee to London Strategic Health Authority
The National Research Ethics Service (NRES) represents the NRES Directorate within the National Patient Safety Agency and Research Ethics Committees in England

The final list of documents reviewed and approved by the Committee is as follows:

<i>Document</i>	<i>Version</i>
Application	5.5 dated 25/10/2007
Application	Dated 25/10/2007
Investigator CV	Mr Neil O'Connell
Protocol	Version number: 1
Letter from Sponsor	Brunel University
Statistician Comments	Dr Louise Marston Brunel
Compensation Arrangements	Brunel University dated 29 November, 2007
Questionnaire: Short-Form McGill Pain Questionnaire	
Questionnaire: Hospital Anxiety and Depression Scale	
Questionnaire: Current Pain Visual Analogue Scale	
Questionnaire: The Roland-Morris Disability Questionnaire	
Questionnaire	Version number:1
GP/Consultant Information Sheets	Version number:1
Participant Information Sheet	Version number:2
Participant Consent Form	Version number: 1
Response to Request for Further Information	Dated 11th December 2007
Article form Clinical Neurophysiology 114 (2003) 589-595	Brain polarization in humans
Non-NHS REC approval	Brunel dated 25th October 2007

R&D approval

All researchers and research collaborators who will be participating in the research at NHS sites should apply for R&D approval from the relevant care organisation, if they have not yet done so. R&D approval is required, whether or not the study is exempt from SSA. You should advise researchers and local collaborators accordingly.

Guidance on applying for R&D approval is available from <http://www.rdforum.nhs.uk/rdform.htm>.

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees (July 2001) and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

After ethical review

Now that you have completed the application process please visit the National Research Ethics Website > After Review

Here you will find links to the following

- a) Providing feedback. You are invited to give your view of the service that you have received from the National Research Ethics Service on the application procedure. If you wish to make your views known please use the feedback form available on the website.
- b) Progress Reports. Please refer to the attached Standard conditions of approval by Research Ethics Committees.

An advisory committee to South East London Strategic Health Authority
The National Research Ethics Service (NRES) represents the NRES Directorate within the National Patient Safety Agency and Research Ethics Committees in England

- c) Safety Reports. Please refer to the attached Standard conditions of approval by Research Ethics Committees.
- d) Amendments. Please refer to the attached Standard conditions of approval by Research Ethics Committees.
- e) End of Study/Project. Please refer to the attached Standard conditions of approval by Research Ethics Committees.

We would also like to inform you that we consult regularly with stakeholders to improve our service. If you would like to join our Reference Group please email referencegroup@nationalres.org.uk.

07/H0808/172	Please quote this number on all correspondence
---------------------	---

With the Committee's best wishes for the success of this project

Yours sincerely



 **Dr David Jewitt**
Chair

Email: william.bowen@kch.nhs.uk

Enclosures: *Standard approval conditions*
 Site approval form

Copy to: Mr David Anderson-Ford

An advisory committee to South East London Strategic Health Authority

The National Research Ethics Service (NRES) represents the NRES Directorate within the National Patient Safety Agency and Research Ethics Committees in England

Research and Development Office,
Education Centre
The Hillingdon Hospital
Uxbridge
Middlesex.
UB8 3NN.
30th November 2007

Mr Neil O'Connell
Lecturer in Physiotherapy,
Centre for Research in Rehabilitation
School for Health Sciences and Social Care
Brunel University

Dear Mr O'Connell,

Re Research Project: Transcranial Direct Simulation in the Treatment of Chronic Non Specific Low Back Pain – A randomised, double-blind, interrupted time-series investigation

Thank you for your letter with details of the above project you are requesting to carry out at the Hillingdon Hospital NHS Trust.

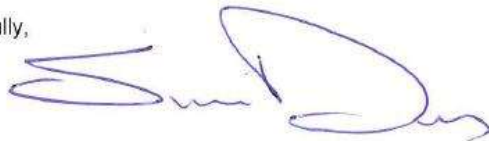
I have looked at the protocol and discussed the implications with others whose services the project may have an impact upon and am happy to give the project approval to be carried out at the Hillingdon Hospital.

I note that this is a no local investigator study and does not require SSA from the local REC. Your project details will be passed onto Gay Bineham, R&D Manager who will log them on our database and, if appropriate, include our participation in the study in the quarterly and annual returns that we are expected to complete as part of our funding agreement with the London Region R&D Office.

