Neuromodulation in Pain

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i. Abstract

Background

Chronic pain is one of the most debilitating disorders afflicting a wide cross-section of the global population. Unfortunately, conventional treatments for chronic pain have proven ineffective for a large subsection of this patient population, prompting the development of new therapeutic paradigms such as neuromodulation. Deep brain stimulation, dorsal root ganglion stimulation and non-invasive brain stimulation have emerged as useful tools in the therapeutic armamentarium for these medically refractory chronic pain patients. We sought to interrogate how these treatments might work and what insights can be gained into the neurophysiology of the pain experience through neuromodulation.

Methods

This thesis describes three categories of experiments into the neurophysiology of chronic pain. The first explored the mechanisms of dorsal root ganglion stimulation in the sensory, cognitive and affective dimensions of pain, as well as its potential to modulate the autonomic nervous system. The second interrogated the utility of non-invasive brain stimulation, transcranial direct current stimulation, to augment the supraspinal effects of dorsal root ganglion stimulation. The final experiment involved a retrospective analysis regarding the effectiveness stimulation frequency in deep brain stimulation for chronic pain and whether these treatments are dependent on underlying neural activity.

Results

1. There were significant neurophysiologic markers of pain (cortical theta activity) and pain relief (cortical beta activity) among dorsal root ganglion stimulation patients, with efficacy in modulating sensory, cognitive and autonomic indicators in chronic pain patients. The affective dimension of

pain revealed mixed results, however demonstrated features consistent with differences of emotional processing in chronic pain compared to healthy controls.

2. Transcranial direct current stimulation significantly enhanced the therapeutic efficacy of dorsal root ganglion stimulation on chronic pain in the acute setting and demonstrated augmentation of predetermined neurophysiologic indicators (cortical beta activity) of pain relief.
3. The efficacy of deep brain stimulation did not appear to be dependent on stimulation frequency. However, baseline local field potential recordings appear to be predictive of the ideal stimulation frequency to optimise analgesic effect in chronic pain patients.

Conclusion

This thesis provides novel evidence of the mechanisms of dorsal root ganglion stimulation and provides preliminary evidence of a synergistic effect between invasive and non-invasive neuromodulation in the treatment of chronic pain. We have also provided supportive evidence for the utility of physiologic biomarkers of pain in evaluating neuromodulatory therapies as a framework for personalising chronic pain treatments.

ii. Acknowledgments

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iii. Table of contents

iv. Abbreviations

ACC – Anterior cingulate cortex

ANS – Autonomic nervous system

CNS – Central nervous system

CRPS – Complex regional pain syndrome

CT – Computerized tomography

DBS – Deep brain stimulation

DLPFC – Dorsolateral prefrontal cortex

DMN- Default mode network

DNIC – Diffuse noxious inhibitory control

DRG – Dorsal root ganglion

DRGS – Dorsal root ganglion stimulation

ECG – Electrocardiogram

EEG – Electroencephalography

EOG – Electrooculography

ERF – Event-related fields

ERP – Event-related potentials

FBSS – Failed back surgery syndrome

FERT – Facial expression recognition task

HRV – Heart rate variability

ICA – Independent component analysis

IPG – Implantable pulse generator

LFP – Local field potential

LTP – Long term potentiation

MCP – Midcommissural point

MEG – Magnetoencephalography

MEP – Motor-evoked potential

MPQ – McGill Pain Questionnaire

MRI – Magnetic Resonance Imaging

MSE – Mean Spectral Energy

NRM – Nucleus Raphe Magnus

NRS – Numerical Rating Scale

PAG – Periaqueductal grey

Pb – Parabrachial area

PDN – Painful diabetic neuropathy

PHN – Postherpetic neuralgia

PNS – Peripheral nervous system

PSD – Power spectral density

PSP – Post-stroke pain

PVG – Periventricular grey

RVM – Rostral ventral medulla

SCS – Spinal cord stimulation

SDNN – Standard deviation of normal-to-normal (intervals)

