

# Induction of descending inhibition of dorsal horn neurons by transcranial direct current stimulation of the primary motor cortex.

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A 90 credit thesis submitted in partial fulfilment of the requirements for the degree of Master of Osteopathy, Unitec Institute of technology, 2016.

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# Abstract

## **Induction of descending inhibition of dorsal horn neurons by transcranial direct current stimulation of the primary motor cortex.**

### Background:

Transcranial direct current stimulation (tDCS) is an inexpensive, safe, and portable therapy that shows promise in the treatment of chronic pain. While this therapy operates by polarizing neuronal membrane potentials, it is unknown whether a component of its action is descending inhibition of the dorsal horn inter-neurons.

### Objectives:

To determine whether tDCS of the primary motor cortex has an effect on the spinal nociceptive flexion reflex of biceps femoris, which would indicate whether descending inhibition of the dorsal horn was resulting from the intervention.

### Methods:

A cross-over structure was utilized to compare the effects of genuine and sham tDCS against measures of the NFR, as provoked by electrical stimulation of the ipsilateral plantar surface. Two measures of the nociceptive flexion reflex (NFR) were employed; the mean strength of the NFR response via the area under an electromyogram, and the threshold at which the NFR was triggered using temporal summation. Comparisons were made between genuine and sham conditions, and time.

### Results:

No statistically significant relationships between either genuine or sham conditions for either measure were found. A statistically significant relationship with respect to time was observed for both measures that consistent with pain habituation, but not indicative of successful tDCS interventions.

### Conclusions:

There does not appear to be any relationship between tDCS of the primary motor cortex and inhibition of the dorsal horn, as measured by changes in the NFR of biceps femoris.

### Keywords:

*tDCS, chronic pain, nociceptive flexion reflex, central sensitization.*



Table of Contents .....	1
<b>Declaration</b> .....	<b>1</b>
<b>CANDIDATE’S DECLARATION</b> .....	<b>1</b>
Abstract .....	2
Table of Contents .....	3
1. Introduction .....	5
2. Literature Review .....	5
2.1 Pain Perception .....	5
2.2 Chronic pain .....	7
2.2.1 Central Sensitization .....	8
2.2.2 Treatment of Chronic Pain .....	9
2.3 Transcranial Direct Current Stimulation .....	10
2.3.1 Chronic Pain Syndromes .....	11
2.3.2 Spinal Cord Injuries .....	12
2.3.3 Non-Neuropathic Pain .....	14
2.3.4 Headaches .....	15
2.4 Mechanisms of tDCS .....	16
3. Methods .....	20
3.1 Aim .....	20
3.2 Participants .....	20
3.3 Study Design .....	20
3.4 Ethics Approval .....	21
3.5 Instrumentation .....	21
3.5.1 Electrode placement .....	21
3.5.2 Signal Processing .....	22
3.6 Procedure .....	22
3.6.1 tDCS Intervention .....	22
3.6.2 Electrocutaneous stimulation procedure .....	22
3.7 Measures .....	24
3.7.1 NFR Threshold .....	24

3.7.2	Temporal Summation Threshold .....	24
3.8	Statistical Analysis .....	25
4.	Results .....	26
5.	Discussion.....	27
5.1	Effects of tDCS on NFR .....	27
5.2	Limitations of study.....	28
6.	Appendix A: Mechanisms and experimental considerations of the NFR.....	30
	Measuring the NFR: .....	32
	References: .....	34

# **1. Introduction**

There is a growing need to address the costs and treatment of chronic pain, especially in an aging population more susceptible to chronic pain than a younger population (Casey, 2014). Emerging evidence of the efficacy of Transcranial Direct Current Stimulation (tDCS) is displaying promise in this field, but the precise underlying mechanisms of operation are unknown at this stage. A greater understanding of those mechanisms may lead to improvements in the application of tDCS as a therapy for chronic pain.

This review aims to contextualize the condition of chronic pain, and outline the seriousness of the problem in the New Zealand context. TDCS will be examined as an avenue for alleviating some of the burden of chronic pain, and the theorised mechanisms of its operation will be discussed before focusing on the primary question; whether tDCS operates in an inhibitory manner at the dorsal horn level, and can therefore affect spinal nociceptive reflexes.

The study itself will attempt to answer that question of descending inhibition experimentally, employing the nociceptive flexion reflex as an outcome measure.

## **2. Literature Review**

### **2.1 Pain Perception**

According to the International Association for the Study of Pain, pain may be defined as *“an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage”* (Pain, 2015). Pain is a normal part of life and serves to warn us of tissue damage or potentially dangerous stimuli. As a result of pain, we are able to make decisions that lesson the likelihood of sustaining significant damage to ourselves. In evolutionary terms, pain is a very good thing.

Physiologically, pain is the experience we associate with the stimulation of a wide variety of receptors. Many factors may influence this perception, including fatigue, mental or emotional states and analgesia (Jurth, Rehberg, & von Dincklage, 2014). The process required for the body to detect and recognise pain is known as nociception, and it involves nerves and receptors in both the peripheral nervous system (PNS) and central nervous system (CNS).

Receptors specific to certain types of stimulation (i.e. temperature, mechanical, chemical) are located in varying amounts throughout the body. These receptors are known as nociceptors, and once a stimulation threshold has been achieved they send information through nerves to the spinal cord. The nerves that carry these impulses form part of what we call the PNS.

Once that signal has reached the spinal cord it is detected by small nerves called interneurons that act like relay switches. Many nerves from the PNS converge on the interneurons, and in turn the interneurons can be connected to both sensory nerves in the CNS and motor nerves in the PNS. The interneurons act much the same way as transistors in electronic circuits do, in that they can make 'decisions' based on their inputs and can send those decisions to other systems. In this way interneurons are both a relay for pain sensation, and the control level of many reflexes such as flinching or pulling away from something hot or painful (Mendell, 2014; Zhang et al., 2015).

If the interneurons determine that the message from the nociceptors is sufficient to be interpreted as pain, they activate ascending nerves in the CNS that connect to various parts of the brain used for signal processing, in particular the thalamus, and eventually make it all the way to the sensory cortex. The sensory cortex is the region of the brain that controls our sensory functions, and is essentially the part that 'feels' for us. The CNS provides many ascending paths, differentiated by fibre type, location, and specialization of the initial receptors. The tracts involved with pain are the spinothalamic and lateral spinothalamic tracts (Waxman, 2010).

## 2.2 Chronic pain

Pain may be classified as acute or chronic. Acute pain is considered to be provoked by a specific injury or disease. It is self-limiting, and serves a biological function (Grichnik & Ferrante, 1991). Chronic pain may be understood to be pain that has persisted longer than expected for an acute onset. Specific definitions vary, however the commonly accepted definition in New Zealand is that employed by the Accident Compensation Commission (ACC); pain that has lasted for three months or more (ACC, 2004). A more complete definition however is *"persistent pain that is unresponsive to, or poorly managed by, 'curative' treatments or routine analgesia"*(Casey, 2014). Regardless of the definition, it is frequently disabling to those who live with it.