I would like to take this opportunity to remind you that The Hillingdon Hospital NHS Trust manages all research in accordance with the requirements of the Research Governance Framework. As a researcher working in the Trust you must comply with all reporting requirements, systems and duties of action put in place by the Trust to deliver research governance.

If the R&D Office can be of any further assistance please do not hesitate to contact myself on the above telephone number or Gay Bineham R&D Manager on 01895 279021.

Yours faithfully,



Simon Dubrey
R&D Director.
Launa Gawne OPD Physiotherapy Manager

INFORMATION FOR VOLUNTEERS

Transcranial Direct Current Stimulation in the Treatment of Chronic Non Specific Low Back Pain – A randomised, double-blinded interrupted time-series investigation

NRES REC reference number: 07/H0808/172

Version number: 3

Researchers

Neil O'Connell*

John Cossar

Prof. Lorraine DeSouza

David Maskill

Dr Benedict Wand

Dr Louise Marston

Dr Lorimer Moseley

Andrew Sharp

Prof. David Bunce

*Principle Investigator

What is the purpose of the study?

Chronic low back pain is a common condition which affects a large number of people and causes significant pain and disability. It also imposes significant costs on society. There is growing evidence of changes in brain function in chronic low back pain sufferers. This evidence suggests that these changes may play a significant role in sustaining the high pain levels experienced by chronic back pain sufferers. Therefore treatments that seek to alter brain activity may have a role to play in the management of this condition.

Transcranial Direct Current Stimulation (tDCS) is a way of stimulating the brain in a safe and painless way to alter brain activity. By stimulating specific areas of the brain researchers have demonstrated that this technique can significantly reduce pain in patients suffering from other chronic pain conditions. However this technique has not yet been used to treat chronic back pain.

Therefore the aim of this study is to investigate the therapeutic potential of tDCS for patients with chronic low back pain. The study is a pilot study that aims to test the proposal that tDCS might have an effect on the pain experienced by people with chronic low back pain. If the study does demonstrate benefits of this treatment then this would lead to further larger studies to confirm its clinical effectiveness. The study will comprise part of the principal investigator Neil O'Connell's PhD studies.

Why have I been invited?

You are being invited to participate in this study because you have experienced problems with low back pain for a period of over 6 months. Participation in this study is on a purely voluntary basis. A decision not to participate in the study will not incur any detrimental effect to volunteers.

You should not participate in this study if:

- You are pregnant
- You have any history of epilepsy or any other neurological condition such as stroke, Parkinson's disease, multiple sclerosis, brain tumours, head injury.
- You have any history of psychotic illness or other significant mental illness.
- You have any other serious illness (e.g.: heart/ chest problems, thyroid problems)
- You have had surgery on your spine in the past.

If you are in any doubt as to whether any of the above apply to you then please ask the researcher to discuss this with you. If you choose to participate in the study you will be asked to delay or stop any current physiotherapy or other therapies such as osteopathy or chiropractic for the duration of the study. On completion of the study, or if you choose to withdraw before completion of the study, you will be offered physiotherapy assessment and treatment at Hillingdon Hospital.

What will the study involve?

Once you have agreed to take part in the study all reasonable attempts will be made to ensure that you commence participation in the study within 4 weeks. During this time you may have commenced physiotherapy treatment, or may be receiving some other treatment for your back pain, but you will be asked to stop this when you commence participation in the study, for the duration of your involvement in the study.

The study will involve daily attendance at the Mary Seacole Building at Brunel University for a period of 23 working days. Each day's proceedings will take between 15 minutes and 1 hour.

The brain stimulation involves attaching 2 electrodes to different sites on your head. The electrodes are made of rubber and placed inside a damp foam pad to assist conductance. There is no risk of electric shock or burns from this procedure. These electrodes are attached to a machine which, when switched on, will send a low intensity direct electrical current through the brain. This process is painless. People sometimes report feeling a light tingling underneath the electrodes which rapidly fades.

For some of this study you will receive a "sham" stimulation. This means that you will have the electrodes attached to you but the machine will be switched off after 30 seconds. You will not be told on which days you are receiving "sham" treatment and on which days you are receiving "active" treatment. The reason for this is to try to rule out the placebo effect. The placebo effect occurs when people feel better when they have received a dummy treatment. By keeping you unaware of which treatment you are receiving it is possible for us to tell with more certainty if the real brain stimulation has a beneficial effect. Studies have demonstrated that it is not possible to distinguish whether the machine is switched on or off as the technique causes little or no sensation.