SN- Salience network

SNRI – Serotonin- norepinephrine reuptake inhibitor

SQUID – Superconducting Quantum Interference Device

SRD – Subnucleus reticularis dorsalis

SSc – Somatosensory cortex

SSRI – Selective serotonin reuptake inhibitor

STT – Spinothalamic tract

tACS – Transcranial alternating current stimulation

TCA – Tricyclic antidepressants

TCD – Thalamocortical dysrhythmia

tDCS – Transcranial direct current stimulation

TENS – Transcutaneous electrical nerve stimulation

TMS – Transcranial Magnetic Stimulation

VAS – Visual Analogue Scale

VPL – Ventral Posterolateral

VPM – Ventral Posteromedial

VZV – Varicella Zoster Virus

v. Related publications, presentations and awards

PUBLICATIONS

Parker, T., Huang, Y., Raghu, A., FitzGerald, J.J., Green, A.L., Aziz, T.Z. Dorsal Root Ganglion Stimulation Modulates Cortical Gamma Activity in the Cognitive Dimension of Chronic Pain. Brain Sciences, 11 February 2020 – **Chapter 5**

Parker, T., Green, A., Aziz, T. Rapid onset and short washout periods of Dorsal Root Ganglion stimulation facilitate multiphase crossover study designs. Brain Stimulation, 4 September 2019 – **Chapter 3**

Parker, T., Zand, A.D., Huang, Y., Aziz, T.Z, Sverrisdottir, Y., Green, A.L. Dorsal Root Ganglion Stimulation: A New Target for Autonomic Neuromodulation? Clinical Autonomic Research, 4 January 2021 – **Chapter 8**

Parker, T., Huang, Y., Raghu, A., FitzGerald, J.J., Aziz, T.Z, Green, A.L. Supraspinal effects of Dorsal Root Ganglion Stimulation. *Provisionally accepted,* Neuromodulation – **Chapter 4**

PRESENTATIONS

Parker, T., Huang, Y., Aziz, T., Green, A. Cognitive Modulation of Pain in Dorsal Root Ganglion Stimulation. Oral presentation at the North American Neuromodulation Society (NANS) Annual Meeting, January 2020. Las Vegas, Nevada, USA – **Chapter 5**

Parker, T., Huang, Y., Raghu, A., Aziz, T., Green, A. Cortical changes in dorsal root ganglion stimulation. Oral presentation at the British Society for Stereotactic and Functional Neurosurgery (BSSFN) Annual Conference, May 2019. Cambridge, UK – **Chapter 4**

AWARDS

Nuffield Department of Surgical Sciences Early Career Researcher of the Year Award 2020

British Society for Stereotactic and Functional Neurosurgery (BSSFN) Annual Conference - Award for Best Oral Presentation 2019

OTHER PUBLICATIONS

Parker, T., Rigney, G., Kallos, J., Stefko, S., Niranjan, A., Kano, H., Green, A., Aziz, T., Rath, P., Lunsford, L.D. - Gamma knife radiosurgery for the treatment of uveal melanomas and metastases: a systematic review and meta-analysis. The Lancet Oncology, 2 November 2020

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1. INTRODUCTION

Pain is defined by the International Association for the Study of Pain (IASP) as “an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage”.(Merskey and Bogduk 1994) The IASP further defines neuropathic pain as “pain caused by a lesion or disease of the somatosensory nervous system”.(Murnion 2018)

Despite these well-recognized definitions, the subjective experience of pain remains loosely tethered to objective measures of pain intensity and various methods for its evaluation. Pain is often described as a “multi-dimensional” experience comprising sensory, cognitive and affective components.(Melzack, R., & Casey 1968) Attempts to generate objectivity from these dimensions of pain have resulted in the established scales used for pain intensity (Numerical Rating Scale [NRS], Visual Analogue Scale [VAS]), emotional/qualitative elements of pain (McGill Pain Questionnaire [MPQ]) and impact of pain on quality of life (Short-form general health survey-36 [SF-36]).(Hawker et al. 2011) In clinical practice, pain is often categorized temporally – acute (lasting less than 12 weeks) or chronic (lasting more than 12 weeks) – and aetiologically – nociceptive or neuropathic.(Hadjipavlou, Cortese, and Ramaswamy 2016) In contrast to the previously described neuropathic pain, nociceptive pain arises from trauma or tissue damage and represents an integral alarm system for human survival, as evidenced by the significant (unintended) trauma experienced by individuals born with congenital insensitivity to pain.(Nagasako, Oaklander, and Dworkin 2003)