Chronic pain presentations may be complex, and are frequently underscored by psychosocial factors (Baird & Haslam, 2013). The physiological process by which chronic pain is thought to be produced may be considered to be either due to peripheral sensitization, central sensitization, or a combination of the two (Fornasari, 2012). Both processes produce long-term changes in a class of neurons known as Wide Dynamic Range (WDR) neurons (Schaible, Schmidt, & Willis, 1987). WDR neurons are involved in both pain processing and in mediating motor reflexes, including the Nociceptive Flexion Reflex (NFR) (Schaible et al., 1987; You, Dahl Morch, Chen, & Arendt-Nielsen, 2003). The process of long-term change of the WDR neurons has been referred to as "wind-up" (Terry et al., 2011).

Approximately 17% of New Zealanders report the presence of chronic pain, with prevalence varying from 9% to 28% depending on the age of the demographic. Of those with chronic pain, almost half (48%) engage in some form of medical treatment to manage their pain, while only 36% do not use any treatment (Dominick, Blyth, & Nicholas, 2011).

Unfortunately figures for the economic costs of chronic pain in New Zealand are elusive but it is estimated to lay in the region of AUS \$10.8bn per annum in Australia in 2007 (Medical Benevolence Foundation, 2007) , and between US\$560-635bn per annum in the U.S.A. in 2008 (Gaskin & Richard, 2012). Individuals are likely to carry over half the economic cost of chronic pain personally, and this in turn puts them at greater risk of co-morbidity and a worse prognosis (National Pain Summit, 2011). Given these levels of economic impact, considerable efforts have put into determining cost-effective treatments for chronic pain by

many health agencies (Evans, Benore, & Banez, 2015; Herman, Szczurko, Cooley, & Mills, 2008; Obradovic et al., 2012; Taylor, Pezzullo, Grant, & Bensoussan, 2014).

Increasingly, chronic pain is being recognised as a disease in its own right at an international level (Siddall & Cousins, 2004; Smith & Torrance, 2011; Tracey & Bushnell, 2009). The causes of chronic pain are many and varied, and often poorly understood. In chronic pain patients managed by Australian general practitioners, osteoarthritis contributed the greatest portion of chronic pain sufferers (41.8%), with lower back pain the second most prevalent (29.4%). Of the remainder, over half (56.2%) of chronic pain cases were attributable to musculoskeletal conditions such as fibromyalgia, tendinopathies, osteoporosis and bursitis. Another 19.6% were neurological in nature, including neuralgia, migraines and peripheral neuropathies (Henderson, Harrison, Britt, Bayram, & Miller, 2013). Lower back pain has been further categorized into specific (identifiable pathological) causes and non-specific (unidentifiable) forms, with approximately a 1:9 prevalence ratio (A. D. Woolf & Pfleger, 2003). Prevalence rates of chronic pain in New Zealanders range from 9.1% (16-25 age group) to 25% (75+ age group), with each age group displaying a higher prevalence than the previous one (Dominick et al., 2011).

### **2.2.1 Central Sensitization**

Chronic pain is generally thought to be the result of plastic adaptation to pain, known as central sensitization. Central sensitization partially occurs in nociceptive neurons located in the dorsal horn of the spinal cord. Notably, hyper-excitability of the neurons may last for longer than initiating peripheral nociceptive input (Ji, Kohno, Moore, & Woolf, 2003) and persistent nociceptive input is able to make plastic changes in the dorsal horn synapses (Sharif Naeini, Cahill, Ribeiro-da-Silva, Ménard, & Henry, 2005).

As well as reducing the activation threshold of dorsal horn neurons, the receptive field of these neurons is also increased allowing nociception to be initiated from non-inflamed sites (Bradley, 2004; Schaible, Ebersberger, & Von Banchet, 2002). WDR neurons are responsible for this widening of the receptive field, as they receive inputs from A- $\beta$ , A- $\delta$  and C fibres from skin, muscles and joint; therefore including touch and pressure receptors as well as nociceptors (Neugebauer & Schaible, 1990). The convergence of afferent signals on the



WDR neurons also includes both excitatory and inhibitory inputs, and they therefore play a pivotal role in pain modulation (Sandrini et al., 2005; You et al., 2003).

Both peripheral and supraspinal mechanisms play a role in the development of central sensitization. During peripheral inflammation nociceptive input may result in the summation of synaptic potentials, causing post-synaptic depolarization to occur (Ji et al., 2003). The result of this process is an increase in the resting potential of the second order neurons and therefore a reduction in the activation threshold of dorsal horn neurons. This change in resting potential can persist up to several hours after the nociceptive stimulus has stopped (Ji et al., 2003; Nijs & Van Houdenhove, 2009). This effect is a form of wind-up, and usually only persists for a short time after the stimuli that generates it is ended (C. J. Woolf & Salter, 2000).

Prolonged exposure to nociceptive inputs may result in longer-lasting structural modifications however. These modifications include alterations to both ion channel and receptor activity, and an increased concentration of excitatory neurotransmitters; both of which increase synaptic efficacy (Sharif Naeini et al., 2005; C. J. Woolf & Salter, 2000). Similarly, inhibitory pain mechanisms may be impaired due to the loss of active neurotransmitters or receptors, and inhibitory interneurons may die as a result of excessive exposure to synaptic discharges (C. J. Woolf & Salter, 2000). Inappropriate plastic changes such as A- $\delta$  fibres synapsing where C fibres normally terminate are also possible and allow for nociception to be triggered by entirely non-noxious stimuli (C. J. Woolf & Salter, 2000).

### **2.2.2 Treatment of Chronic Pain**

In practical terms, the physiological processes of chronic pain are heavily influenced by previous learning histories, environmental and socioeconomic resources, cognitive, emotional and behavioural factors, and physical pathology (Gatchel, Peng, Peters, Fuchs, & Turk, 2007). As a result, treatment of chronic pain must encompass a wide range of modalities in order to achieve desirable results. In New Zealand, all District Health Boards provide multidisciplinary pain clinics to address this issue.

Treatment for chronic pain has necessarily been varied, and a complete review of all methods is outside the scope of this work. Pharmacological therapy includes the use of

opioids, non-steroidal anti-inflammatory agents, anticonvulsants, anti-depressants, topical agents and muscle relaxants. Interventional treatments include surgery, nerve blocks and implantable devices. Physical therapy has been shown to improve pain by up to 30% and function by 20% (van Tulder, Malmivaara, Hayden, & Koes, 2007). Psychological and cognition therapy similarly appear to provide only modest benefit to perceived pain levels, but significantly impact the patients ability to manage that pain (Hoffman, Papas, Chatkoff, & Kerns, 2007; Morley, Eccleston, & Williams, 1999). When considered in combination, only a half of chronic pain sufferers manage a reduction in pain of 30% or greater despite the multitude of treatment methodologies (Turk, Wilson, & Cahana, 2011).

Given the high economic cost of chronic pain, and the relatively low degree of recovery currently experienced, new methodologies should be investigated and added to the tool box for pain clinics. It is precisely because it is both prevalent and debilitating that we should increase our efforts in understanding chronic pain, particularly as the population ages.