For the first 3 days you will not receive any brain stimulation. The researchers will ask you to fill in a number of questionnaires relating to your current back pain symptoms and to complete

5 simple tasks on a computer. These tasks involve correctly spotting words, colours and shapes and pictures of the spine presented on a screen. You will be given full explanations by the researchers regarding how to complete these appropriately. This is to provide the researchers with some “baseline” measures of how your pain is normally and to monitor your normal brain function before and after treatments. You will also be asked about your current pain medication.

After the 3rd day of assessment you will be randomly allocated to a specific day within the following 15 weekdays to commence the real brain stimulation. Prior to this randomly decided day you will receive a sham brain stimulation, wherein the equipment will be attached as if you are receiving a “real” stimulation but will be switched off after 30 seconds so that you will not receive any significant stimulation. Once you begin the real stimulation you will continue to receive this treatment daily for the rest of the 15 days. On all of these 15 days you will be asked to complete the same questionnaires and computer tasks. You will also be asked about what pain medication you are taking throughout the duration of the study.

Following the 15 days of stimulation you will be asked to attend daily for the next 3 working days so that the researchers can take 3 days of “after-treatment” baseline measures of your pain and disability. You will also be asked to attend once more to complete all of the same measures again on a date 3 weeks after your last session.

During the time that you are involved with the study you will be asked to stop any physiotherapy (or other active) treatment that you are receiving. This is so that the effects of the brain stimulation can be clearly measured.

Figure 1. shows a timeline of what the study will involve.

What are the possible disadvantages and risks of taking part?

If you choose to take part in the study you will be asked to stop physiotherapy or other non-medication therapies such as osteopathy or chiropractic for your back pain for the duration of the study. However at the end of the study, or at the point of your withdrawal from the study you will be offered access to physiotherapy care at Hillingdon Hospital, or you may recommence any other treatment that you have been receiving.

It is possible that your pain may not improve or may worsen during the study. However there is evidence that this technique reduces pain in other painful syndromes and no studies have found that this procedure increased pain or caused symptoms to worsen.

The study does require a substantial time commitment from you. You will be asked to be present at the laboratory for up to 1 hour on a daily basis for 21 consecutive working days.

What are the possible side effects of the brain stimulation?

Numerous studies have shown this procedure to be safe. Side-effects sometimes reported are mild, transient scalp redness or itching at the site of stimulation, sleepiness, headache and moderate fatigue. Side-effects infrequently reported are nausea and insomnia. Since the studied intervention is exploratory in nature it is possible that it may be ineffective in changing your symptoms. You will be asked on each day of testing whether you have experienced any side effects but if you have any concerns prior to taking part or during the study, please don't hesitate to bring them to the attention of any member of the research team.

What if I want to withdraw from the study?

You are fully entitled to withdraw from the study at any time that you wish. You are in no way obliged to continue against your wishes, or to give a reason for your withdrawal. Withdrawal will incur no detriment to the participant. On withdrawal from the study you will be offered Physiotherapy treatment at the Hillingdon Hospital and will be free to resume any other treatments for your low back pain.

Will my details be kept confidential?

All of the results taken will be recorded in an anonymous format. In addition the only people with access to the data will be those directly involved in carrying out the study. Any publication of the results will provide no personal information specific to any of the volunteers.

What happens when the study ends?

At the end of the study you will be offered Physiotherapy at the Hillingdon Hospital and will be free to resume or begin any other treatments for your low back pain. Also when the data has been analysed you will be informed of the findings of the study.

What if there is a problem?

Complaints procedures

If you are concerned about anything relating to the study please do not hesitate to express your concerns to Neil O'Connell, the principal researcher. If however you do not wish to discuss your concerns with members the research team, or wish to make a complaint then please contact the following person:

David Anderson-Ford
Chair of School Research Ethics Committee
School of Health Sciences and Social Care
Brunel University
Uxbridge
Middlesex UB8 3PH
Tel: 01895 268731
Email: david.anderson-ford@brunel.ac.uk

Compensation for harm

Brunel University has public liability insurance for persons who are authorised to be on their property. Further, subjects are covered for any negligence on the part of the University.

Expenses and payments

You will be reimbursed for any travel expenses that you may incur whilst travelling to and from the study location by public transport. The amount will be calculated from travel receipts provided to the researchers by you.