When pain no longer serves this evolutionary purpose and persists in the absence of noxious stimuli it becomes a source of significant human suffering. Chronic neuropathic pain represents one of the most debilitating diseases worldwide and, as such, has become the focus of emerging therapies in neurosurgery and neuromodulation. The prevalence of chronic pain is variable, but reports estimate it may affect up to 35% of the general population,(Gilron et al. 2006; Toth, Lander, and Wiebe 2009)

amounting to approximately $560 – $635 billion in health care costs annually in the U.S. alone.(Institute of Medicine (US) Committee on Advancing Pain Research, Care 2011) Conventional treatment strategies for chronic pain have primarily been based on pharmacologic therapy. The non-steroidal anti-inflammatory drugs (NSAIDs) are still generally considered first-line management, especially for pain of nociceptive origin, while cautious use of opioids, anti-epileptic drugs (eg. gabapentin, pregabalin) and select antidepressants – tricyclic antidepressants (TCAs)(eg. amitriptyline, imipramine) and serotonin-norepinephrine reuptake inhibitors (SNRIs) (eg. duloxetine, venlafaxine) – have been proven effective in the management of neuropathic pain. However, more modern strategies towards chronic pain management include greater emphasis on non-pharmacologic therapies (physical therapy, cognitive behavioural therapy [CBT], mindfulness) and multi-disciplinary management involving primary care physicians, pain specialists, neurologists and/or neurosurgeons. Unfortunately, up to 60% of chronic pain patients may be unsatisfactorily treated with best medical therapy,(Hansson et al. 2009) a problem which has served as the catalyst for considerable research and development in the field of neuromodulation.

1.1 The Anatomy of Pain

1.1.1 *The Dorsal Root Ganglion*

Nociceptors are peripherally located free nerve endings of pseudounipolar neurons which are sensitive to noxious mechanical or thermal stimuli.(Dubin and Patapoutian 2010) Nociceptive stimuli are transmitted along myelinated Aδ fibres and smaller unmyelinated C fibres which have their cell bodies located within the dorsal root ganglion, or trigeminal ganglion, at the respective dermatomal level. Nociceptors can be quite heterogenous in their receptive fields and the dynamic range of stimuli which can stimulate them. Nociceptors transduce thermal (heat/cold) and mechanical stimuli via a diverse group of ion channels including non-selective cation channels (TRPV1 – TRPV4, TRPM8, TRPA1),

constitutively active K^+ channels (KCNK2, KCNK4), voltage-gated sodium(Na_V) and calcium channels(Ca_V).(Dubin and Patapoutian 2010; Park and Luo 2010; Waxman and Zamponi 2014)

These nociceptors transmit fast-onset pain (via Aδ fibers) and slowly developing pain (via C fibers) towards the spinal cord. These axons enter the spinal cord via the dorsal horn, synapse with interneurons and second-order neurons in lamina I (marginal nucleus), II (substantia gelatinosa of Rolando) and V of the spinal cord using predominantly glutamate and neuropeptides (Calcitonin gene-related peptide [CGRP], substance P, neuropeptide Y) as neurotransmitters. These synaptic connections between nociceptive afferents, interneurons and efferent neurons of the Rexed laminae are the components of the gate control theory of pain,(Melzack and Wall 1965) and are responsible for the flexor withdrawal reflex away from aversive stimuli.(Linde et al. 2020)

1.1.2 *Ascending pain pathways*

Second-order neurons from lamina I and the nucleus proprius (laminae IV – VI) cross in the anterior white commissure and ascend as the anterolateral spinothalamic tract (STT). In the brainstem, the STT, along with the spinoreticulothalamic and spinotectal tracts form the ascending spinal lemniscus. There are extensive connections and terminations with nuclei of the medulla, pons and midbrain. Terminations in the nucleus of tractus solitarius are associated with cardiovascular and respiratory responses to painful stimuli,(Esteves, Lima, and Coimbra 1993) while connectivity with the reticular formation contributes to descending pain modulation pathways. Lamina V/VI neurons terminate largely in the parabrachial area (Pb) of the pons, which relays large areas of the body's receptive fields to limbic regions including the stria terminalis, periventricular hypothalamus, central nucleus of amygdala, intralaminar and ventromedial posterior nuclei of thalamus, insular and anterior cingulate cortex (ACC).(Rodriguez et al. 2017; Yam et al. 2018) These projections primarily represent the affective-motivational dimension of pain (pain unpleasantness, emotional responses) and are also known as the

medial pain pathway [See Figure 1].(Ab Aziz and Ahmad 2006) Lamina I neurons comprise the majority of the lateral pain pathway which project to the posterior nucleus and ventrobasal complex (ventral posterolateral [VPL] and ventral posteromedial [VPM] nuclei) of thalamus, and encode the sensory-discriminative dimension (pain intensity, localization) of pain.(Yen and Lu 2013) Thalamocortical projections from the ventrobasal complex to the primary somatosensory cortex (SSc) generate a somatotopic organization (sensory homunculus) which facilitates sensory discrimination and location.