*“Chronic disease comes low on the political priority list, and chronic pain just gets forgotten. The burden for the sufferers, their families, and society is substantial and merits better treatment. The mark of a gracious society is how it treats those with least voice. That chronic pain puts people at the bottom of the pile is precisely why we should be agitating on their behalf for a fairer share of the medical resource cake” (McQuay, 2008, p. 954)*

## **2.3 Transcranial Direct Current Stimulation**

In response to the realization that more tools are needed to combat chronic pain, neuromodulatory approaches have generated a greater interest in recent years (Antal, Terney, Kühnl, & Paulus, 2010). Early research demonstrated that post-stroke thalamic pain can be modulated via epidural electrodes, and that this technique could be successfully applied to trigeminal neurogenic pain as well (Delavallee, Rooijackers, Koerts, & Raftopoulos, 2011; Meyerson, Lindblom, Linderöth, Lind, & Herregodts, 1993; Tsubokawa, Katayama, Yamamoto, Hirayama, & Koyama, 1993). This form of motor cortex stimulation (MCS) has been extended to deep brain stimulation of the anterior cingulate cortex (Russo & Sheth, 2015), a region known to respond to thalamic stimulation (Chai, Kung, & Shyu,

2010; Davis et al., 2000).

Non-invasive measures have shown considerable success in the treatment of neuropathic pain, the most frequently cited being repetitive transcranial magnetic stimulation (rTMS) (Hasan et al., 2014; J. Lefaucheur et al., 2004; J. P. Lefaucheur, Drouot, Keravel, & Nguyen, 2001). However, a different method of primary motor cortex (M1) stimulation known as transcranial direct current stimulation (tDCS) has also demonstrated effectiveness in modulating central pain (Fregni, Boggio, et al., 2006; Fregni, Gimenes, et al., 2006).

Under tDCS, weak direct currents are applied to cortical areas in order to modify cognitive, perceptual and behavioural functions (Nitsche et al., 2008). This has been shown to reliably alter human cortical function by inducing cortical excitability or depression in a focused region that lasts for a prolonged period between two weeks and four months, yet is completely reversible (Nitsche et al., 2008; Nitsche et al., 2004; Nitsche et al., 2003; Alberto Priori, 2003; A. Priori, Berardelli, Rona, Accornero, & Manfredi, 1998).

When compared to rTMS, tDCS has been demonstrated to be the more cost-effective method per unit of VRS (Verbal Rating Scale) over a 1-year period (Zaghi, Heine, & Fregni, 2009). The cost of tDCS is estimated to be US\$167.72 per treatment, as compared to US\$204.24 for rTMS, with tDCS providing an improved VRS score of 1.3 compared to rTMS. TDCS therefore proves to be both more effective and less costly than rTMS. In addition, portable tDCS devices have since been developed for home use, with almost no seizure risk, eliminating most of the technician time component of the cost (Magstim, 2010) and therefore further reducing the treatment costs.

### **2.3.1 Chronic Pain Syndromes**

TDCS has been investigated in numerous contexts of acute and chronic pain treatment. Early RCTs were conducted on participants with a mix of chronic pain conditions, and produced very promising results. Clinically significant drops of 37-58% in patient reported VAS pain when compared with sham tDCS. In both cases the difference was still apparent three weeks after the tDCS sessions had ended (Antal et al., 2010; Fregni, Boggio, et al., 2006). While immediate results are seen in VAS ratings after each session there is little consensus as to the overall distribution of the improvement in pain intensity, with significant gains

being described as occurring linearly, or disproportionately large in the final two of five sessions (Antal et al., 2010; Fregni, Boggio, et al., 2006). Multiple sclerosis patients demonstrated an improvement of 45% in VRS intensity immediately after real tDCS when compared to sham, and that this difference increased over the following three weeks without stimulation to a 73.6% difference (Mori et al., 2010).

Fibromyalgia has received relatively little attention as a target for tDCS, and more studies targeting this particular chronic pain syndrome would be useful for comparative purposes (Fregni, Gimenes, et al., 2006). Treister et al. conducted a 10-day treatment trial on chronic pain patients consisting mostly of neuralgia patients, but with two fibromyalgia patients included in the 11 participants. They saw a reduction of 20% in VRS rating over two weeks in just over a quarter of their cohort, but even those participants had returned to baseline after three weeks. None of the responders were fibromyalgia patients (Treister, Lang, Klein, & Oaklander, 2015).

### **2.3.2 Spinal Cord Injuries**

Spinal cord injuries have received considerably more attention due to the severity of disability and relative ease of recruitment (Ngernyam et al., 2015). Injuries of this nature are associated with varying degrees of centrally mediated pain with prevalence of between 40% - 81% reported (Ngernyam et al., 2015; Nicholson, 2004; Siddall, McClelland, Rutkowski, & Cousins, 2003; Soler et al., 2007). Both cognitive and anxiety components have been investigated, although ultimately failed to show significant effects. Mirroring the results for non-specific chronic pain closely a drop of 2.6 VRS compared to baseline (approximately 43%) for the active group at the 16-day follow-up has been observed. The progression over treatments appears fairly linear, with no significant difference between the end of one treatment and the beginning of the next on any of the consecutive days of treatment (Fregni, Boggio, et al., 2006). The same process has been used with only half the treatment time and found a drop of 1.7 VRS for the real tDCS, but failed to perform follow-ups (Yoon et al., 2014).

A more nuanced approach has been taken, categorizing the pain quality of the spinal cord injury participants (continuous pain, allodynia, paroxysmal, and dysesthesia ) and comparing tDCS with visual illusion therapy, a combination of visual illusion and tDCS, and a placebo

group (Soler et al., 2010). It appears that the effect of tDCS may vary across all pain categories, with the strongest and longest lasting effects being related to paroxysmal pain. The other categories produced only weak change initially and no change lasting longer than two weeks. However, tDCS when combined with illusion therapy seems to be considerably more effective than either therapy on its own across all categories (Soler et al., 2010). Given the tDCS methodology very closely matched Fregni et al's work it is unclear why there such a difference in the strength of result, except that it may have been due to the nature of the injuries seen in each study. The severity of spinal cord injury has been shown to influence hyperalgesia responses in other experimental modes (Knerlich-Lukoschus et al., 2008; Young Wook, Hongxin, Arends, & JacQuin, 2004).

Further adding to the incongruities, another study conducted in the same manner as Fregni et al. demonstrated no difference between real and sham tDCS after any of the five treatments, or during follow-up (Wrigley et al., 2013). The major point of difference between the Fregni et al. and Wrigley et al. studies appears to be the duration of injury;  $3.7 \pm 1.8$  years and  $21.3 \pm 13.8$  years respectively. Fregni et al noted that the greater the injury duration the less effective the tDCS therapy in their sample, but no such pattern was seen with Wrigley et al (Fregni, Boggio, et al., 2006; Wrigley et al., 2013). It may be possible that after sufficient duration post-injury, adaptations leading to differently mediated forms of chronic pain than the type seen shortly after injury are playing a part in the total pain experience of the participants. This is conjecture, but would make both studies consistent with the difference between paroxysmal and continuous pain results in the work of Soler et al.