Informed Consent

If you wish to participate in the study please contact the lead researcher Neil O'Connell. Feel free to ask any questions that you may have regarding the study. If you wish to participate in the study then on your first visit to the laboratory a researcher will ask you to complete an informed consent form to acknowledge that you understand what the study entails and wish to take part as a participant.

Contact details:

Neil O'Connell

Lecturer in Physiotherapy

Tel : 01895 268814

School of Health Sciences and Social
Care

Email:

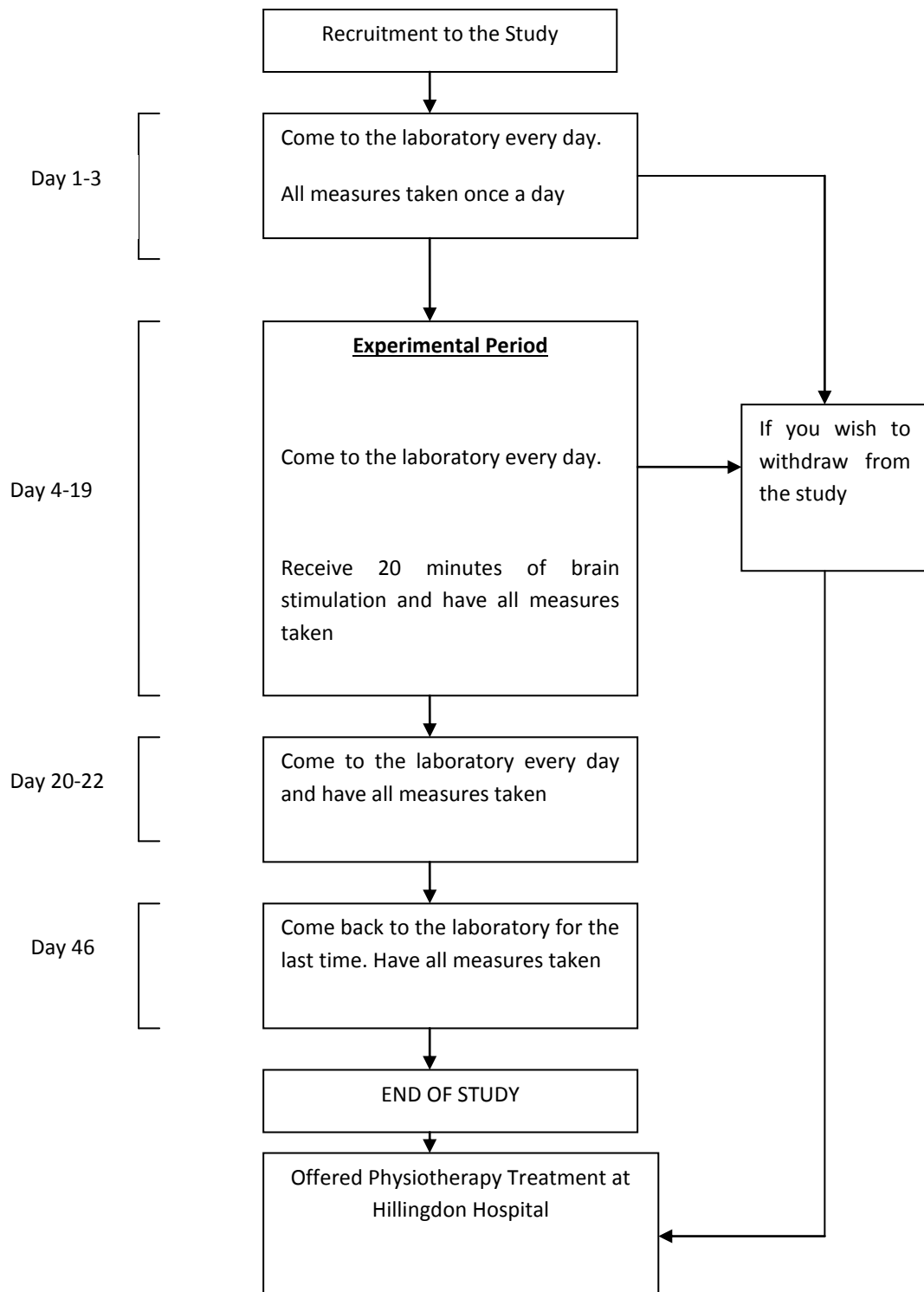
Brunel University

neil.oconnell@brunel.ac.uk

Uxbridge, Middlesex

UB83PH

Figure 1: A timeline of the study process



Transcranial direct current stimulation in the treatment of chronic non-specific low back pain - a randomised, doubled-blinded interrupted time series investigation