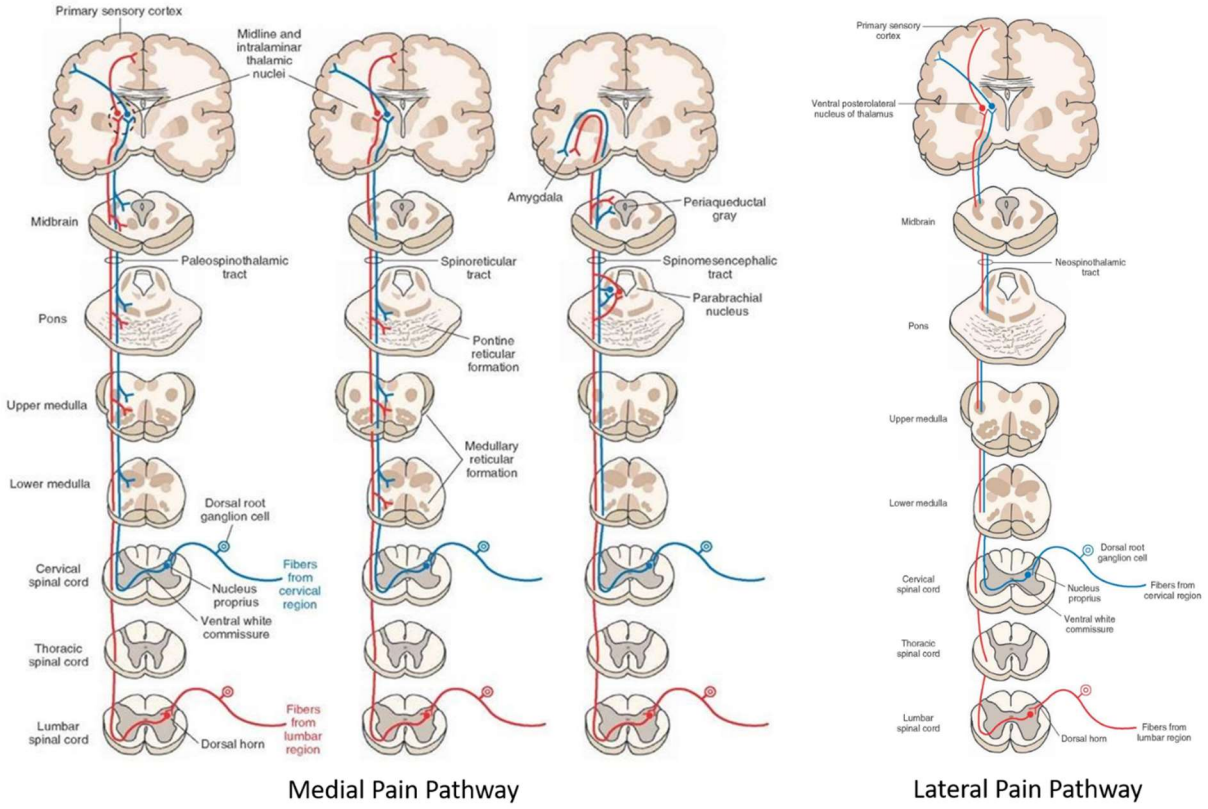

Figure 1. *Illustrations of the medial and lateral ascending pain pathways adapted from Dekker et al. 2016*