Also dealing with spinal cord injury participants, Ngernyam et al. concluded there was a significant reduction in pain intensity (approximately 16%) experienced immediately after tDCS. This intensity reduced 8% further over the following 24 hours where, it remained stable for the next 24 hours at the final follow-up (Ngernyam et al., 2015). The primary purpose of this study was to collect peak theta-alpha frequency readings of the stimulated cortex. A correlation between an increase in these readings with real tDCS is indicative of possible thalamic involvement in the mechanism of pain reduction (Llinas & Ribary, 1999).

The majority of participants in the above studies were medicated during the course of the trials. All studies relied on patient-reporting for changes in medication use during the course of tDCS and during the follow-ups, but no confounding factors were found in any case.

Reporting on the effectiveness and efficacy of tDCS for spinal cord injury has not been clear to date. A systemic study on the impact of tDCS on pain in spinal cord injuries was published in November 2015, consisting of five papers (Mehta, McIntyre, Guy, Teasell, & Loh, 2015). The conclusion of this author was that when taken as a group, the evidence shows that tDCS does not meet the minimum threshold of significance to be considered a clinically relevant treatment for these patients (Mehta et al., 2015). Clinical relevance in this case was defined as a drop of 1.5 to 1.8 on the VRS scale post tDCS (Hanley et al., 2006; Ostelo et al., 2008) and the pooled result gave a reduction of only 1.33. However, of those five papers, one was in clear contrast to the others in that it demonstrated no result for real tDCS (Wrigley et al., 2013), a second employed only a single session of tDCS (Ngernyam et al., 2015), and a third was excluded because the study included participants with incomplete spinal trauma injuries (Soler et al., 2007). The mean drop was therefore calculated across only three of the studies, including the only one displaying no significance, and is of questionable value as a result. A significant result may have been achieved with different exclusion criteria.

### **2.3.3 Non-Neuropathic Pain**

The results for treatment of non-neuropathic pain are similarly varied. An RCT comparing a five-day course of real and sham tDCS preceding four weeks of exercises for temporomandibular pain displayed no difference between the groups, although there was no comparison of only tDCS or only exercise (Oliveira et al., 2015). Plantar fasciitis in an elderly population produced significant improvements in VRS ratings, as well as foot function index and the pain anxiety symptom scale, immediately after a 5-day course of tDCS. The results were still holding after each of the four weekly follow-ups (Concerto et al., 2015). Participants whose chronic pain is attributed to arthrosis perform better than participants with lower back pain, although exact figures are not reported (Antal et al., 2010). tDCS has even demonstrated significant reductions in VRS for irritable bowel disease

after a 5-day course, although follow-up was only continued for a single week after treatment (Volz, Farmer, & Siegmund, 2015).

### **2.3.4 Headaches**

While headaches display a varied aetiology, including neuralgic pain such trigeminal or C2 neuralgia, they are common enough that they warrant a discussion in their own right (Feoktistov & Diamond, 2014). A retrospective study of patients from the Municipal Centre for Rehabilitation of Children with Psychoneurological Disorders compares the treatment of migraines, chronic and frequent tension headaches, and traumatic headaches. Four electrode configurations were used, including the M1 configuration used in other studies. The results were not promising, with at most only 62% of migraine sufferers reporting a fall of 50% in migraine frequency of 4.5 months.

Other headache varieties experienced the same reduction in frequency with a prevalence of between 29% (chronic tension headaches) to 51% (migraines, using a different electrode configuration). In addition, the commonly used M1 configuration proved to have the weakest effect on all categories of headache, including having no detectable effect on migraines at all (Pinchuk, Pinchuk, Sirbiladze, & Shugar, 2013), although when higher current densities are used significant improvements in have been recorded (DaSilva et al., 2012). Trigeminal headaches, a form or neuralgia, have responded very well to tDCS of M1 (Hansen et al., 2011). Based on this evidence it is likely that configurations that have proven to be effective for the treatment of neuralgic chronic pain act in a different manner, or with different thresholds, to those required for many varieties of headache. A possible explanation for this may be that the nociceptors triggered in these forms of headache are not mediated at the spinal level, and therefore lack the same descending inhibition pathways of the less caudal sources of chronic pain.

More studies, employing control groups and using more standardized parameters are required to draw any conclusions about the efficacy of tDCS for headache treatment.

## 2.4 Mechanisms of tDCS

The mechanisms by which tDCS appears to work are not well understood. What is known is that the application of a current through the M1 tissue generates an electric field across it (Nitsche et al., 2008; Nitsche et al., 2003). Axonal synapses respond to electrical stimulation, becoming more or less excitable depending on the orientation of the electric field and the membranes of the cell. Anodal tDCS increases the resting membrane potential, making action potentials more likely to be generated from small inputs, whereas cathodal tDCS depresses the resting membrane potential (Nitsche et al., 2003; Nitsche & Paulus, 2000). It is presumed that the primary mechanism of tDCS is due to this polarization effect on the axonal synapses (Knotkova, Nitsche, & Cruciani, 2013; Wagner, Valero-Cabre, & Pascual-Leone, 2007). Secondary mechanisms also appear to be a factor, with evidence for interactions with neurotransmitters (Kuo, Grosch, Fregni, Paulus, & Nitsche, 2007; Nitsche et al., 2004; Terney et al., 2008) and brain-derived neurotrophic factor (Stefani et al., 2012).

Motor cortex stimulation inhibits the transmission of somatosensory information to the primary sensory cortex (S1) in animals, although to date this has only been performed at supra-threshold stimulation levels and may not be generalizable to tDCS as a result (Chiou, Lee, Chang, Lin, & Kuo, 2012). Monosynaptic inhibitory neurons have been discovered in the somatosensory cortex of rats from the thalamus and ipsilateral motor cortex however, lending further weight to the possibility that direct M1 to S1 inhibition is possible (Choi & Callaway, 2011). Direct inhibition of S1 by tDCS of M1 is a potential source of nociceptive inhibition with tDCS, although on balance the evidence supporting this as a primary mechanism is weak.

The prefrontal cortex is associated with modulations of the functions of the limbic system, including the parahippocampal areas and cingulate gyrus (Catafau et al., 2001; Mottaghy et al., 2000). In particular, the prefrontal cortex contains serotonin and dopamine dependent circuits that control aspects of behaviour including impulse control, attention, memory and decision-making processes. Several studies have indicated that activation of certain structures associated with affective appraisal of pain induce a perceived reduction in pain intensity upon activation (García-Larrea et al., 1999; Peyron et al., 1995). More recent studies have indicated that tDCS of the prefrontal dorsolateral cortex relieves chronic pain



(Valle et al., 2009), as well as increase pain thresholds in healthy subjects (P. S. Boggio, Zaghi, Lopes, & Fregni, 2008).