NRES REC reference number: 07/H0808/172/ Version no:1

INFORMED CONSENT FORM

The participant should complete the whole of this sheet him/herself

Please tick appropriate box

	YES	NO
Have you read the Research Participant Information Sheet?	<input type="checkbox"/>	<input type="checkbox"/>
Have you had an opportunity to ask questions and discuss this study?	<input type="checkbox"/>	<input type="checkbox"/>
Have you received satisfactory answers to all your questions?	<input type="checkbox"/>	<input type="checkbox"/>
Who have you spoken to?.....		
Do you understand that you will not be referred to by name in any report concerning the study?	<input type="checkbox"/>	<input type="checkbox"/>
Do you understand that you are free to withdraw from the study:		
- at any time	<input type="checkbox"/>	<input type="checkbox"/>

- without having to give a reason for withdrawing?

- (*where relevant*) without incurring any detriment?

Do you agree to take part in the study?

Signature of Research Participant.....

Date.....

Name in capitals.....

Witness statement

I am satisfied that the above-named has given informed consent.

Witnessed by.....Date:.....

Name in capitals:.....

APPENDIX 4

STUDY 3: BRUNEL REC ETHICAL APPROVAL, PARTICIPANT INFORMATION SHEET,
CONSENT FORM

School of Health Sciences and
Social Care

Research Ethics Committee

School of Health Sciences and
Social Care
Brunel University,
Uxbridge
Middlesex UB8 3PH
Telephone: +44 (0)1895 274000
Web www.brunel.ac.uk

1 December 2010

Proposer: Neil O'Connell

Title: An investigation into the integrity of a commonly used sham control condition for anodal transcranial direct current stimulation

Reference: 11/STF/02

Letter of Approval

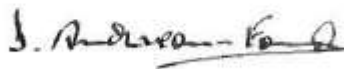
The School Research Ethics Committee has considered the amendments recently submitted by you in response to the Committee's earlier review of the above application.

The Chair, acting under delegated authority, is satisfied that the amendments accord with the decision of the Committee and has agreed that there is no objection on ethical grounds to the proposed study. Approval is given on the understanding that the conditions of approval set out below are followed:

- *The agreed protocol must be followed. Any changes to the protocol will require prior approval from the Committee.*

NB:

- Research Participant Information Sheets and (where relevant) flyers, posters, and consent forms should include a clear statement that research ethics approval has been obtained from the School of Health Sciences and Social Care Research Ethics Committee.
- The Research Participant Information Sheets should include a clear statement that queries should be directed, in the first instance, to the Supervisor (where relevant), or the researcher. Complaints, on the other hand, should be directed, in the first instance, to the Chair of the School Research Ethics Committee
- Approval to proceed with the study is granted subject to receipt by the Committee of satisfactory responses to any conditions that may appear above, in addition to any subsequent changes to the protocol.
- The School Research Ethics Committee reserves the right to sample and review documentation, including raw data, relevant to the study.



David Anderson-Ford
School Research Ethics Officer
School of Health Sciences and Social Care

INFORMATION FOR VOLUNTEERS

The effect of transcranial direct current stimulation on a word memory task: A sham controlled, double blind trial.

Researchers

Neil O'Connell*

Dr Lorimer Moseley

Prof. Lorraine DeSouza

John Cossar

Dr Benedict Wand

Dr Louise Marston

*Principle Investigator

What is the purpose of the study?

Transcranial direct current stimulation (TDCS) involves the safe and painless application of low intensity electrical current to the brain and has been shown to temporarily alter brain activity and performance on a variety of mental tasks. Studies have demonstrated that TDCS, applied to different brain regions may have an effect on a number of behavioural measures. Studies suggest that TDCS may lead to short-term improvements in tactile acuity, performance of learning tasks, verbal fluency and reaction time.

The purpose of this project is to determine whether TDCS improves performance of a word memory task. We recently found exploratory evidence to suggest that this might be the case and the current study aims to test this finding more rigorously. The study will comprise part of the principal investigator (Neil O'Connell's) PhD studies.

Why have I been invited?