1.1.3 *Cortical Pain Networks/Connectome*

The broad regions of cortex that are involved in the process of tonic (acute) and phasic (chronic) pain have been well-established over decades of research. The regions associated with pain processing, and

the synaptic interactions between them, have been referred to as a pain neuromatrix/network. (Melzack 2001) However, based on the complex interactions between different cortical networks that contribute to the pain percept, it is likely to be more accurately described as a dynamic pain connectome.(Mouraux and Iannetti 2018) The pain connectome describes the spatio-temporal connectivity of brain oscillations between different cortical networks, namely the default mode network (DMN), salience network (SN) and descending pain modulation system. The DMN is generally most active at rest in the absence of sensory stimuli and includes the precuneus, posterior cingulate cortex, medial prefrontal cortex and medial temporal lobe. In contrast, the SN is responsible for directing awareness towards external stimuli and has active nodes in the temporoparietal junction, anterior insula, mid-cingulate cortex and dorsolateral prefrontal cortex (DLPFC).(Kucyi and Davis 2015) Abnormal structure and activity within and between various nodes of the salience and default mode networks have been observed in chronic pain disorders.(Davis and Moayedi 2013; A. May 2011) The exploration of these neuroanatomic interactions, coupled with advances in neuroimaging and physiology represent a shift towards representing chronic pain based on its static and dynamic functional connectivity with regions of the ascending and descending pain networks.(Bosma et al. 2018)

1.1.4 *Descending pain pathways*

In addition to the well-characterized ascending pain pathways, more recent evidence has begun to describe the structures which contribute to the descending modulatory inputs on pain processing. The major descending inputs which influence nociception are the periaqueductal grey (PAG), the rostroventral medulla (RVM) and the dorsal nucleus of the reticular formation or subnucleus reticularis dorsalis (SRD). The PAG was one of the first brain regions identified to be capable of producing analgesia,(Reynolds 1969) which functions by incorporating afferents from both ascending nociceptive inputs and descending cortical centres. The anti-nociceptive effects of the PAG includes opioidergic

mechanisms,(Sims-Williams et al. 2017) based on its reversibility on administration of naloxone.(Hosobuchi, Adams, and Linchitz 1977) However, non-opioidergic projections have also been described,(Benarroch 2012) with a large fraction of PAG-dependent pain modulation mediated via its connectivity with the RVM. The RVM includes the nucleus raphe magnus (NRM), the nucleus reticularis gigantocellularis-pars alpha and the nucleus paragiganto-cellularis lateralis. The RVM contains "on cells" and "off cells" which respond to afferent inputs to facilitate nociception or analgesia respectively. The descending serotonergic projections of the RVM can, therefore, either be pro-nociceptive or anti-nociceptive depending on which cells are activated and the subtype of 5HT receptor activated.(Ossipov, Morimura, and Porreca 2014) This type of bidirectional pain modulation is also observed in the SRD. The SRD, located in the caudal medulla, also integrates afferent information from cortical centers (amygdala, hypothalamus, ACC, SSc), and has reciprocal connectivity with the RVM and spinal cord laminae which facilitates the role of the SRD in the homeostatic regulation of pain.(Martins and Tavares 2017) The SRD is an important structure of the diffuse noxious inhibitory control (DNIC) system which is an example of top-down cortical control of pain signals. The function of the DNIC is to reduce the perception of a secondary painful stimulus after conditioning from a primary nociceptive stimulus carried by Aδ or C fibres. These anatomical structures are important for the normal regulation of pain sensation, amplification and attenuation. However, when disease or dysfunction affects any component of these pain pathways, they may be implicated in the genesis and persistence of pain.

1.2 The Mechanisms of Pain

The mechanisms by which pathologies of the nervous system manifest as persistent aversive sensations have been explored by molecular (Ueda and Rashid 2003) and genetic (H. Wang et al. 2002) techniques, in a variety of animal (Jaggi, Jain, and Singh 2011) and human experimental pain models (Reddy et al.

2012). However there have been two important mechanisms which can be identified in most chronic pain syndromes – central and peripheral sensitization.