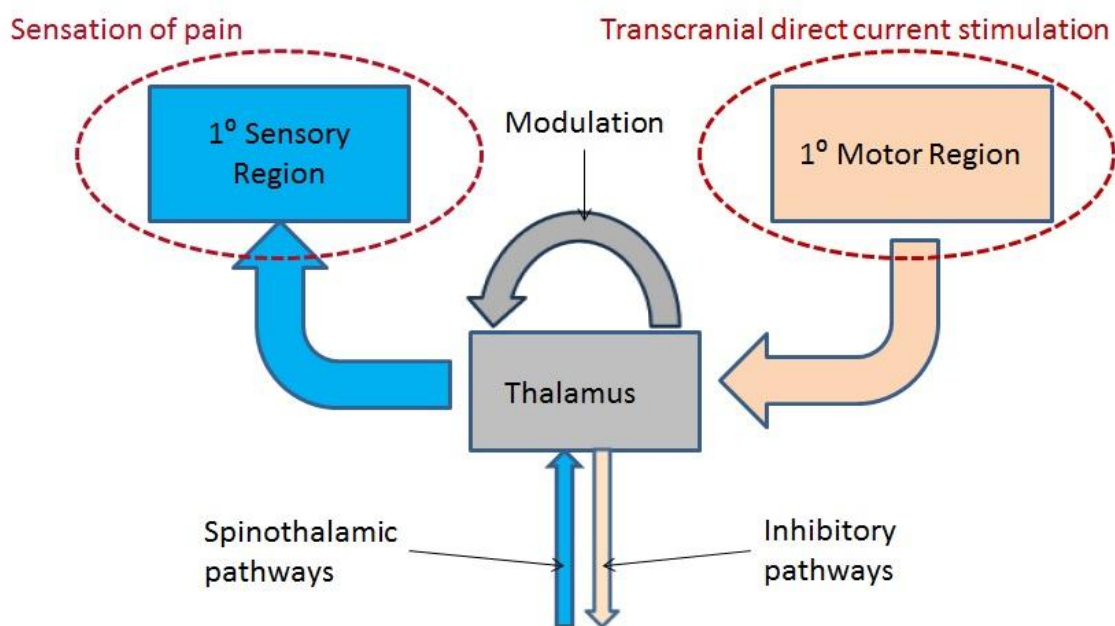
tDCS over M1 results in a reduction in the mu opioid receptor ligands binding in the pain matrix (Marcos Fabio DosSantos et al., 2012). This binding reduction is detected in the both the cortical and subcortical areas of the pain matrix, including the cingulate cortex, insula and thalamus. These changes are accompanied by an increased threshold for experimentally induced cold pain, although any gains appear to be sub-clinical after a single tDCS session. A follow-up study determined that tDCS may perpetuate the same analgesic responses witnessed with the placebo effect, but did not examine the long-term effects or the effects outside of a healthy cohort (Marcos F. DosSantos et al., 2014). At the moment it appears that there is little evidence to suggest opioid receptor availability is a significant contributor to the long-term analgesic effects witnessed with tDCS, but it remains a possibility given the lack of research the mechanism has received to date.

The effects of tDCS are dependent upon the region of brain stimulated (Nitsche et al., 2007), but altered activity in remote cortical and sub-cortical tissues have also been described. In particular, the cingulate cortex, thalamus and regions in the brainstem displayed activity directly attributable to the application of tDCS to M1 (DaSilva et al., 2012; Polanía, Paulus, & Nitsche, 2012). These images are consistent with the results Ngernyam et al. obtained on their work with spinal cord patients (Ngernyam et al., 2015). Thalamic activity is vital for the processing of nociceptive signals and is a critical component of the pain pathways linking the peripheral nervous system with the cortical pain matrix (Knotkova et al., 2013). In particular, anodal tDCS over M1 has been shown to increase the functional coupling between the ipsilateral M1 and sensory neurons of the thalamus (Polanía et al., 2012), specifically the ventral posterolateral nuclei and centromedian-parafascicular thalamic complex receptive to peripheral nociceptive stimulation (Pagano et al., 2012). It has been speculated that the lateral thalamus is providing an inhibitory effect on these more medially located sensory neurons (Knotkova et al., 2013).

Epidural motor cortex stimulation has been used to alter regional cerebral blood flow, and shown to activate the lateral thalamus, medial thalamus, anterior cingulate gyrus, insula and

upper brainstem (Garcia-Larrea & Peyron, 2007; García-Larrea et al., 1999). This may indicate a link between M1 and the affective components of the pain neuromatrix. This activation alone cannot contribute to a reduction in pain perception, but is likely to be a trigger of important modulatory events. Neuronal activity in the deeper thalamic sensory neurons under the same conditions has been noted however (Pagano et al., 2012). The model of thalamic intervention in the perception of pain that has developed so far can be described broadly in pictorial terms, below.

**Figure 1: Theorised path of pain modulation**



The inhibitory pathways are descending tracts to the WDR neurons in the spinal cord thought to be a factor in chronic pain conditions (Sandrini et al., 2005; You et al., 2003). It is unknown whether tDCS of M1 causes an inhibition of the nociceptive signals received at the thalamus, whether it stimulates the inhibitory pathways and inhibits nociceptive signals at the spinal level, or both. Understanding where the modulation of nociception is occurring may allow us to further focus research efforts to advance our understanding and treatment of chronic pain conditions.

In order to answer that question we must look to the effect tDCS has on reflex actions that are not dependent on higher sensory and motor control, but are instead decided at the

spinal level. The NFR is a reflex arc that occurs at the spinal level as a response to nociceptive stimulation, causing the ipsilateral limb to be withdrawn from the stimulus. It is adjudicated by the dorsal horn neurons and is not reliant upon supraspinal levels of decision making (Rhudy, Williams, McCabe, Nguyen, & Rambo, 2005; Sandrini et al., 2005), but is responsive to inhibition from higher thalamic centres (Robert Dowman, 2002; Goffaux, Redmond, Rainville, & Marchand, 2007; Sandrini et al., 2005). Because the NFR is a physiological measure it is more reliable than subjective pain ratings as a nociceptive measure (Aslaksen, Myrbakk, Høifødt, & Flaten, 2007). As the NFR is centrally mediated at the spinal level, it is possible that that the mechanism is related to the wind-up of the CNS. Assuming that tDCS of M1 does impact the NFR, it may reduce the need to employ more expensive imaging techniques to study the phenomenon.

The NFR has been demonstrated to be a highly reliable and effective measure of testing nociceptive changes in response to descending inhibition (Desmeules et al., 2003; Jurth et al., 2014; Lewis, Leys, Rice, & McNair, 2015). While usually elicited with a single supra-threshold voltage, Temporal Summation (TS) of closely spaced sub-threshold pulses may also result in activation of the reflex and has been used as a measure with acceptable reliability as well (Cathcart, Winefield, Rolan, & Lushington, 2009; Roland Staud, Robinson, Vierck Jr, & Price, 2003) (Appendix A.).

## **3. Methods**

### **3.1 Aim**

To determine if tDCS of M1 has an effect on the spinal NFR, and therefore activates a descending inhibitory pathway to the spinal column interneurons.