You are being invited to participate in this study because you are a healthy individual. Participation in this study is entirely voluntary and you should not participate if you do not wish to.

You should not participate in this study if:

- you have any history of epilepsy, neurological disease, psychiatric disorder, dyslexia, diabetes, head injury, stroke, Parkinson's disease, multiple sclerosis, brain tumours, musculoskeletal or neurological injury to any limb.

- you have a poor understanding of written English.
- you are pregnant
- You have any other serious illness (e.g.: heart/ chest problems, thyroid problems)
- You have experience of receiving TDCS in the past.

If you are in any doubt as to whether any of the above apply to you then please ask the researcher to discuss this with you.

What will the study involve?

The study will involve attendance at the Mary Seacole Building at Brunel University on 2 separate occasions with at least one week separating each session. Each session's proceedings will take up to 1 hour.

On each occasion you will receive brain stimulation at one of 2 different stimulation parameters: real "active" stimulation or fake "sham" stimulation wherein the equipment will be attached as if you are receiving a "real" stimulation but will be switched off after 30 seconds without your knowledge so that you will not receive any significant stimulation. The order in which you receive these different stimulations will be determined randomly. You will not be told until the completion of the study which stimulation you received on which day. This is so that your expectations of the stimulation do not affect the results of the study.

The brain stimulation

This involves attaching 2 electrodes to different sites on your head. The electrodes are made of rubber and placed inside a damp foam pad to assist conductance. There is no risk of electric shock or burns from this procedure. These electrodes are attached to a machine which, when switched on, will send a low intensity direct electrical current through the brain. This process is painless. People sometimes report feeling a light tingling underneath the electrodes which rapidly fades. To accurately place the electrodes the researchers will use a measuring tape to locate specific points on your scalp. The stimulation will last for 20 minutes during which you will be sat down in a relaxed position.

The word memory task

You will be asked to perform a simple memory task and a reaction time on a laptop computer before and after the stimulation. You will be given full instructions as to how to carry out the task and an opportunity to practice.

Are there any advantages to me taking part?

You will receive no direct personal benefit from participating in this study.

What are the possible disadvantages and risks of taking part?

The study does require a commitment from you. You will be asked to be present at the laboratory for up to 1 hour on 2 separate consecutive days.

What are the possible side effects of the brain stimulation?

Numerous studies have shown this procedure to be safe. Short-lasting side-effects sometimes reported are mild, transient scalp redness or itching at the site of stimulation, sleepiness, headache and moderate fatigue. Short-lasting side-effects infrequently reported are nausea and insomnia. You will be asked on each day of testing whether you have experienced any side effects but if you have any concerns prior to taking part or during the

study, please don't hesitate to bring them to the attention of any member of the research team.

What if I want to withdraw from the study

You are fully entitled to withdraw from the study at any time that you wish. You are in no way obliged to continue against your wishes, or to give a reason for your withdrawal. Should you choose not to participate or to withdraw from a session, your status as a student or staff of Brunel University will in no way be affected.

Will my details be kept confidential?

All of the results taken will be recorded in an anonymous format. In addition the only people with access to the data will be those directly involved in carrying out the study. Any publication of the results will provide no personal information specific to any of the volunteers.

What happens when the study ends?

When the study is completed and all of the data is analysed you will be informed of the findings of the study.

What if there is a problem?

Queries

If you are concerned about anything relating to the study please do not hesitate to express your concerns to Neil O'Connell (contact details below), the principal researcher or the research supervisor, Professor Lorraine DeSouza: lorraine.desouza@brunel.ac.uk

Complaints procedures

If however you do not wish to discuss your concerns with members the research team, or you wish to make a complaint then please contact the following person:

David Anderson-Ford

Research Ethics Officer

School of Health Sciences and Social Care

Brunel University

Uxbridge

Middlesex UB8 3PH

Tel: 01895 268731

Email: david.anderson-ford@brunel.ac.uk

Compensation for harm

Brunel University has public liability insurance for persons who are authorised to be on their property. Further, subjects are covered for any negligence on the part of the University.

Expenses and payments

No financial reimbursement will be offered for participation in the study.

Informed consent

If you wish to participate in the study please contact the lead researcher Neil O'Connell. Feel free to ask any questions that you may have regarding the study. If you wish to participate in the study then on your first visit to the laboratory a researcher will ask you to complete an informed consent form to acknowledge that you understand what the study entails and wish to take part as a participant.