1.2.1 *Peripheral Sensitization*

Any insult or injury to the peripheral nervous system results in well-known inflammatory responses which may initiate the cascade to neuropathy. Repetitive exposure to prostaglandins,(Moriyama et al. 2005) leukotrienes(Okubo et al. 2009) and inflammatory cytokines(Sommer and Kress 2004) released at the site of injury cause a decrease in threshold and increase in responsiveness of surrounding nociceptors. This phenomenon is known as peripheral sensitization and underlies the hypersensitivity response to painful stimuli often observed in chronic pain – primary hyperalgesia. Altered gene(Martin et al. 2019) and channel expression (Devor 2006) of the surrounding neural tissues, as well as abnormal sprouting in regions of axonal damage during Wallerian degeneration (Mantyh et al. 2010; McLachlan et al. 1993) have also been implicated in generating the neuronal hyperexcitability seen in neuropathic pain [See Figure 2]. When this hypersensitivity to mechanical stimuli extends to adjacent non-injured tissues it is known as secondary hyperalgesia. The perception of non-noxious stimuli (eg. light touch) as painful is known as allodynia and typically develops as these maladaptive peripheral responses to injury induce changes in the dorsal horn and supraspinal structures. Lowered thresholds for action potential generation in these peripheral nociceptors,(Torebjork, LaMotte, and Robinson 1984) is hypothesized to contribute to bottom-up cortical reorganization and, eventually the phenomenon of central sensitization.

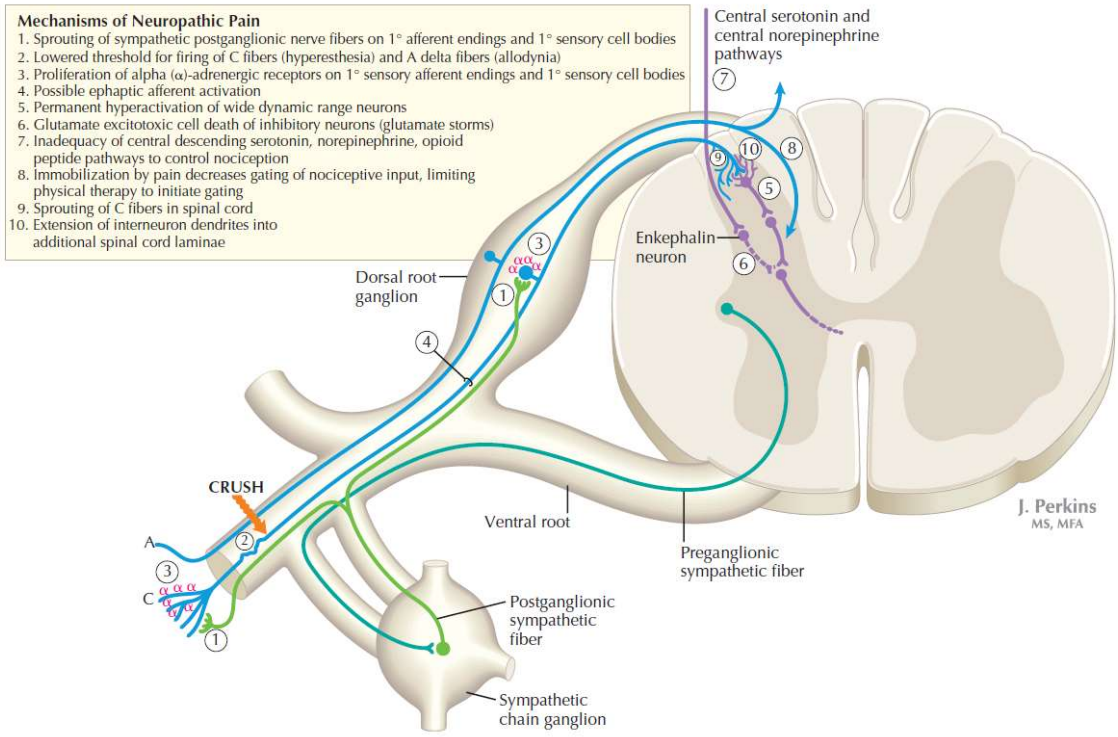

***Figure 2**. Illustration demonstrating various proposed mechanisms contributing to neuropathic pain (reproduced from Netter's Atlas of Neuroanatomy, third edition, 2016)*

1.2.2 *Central Sensitization*

Central sensitization describes the increased responsiveness of pain-sensitive neurons in the central nervous system via recruitment of non-nociceptive afferents.(Woolf 2011) Exposure to an intense, noxious stimulus can condition nociceptive neurons to respond to subthreshold stimuli as a part of the body's normal adaptive response to avoid further harm. These changes are usually reversible once the aversive stimulus has been removed, however central sensitization may become pathological when it results in the de-coupling of pain sensation from peripheral nociceptive stimuli.