### **3.2 Participants**

16 healthy participants (12 male, 4 female), aged between 18 and 40 years were recruited for the study. Participants with a history of back pain, knee injury or lower extremity surgery were excluded. The study was conducted with ethical approval from Unitec and the Auckland University of Technology. All participants granted written informed consent prior to commencing the study.

### **3.3 Study Design**

This was a cross-over study consisting of two sessions; one with real tDCS and one with sham tDCS. Participants were randomised as to which group they were placed in initially, with each group receiving treatment from one of two tDCS devices. The examiner was blinded to which of the devices provided real tDCS treatment.

Sessions were approximately 90 minutes long, and were held on separate days to allow for any effects from real tDCS treatment to diminish to inconsequential amount. The time between sessions varied from days to weeks, but this is accounted for in the test-retest structure of the sessions. Participants were required to avoid analgesic medication for 24 hours prior to the sessions. Alcohol, caffeine, nicotine and strenuous activity were avoided for four or more hours prior to the sessions.

The biceps femoris NFR was observed with both single impulse stimulation and temporal summation applied to the sole of the foot. Each procedure was run twice per session; before and after real or sham tDCS to the motor cortex of the respective foot. Each

participant was submitted to both real and sham tDCS in different sessions. Most subjects only experience a slight cutaneous tingling initially under tDCS, and this quickly reduces to nothing (Gandiga, Hummel, & Cohen, 2006). This property allows sham trials to be conducted easily, as real stimulation need only be applied briefly before being stopped in order to mimic the full round of real therapy (Siebner et al., 2004).

## **3.4 Ethics Approval**

Ethical approval was granted by both the Unitec Research Ethics Committee (UREC) and the Auckland University of Technology Ethics Committee (AUTEK). Informed consent was obtained from each participant prior to their initial experimental session.

## **3.5 Instrumentation**

### **3.5.1 Electrode placement**

The NFR was obtained by applying stimulation to the sural nerve of the dominant foot, approximately two centimetres proximally to the 1<sup>st</sup> metatarsophalangeal joint. The NFR was measured from the biceps femoris muscle, approximately 10 centimetres proximal to the knee joint line. The surfaces were prepared by shaving the area, scraped thoroughly with cotton wool, and then cleansed with an alcohol wipe.

The electrode applied to the foot was a Nicolet bar electrode with 9 mm gold cups and 30 mm inter-electrode distance. The cups were coated with an electrically conductive gel. It was secured in place by taping a Styrofoam block in place over the top and finally fixing it in place with a compression bandage.

The biceps femoris electrode was silver-silver chloride and was self-adherent. The anode and cathode were both connected along the line of the tendon, with the anode inferiorly. The readings from this electrode were referenced against a ground electrode connected to the anterior tibia of the ipsilateral shin.

### **3.5.2 Signal Processing**

EMG signals were amplified, filtered (10 Hz to 1000 Hz; AMT-8, Bortec Biomedical, Canada) and sampled at 2000 Hz using a Micro 1401 data acquisition board and Signal software (Cambridge Electronic Design, United Kingdom).

## **3.6 Procedure**

### **3.6.1 tDCS Intervention**

The intervention was applied via a Magstim DC-Stimulator PLUS device. This is micro-processor controlled constant current supply (Magstim, 2010). Participants were randomly assigned to Group A or B, representing real or sham treatment. The examiner was blinded to the nature of each group. In the second session, each group swapped tDCS device and received the other therapy. On both real and sham modes, a 2mA DC current is applied for a period of 30 seconds. This ensures consistency in the initial sensation for control purposes. The anode was fixed over the contralateral motor cortex and the cathode over the ipsilateral orbital region. Both electrodes were 35cm<sup>2</sup> and imbedded in damp sponges containing a 0.5 mol/L saline solution.

Both sessions lasted 20 minutes, with real tDCS being applied at a current of 2mA. After the intervention a stand-down period of five minutes was observed, and the NFR and temporal summation procedures repeated at the same thresholds determined prior to the intervention.

### **3.6.2 Electrocutaneous stimulation procedure**

Participants stood on a wooden box (150cm × 40cm × 26cm) on their non-dominant leg, and let their dominant leg hang freely over the edge. They were able to hold onto either an insulated rail or a nonconductive bench top to aid their balance. Their dominant leg was not able to touch the floor, and the participant was instructed to relax that leg as much as possible. The biceps femoris EMG was displayed on an oscilloscope to allow the examiner to monitor background activation.

Each session was initiated with the participant receiving 10 rectangular shocks of 1ms duration and reporting pain intensity for each on a VRS scale of 0-100. The purposes of these initial shocks were to acclimatise the patient to the sensation before readings were recorded and to give them practice in determining VRS pain intensities quickly. Stimulation was applied at computer determined random intervals, 8-12s apart.

The presence of a genuine NFR response was defined by measuring the peak z-score EMG activity of Biceps femoris, measured over an interval of 85ms to 150ms post-stimulation. This window provides an opportunity to observe the NFR without contamination from involuntary or startle responses, or from non-nociceptive reflexes (R. Dowman, 1992). A baseline mean was taken between -65ms and -5ms prior to stimulation. The NFR Interval Z-score was employed to determine whether the activity indicated the presence of the NFR. A Z-score of 1.38 provides the optimum combination of sensitivity and specificity at 85% each (Rhudy & France, 2007).

$$Z - score = \frac{NFR\ interval\ peak - baseline\ mean}{Baseline\ SD}$$

The NFR was determined using the staircase method described by Rhudy and France (Rhudy & France, 2007). Stimulation was set initially to 0mA, and then increased in 4mA intervals until a NFR was registered with a Z-score of 1.4 or higher. The stimulation was then lowered in units of 2mA until a Z-score lower than 1.4 was found. From this point the stimulation was raised again in units of 1mA until the Z-score broke 1.4 again, dropped by 1mA increments until it fell below 1.4, and then repeated one more time in 1mA increments. By the end of the process four data points indicating the beginning and cessation of the NFR reflex while using the staircase in 1mA were obtained. These data points were averaged to determine the base-line for the NFR.

For each of the stimulations the participant was required to report pain intensity on a 0-100 VRS scale. A subjective pain rating was required when determining the NFR, with 0 being no pain and 100 being the worst pain imaginable. The experiment was discontinued if the pain rating reached over 75. A minimum pain rating of 30 was required to ensure the NFR was a result of nociceptive input and that the stimulation was perceived as pain. If a Z-score higher than 1.4 was obtained before a VRS of 30 was, the stimulation was increased until the VRS was at least 30.

## **3.7 Measures**

### **3.7.1 NFR Threshold**

The mean NFR threshold was tested by applying a series of stimuli to the foot at the obtained current. If three out of four stimulations registered a Z-score of 1.4 this intensity was determined to be the NFR threshold for the patient. If fewer than three stimuli registered that z-score the current was increased by 1mA and the test repeated until three or four z-score successes were obtained. If four z-scores of 1.4 were obtained initially, the stimulation was reduced by 1mA intervals until fewer than four successes were obtained. This intensity was then used as the NFR threshold.