Research Ethics Approval

Research Ethics Approval has been obtained for this study from the School of Health Sciences and Social Care Research Ethics Committee.

Contact details

Neil O'Connell

School of Health Sciences and Social Care

Brunel University

Uxbridge

Middlesex UB8305

Tel: 01895 268814

Email: neil.oconnell@brunel.ac.uk

The effect of transcranial direct current stimulation on a word memory task. A sham controlled, double blind trial.

HEALTH CHECKLIST AND INFORMED CONSENT FORM

Health Checklist

Please answer the following health related questions. You should only complete this screen if you know that you are fit and healthy.

If you answer yes to any of these questions then you should discuss them with the researcher.

Please circle your responses

I feel unwell today	Yes / No
I suffer from dizziness	Yes / No
I suffer from balance disturbances	Yes / No
I am on prescribed medication	Yes / No
I have back or arm pain	Yes / No
I have a heart condition and /or have a cardiac pacemaker.	Yes / No
I have a dermatological condition.	Yes / No
I have a (metal) prosthesis or implant in my body.	Yes / No
I have had a neurosurgical procedure (operation to the skull).	Yes / No
I have an aneurysm clip in my head.	Yes / No
I have a neurological condition (including epilepsy)	Yes / No
I have a history of psychiatric or mental illness	Yes / No
I am pregnant.	Yes / No
I am dyslexic	Yes / No

If you have answered “no” to all of the above questions then you may participate in the research using these techniques. Your participation is entirely voluntary. You may withdraw at any time from any session for any or no reason. Should you choose not to participate or to

withdraw from a session, your status as a student or staff of Brunel University will in no way be affected.

INFORMED CONSENT CHECKLIST

The participant should complete the whole of this sheet him/herself

<i>box</i>	<i>Please tick appropriate</i>	
	<i>YES</i>	<i>NO</i>
Have you read the Research Participant Information Sheet?	<input type="checkbox"/>	<input type="checkbox"/>
Have you had an opportunity to ask questions and discuss this study?	<input type="checkbox"/>	<input type="checkbox"/>
Have you received satisfactory answers to all your questions?	<input type="checkbox"/>	<input type="checkbox"/>
Who have you spoken to?.....		
Do you understand that you will not be referred to by name in any report concerning the study?	<input type="checkbox"/>	<input type="checkbox"/>
Do you understand that you are free to withdraw from the study:		
- at any time	<input type="checkbox"/>	<input type="checkbox"/>
- without having to give a reason for withdrawing?	<input type="checkbox"/>	<input type="checkbox"/>
- (<i>where relevant</i>) without incurring any detriment?	<input type="checkbox"/>	<input type="checkbox"/>

Do you agree to take part in this study?

Signature of Research Participant.....

Date.....

Name in capitals.....

Witness statement

I am satisfied that the above-named has given informed consent.

Witnessed by.....Date:.....

Name in capitals:.....

APPENDIX 5

PUBLISHED STUDY: TRANSCRANIAL DIRECT CURRENT STIMULATION OF THE MOTOR
CORTEX IN THE TREATMENT OF CHRONIC NON-SPECIFIC LOW BACK PAIN. A
RANDOMISED, DOUBLE-BLIND EXPLORATORY STUDY. CLINICAL JOURNAL OF PAIN
(O'CONNELL ET AL. 2012A)

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The full text can be found at: DOI: [10.1097/AJP.0b013e318247ec09](https://doi.org/10.1097/AJP.0b013e318247ec09)

APPENDIX 6

PUBLISHED STUDY: RETHINKING CLINICAL TRIALS OF TRANSCRANIAL DIRECT CURRENT STIMULATION: PARTICIPANT AND ASSESSOR BLINDING IS INADEQUATE AT INTENSITIES OF 2MA. PLOS ONE (O'CONNELL ET AL. 2012B)

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The full text can be found at: DOI: [10.1371/journal.pone.0047514](https://doi.org/10.1371/journal.pone.0047514)

APPENDIX 7

PUBLISHED EDITORIAL: REPETITIVE TRANSCRANIAL MAGNETIC STIMULATION FOR
CHRONIC PAIN: TIME TO EVOLVE FROM EXPLORATION TO CONFIRMATION?

O'CONNELL ET AL. (2011)

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The full text can be found at: DOI: [10.1016/j.pain.2011.06.004](https://doi.org/10.1016/j.pain.2011.06.004)