A series of 10-20 pulses at the NFR threshold was applied at 8-12 second intervals, until either 10 z-score successes had been obtained or a total of 20 stimuli had been administered. The EMG data from the first 10 successes for each participant was isolated and averaged to form a single average trace. In the event that 10 successes were not obtained initially, the process was repeated at 2mA higher current until 10 successes were achieved. An area under the root mean square (RMS) curve between 85ms and 150ms was calculated to determine the overall strength of the NFR. This value was statistically analysed and reported as Integrated RMS (iRMS).

### **3.7.2 Temporal Summation Threshold**

In addition to the NFR, the effects of temporal summation were also investigated. Each participant was subjected to a series of five 1ms pulses, with an interpulse distance of 3ms. Each of these chains was separated by 8-12 seconds, determined randomly.



The stimuli was initiated at one fifth the value of the NFR reflex, and increased in 1mA intervals until the final two of the five pulses registered a z-score of 1.4 or higher. No pain rating data was obtained for this measurement.

### **3.8 Statistical Analysis**

Variables were explored for assumptions of normality by analysing the values for skewness and kurtosis with their standard errors and completing a Shapiro-Wilk test. Minor violations of normality were accepted (Schmider, Ziegler, Danay, Beyer, & Bühner, 2010) and two-way repeated-measure ANOVA models were used to test for effects of Condition and Time factors for both measures of iRMS and TS thresholds. Statistical significance was set at  $P = 0.05$ . Data is presented as mean (standard deviation).

|

## 4. Results

Integrated RMS values for the NFR were obtained for all 16 participants (12 male, 4 female). Due to technical issues complete Temporal Summation Thresholds were only obtained for 13 participants (10 male, 3 female).

**Table 1: Means (SD) for iRMS NFR and TS Threshold, pre and post tDCS**

Condition	Pre-tDCS (SD)	Post-tDCS (SD)
NFR Sham (iRMS)	9.46 (9.67)	7.89 (7.79)
NFR Genuine (iRMS)	8.38 (5.38)	6.12 (4.87)
TS Threshold Sham (mA)	14.39 (8.70)	15.73 (9.24)
TS Threshold Genuine (mA)	16.82 (8.42)	18.95 (9.98)

Two-way ANOVAs were conducted that examined the effect of Condition (Sham, Genuine) and Time (Pre, Post) on iRMS NFR and TS Threshold. There was no statistically significant interaction observed for Condition for either iRMS NFR,  $F(1,15) = 0.204$ ,  $p = 0.43$ , or for TS Threshold  $F(1,12) = 0.182$ ,  $p = 0.68$ .

A main effect for Time was observed for both iRMS NFR,  $F(1,15) = 14.58$ ,  $p = 0.002$ , and for TS Threshold  $F(1,12) = 4.94$ ,  $p = 0.046$ . The iRMS NFR values trended downward across tDCS sessions, while the TS Threshold values trended upward.

## 5. Discussion

### 5.1 Effects of tDCS on NFR

The results of this study indicate that transcranial direct current stimulation does not appear to have a significant effect on descending pathways as measured by the strength of the NFR (as quantified by iRMS), to either direct supra-threshold or temporal summation electrical stimulation of the ipsilateral plantar surface. This may be considered evidence that tDCS of M1 does not significantly influence spinal reflexes, and it is therefore unlikely there is significant descending inhibition acting on the WDR neurons in the dorsal horn due to this process. As a result, it appears that tDCS influences nociceptive signals higher in the CNS. Previous literature suggests the cingulate cortex and medial thalamus as likely areas where nociceptive modulation is occurring (Chai et al., 2010; Davis et al., 2000; Russo & Sheth, 2015). In practical terms, our results indicate that future research of tDCS for the treatment of chronic pain should focus on portions of the CNS higher than the WDR neurons of the dorsal horn. Thalamic, anterior cingulate cortex and direct inhibition of S1 by M1 are avenues open to further study.

The results of the Time comparison indicate that after tDCS the iRMS NFR at the same level of stimulation produces a weaker response, and the TS Threshold is similarly increased. This is consistent with pain habituation (Rennefeld, Wiech, Schoell, Lorenz, & Bingel, 2010), and when considered with the lack of a significant relationship between genuine and sham conditions does not indicate a successful intervention.

It is important to note that although no effect was detected at the dorsal horn level, no attempt to investigate mechanisms of action at higher levels was conducted. Therefore no comment can be made on the effectiveness or efficacy of tDCS as a chronic pain therapy outside of pain processes occurring at this level. Given the apparent lack of influence on the NFR, it is likely that tDCS does not influence wind-up of the WDR dorsal horn neurons in the spinal cord. Wind-up of these neurons constitutes an important contributor to chronic pain,

and an inability to modulate central centralization at this level may prove to be a limiting factor in the ubiquity of tDCS as a form of chronic pain therapy (Schaible et al., 1987; You et al., 2003). A sample of participants with central sensitization is required to confirm whether this is the case.

It may be reasonable to conclude that in the absence of meaningful WDR neuron involvement, tDCS could be considered appropriate for all manner of spinal cord injury chronic pain. However, the clinical picture provided by current studies is non-conclusive regarding the efficacy of tDCS under spinal cord injury conditions (Fregni, Boggio, et al., 2006; Ngernyam et al., 2015; Soler et al., 2007; Wrigley et al., 2013). It is likely that the specific nature of spinal cord injury and the neuropathic pain in subjects influences their susceptibility to desensitization due to tDCS. There is preliminary evidence to suggest that different qualities of pain may be influenced to varying degrees under such treatment, and more studies are required to further investigate this phenomenon (Soler et al., 2010). The duration of injury and chronicity may similarly influence the experience of chronic pain from spinal cord injuries, with older injuries appearing less affected by tDCS than more recent ones (Fregni, Boggio, et al., 2006; Wrigley et al., 2013). However, the effect of duration of spinal injuries and the response to tDCS has yet to be evaluated. Such a study may reveal links between plastic adaptations at different levels of the CNS over time, and the efficacy of tDCS in the treatment of each of those levels.

## **5.2 Limitations of study**

Given that there appears to be variation in tDCS efficacy on different forms of pain, it should not be assumed that the effects on subjects without chronic pain can be compared to those with it. It may be possible that plastic adaptations in the WDR neurons associated with chronic pain may increase any sensitivity to tDCS at that level. Age and general health status of the subjects may similarly influence the findings, as all participants were healthy and between the ages of 18-40 years. Rates of chronic pain are approximately three times higher in the elderly than younger demographics (Dominick et al., 2011). Additionally, some studies have noted a gender difference in tDCS response to a number of methodologies (Paulo Sérgio Boggio, Rocha, da Silva, & Fregni, 2008; Chaieb, Antal, & Paulus, 2008; Knops,

Nuerk, Sparing, Foltys, & Willmes, 2006). The majority of participants in this study were male, which may have biased the data.

Although the methodology for the iRMS NFR data collection was rigorous, the methodology of data collection for TS Threshold lacked the same test-retest rigour and averaging of multiple data samples. TS Threshold responses proved to be relatively unstable when compared to single-stimulation NFR at set currents. In addition, the response of many participants indicated an increased anxiety compared to single pulse stimulation, and anxiety is a powerful influence on nociceptive perception (Chen et al., 2015; Tsao, Lu, Kim, & Zeltzer, 2006). Reliability measures of TS lay outside the scope of this investigation, but should be pursued before TS Thresholds are employed as a measure of the NFR in future research.

In conclusion it appears that tDCS of M1 does not induce inhibition of the dorsal horn wide dynamic range neurons, as tested by its effect on the nociceptive flexion reflex response in biceps femoris.

## 6. Appendix A: Mechanisms and experimental considerations of the NFR

The nociceptive flexion reflex (NFR) is a non-invasive measure that has been used in numerous studies to determine the effects of central sensitization (Courtney, Lewek, Witte, Chmell, & Hornby, 2009; Desmeules et al., 2003; Filatova, Latysheva, & Kurenkov, 2008). The reflex itself acts to remove a limb from a potentially damaging stimulus by inducing flexion, and thus it is sometimes referred to as a nociceptive withdrawal reflex. The magnitude of the response appears to be linearly related to the perception of pain from the stimuli, with the maximum response correlating with the perception of intolerable pain (Skljarevski & Ramadan, 2002).

The NFR is a polysynaptic reflex mediated by WDR neurons (France, France, al'Absi, Ring, & McIntyre, 2002; Sandrini et al., 2005). The excitability of the NFR is increased under wind-up of the WDR neurons, as well as in patient exhibiting knee pain, chronic headaches, or fibromyalgia (Courtney et al., 2009; Desmeules et al., 2003; Filatova et al., 2008; You et al., 2003). The NFR consists of two periods of motor unit contraction that correlate to the conduction velocities of A- $\beta$  (40-60ms) and A- $\delta$  fibres (85-120ms) respectively. These responses are labelled RII and RIII respectively, with RIII being the larger and more stable of the two (Sandrini et al., 2005).

The NFR may be stimulated by a single event that reaches the action potential threshold, or as a result of multiple inputs combining to reach the same threshold (temporal or spatial summation). WDR neurons synapse with multiple excitatory and inhibitory neurons (Sandrini et al., 2005). This style of convergence is termed spatial summation, and pits inhibitory and excitatory afferents directly against each other in determining whether the WDR neuron will generate an action potential.

Temporal summation is another possible mechanism for the activation of the WDR neurons, where multiple sub-threshold stimuli are applied within a timeframe that does not allow for

a complete return to the resting membrane potential. Over time, the membrane potential is steadily increased until the threshold is eventually reached and an action potential generated. This process is analogous to facilitated wind-up, resulting in an increased excitability of WDR neurons in the dorsal horn (Arendt-Nielsen, Sonnenborg, & Andersen, 2000; Weissman-Fogel et al., 2009).

**Figure 24: Mechanism of Temporal Summation**

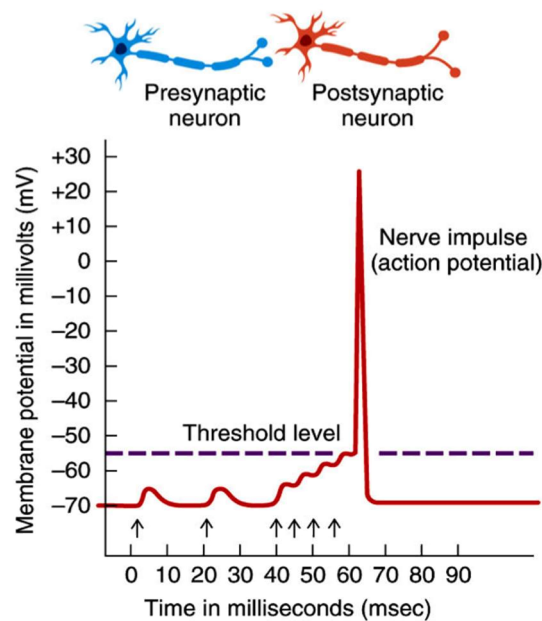


Figure courtesy of studyblue.com, <http://www.studyblue.com/notes/note/n/ch-1-6/deck/5298879>

Temporal summation has been theorised to be a mechanism by which knee osteoarthritis may cause chronic and widespread pain despite a lack of radiological findings (Arendt-Nielsen et al., 2000). It has also been demonstrated to be a factor in temporomandibular disorders, chronic headaches, chronic whiplash pain and fibromyalgia (Maixner, Fillingim, Sigurdsson, Kincaid, & Silva, 1998; R. Staud, Vierck, Cannon, Mauderli, & Price, 2001). It has been proven experimentally that an increase in the frequency of electrical stimulation facilitated both the NFR's amplitude and the patients perceived pain, and therefore the

temporal summation threshold of the reflex may indicate changes in central nociceptive programming (Arendt-Nielsen et al., 2000; Weissman-Fogel et al., 2009).

### **Measuring the NFR:**

The NFR is often quantified in terms of the threshold which is required to evoke a response, however there has not been a consistent definition of the NFR threshold. The method proposed by Willer, whereby the NFR threshold is defined as the lowest level of stimulation that results in a 60-90% rate of response from 20 consecutive stimuli, has been the predominant one (Willer, 1977). This has proven to be a rather crude measure however, and does not provide the detail required for an in-depth analysis. As a result, recent researchers have shifted their definitions to an EMG based criteria involving an activation window and a post-stimulation response window (Banic et al., 2004; Desmeules et al., 2003; Terkelsen, Andersen, Mølgaard, Hansen, & Jensen, 2004). Other researchers have gone further, comparing changes within individual subjects in order to address such factors as electrode design, quality of preparation and tissue disposition (Edwards, Ring, McIntyre, & Carroll, 2001; France et al., 2002; Rhudy et al., 2005).

In an effort to provide a comparable framework from which to compare studies, France and Rhudy conducted a trial in 2007 to determine appropriate methods of measurement for the NFR in biceps femoris (Rhudy & France, 2007). The authors compared the results determined by both subjective (expert raters reviewing the EMG files) and a number of objective measures. The objective measures were all computer generated analysis of the EMG in the 90ms-150ms reflex window. They included:

- NFR interval peak.
- NFR interval mean.
- NFR interval area under curve.
- Number of samples above 10 $\mu$ V.
- Number of samples above 20 $\mu$ V.
- Number of samples above 50 $\mu$ V.



In addition, they also analysed the increase of EMG activity in the NFR reflex window compared to the pre-reflex baseline and the shape of the waveform inside the window.

There measurements were:

- Baseline adjusted NFR interval peaks.
- NFR interval peak Z-score.
- Baseline adjusted NFR interval mean.
- NFR interval Z-score.
- Baseline adjusted NFR area under curve.
- NFR interval Cohens.
- NFR interval Kurtosis.

NFR interval Cohens and Kurtosis are statistical processes used to describe the shape of the curve.

The authors concluded that of these measurements the NFR interval peak Z-score and NFR interval mean Z-score provided 99% confidence intervals. Additionally, it was determined that the optimum balance of Z-scores between specificity and sensitivity for the NFR was at  $Z=1.38$ . For the purposes of this investigation we will be using  $Z=1.4$ .

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