Unlike peripheral sensitization, which is usually limited to its receptive field, central sensitization recruits new low threshold afferents in the CNS which results in the expansion of the normal receptive

fields of nociceptive-specific neurons. Brain regions that have been commonly affected by the process of central sensitization in the generation of chronic pain include the somatosensory, cingulate, and prefrontal cortex (Ashmawi et al. 2016; Maihöfner et al. 2010). Central sensitization occurs via heterosynaptic potentiation, a mechanism of activity-dependent synaptic plasticity.(Latremoliere and Woolf 2009) In contrast to the well-known phenomenon of long-term (homosynaptic) potentiation (LTP), heterosynaptic potentiation increases the efficacy of other synaptic afferents, in addition to its own.[See Figure 3] This synaptic facilitation promotes action potential generation in central pain pathways in the presence of both nociceptive and non-nociceptive stimuli which manifests as chronic ongoing pain. Other mechanisms which have been implicated in central sensitization include glutamate-mediated augmentation of membrane excitability via NMDA and AMPA receptors,(Ma and Woolf 2002) as well as central disinhibition due to apoptosis/inhibition of GABAergic and glycinergic interneurons in the spinal cord.(Zeilhofer 2008)

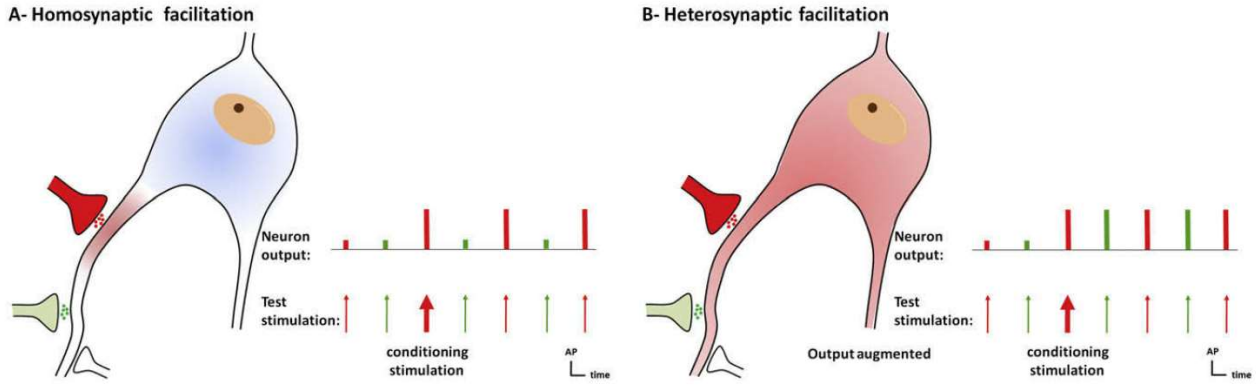

***Figure 3**. Illustration of homosynaptic facilitation seen in LTP vs. heterosynaptic facilitation seen in central sensitization (adapted from Latremoliere and Woolf 2009)*

1.3 Aetiologies of Chronic Pain

Chronic pain can result from a wide variety of aetiologies including inflammatory (eg. rheumatoid arthritis), degenerative (eg. osteoarthritis), neoplastic (cancer pain), musculoskeletal (eg. spondylosis)

and idiopathic (eg. fibromyalgia) disorders. While there is interest in the treatment of many of these disorders by neuromodulation, the conditions seen and treated by neurosurgical intervention most commonly fall under one of the following headings.

1.3.1 *Post-surgical Pain*

Chronic post-surgical pain is diagnosed in a patient with persistent pain at or adjacent to the operative region two or more months after a surgical procedure. Between 10 and 50% of post-operative patients will have prolonged pain after the acute peri-operative pain should have subsided.(Kehlet, Jensen, and Woolf 2006) Surgical procedures that most commonly result in chronic post-surgical pain include mastectomies, thoracic surgery due to traction on intercostal nerves, hernia repair and amputations.(Searle and Simpson 2009) Phantom limb pain is a specific category of post-surgical pain affecting a variable proportion (42% - 79%) of amputees.(Sherman, Sherman, and Parker 1984; Subedi and Grossberg 2011) While often referred to as “phantom limb pain” when occurring after extremity amputation, reports of phantom breast pain post-mastectomy,(Krøner et al. 1989) and phantom tooth pain after dental procedures have also been described.(Marbach and Raphael 2000) The pain is generally intermittent, typically originating from the distal aspect of the involved region and likely results from a combination of central and peripheral maladaptive neuronal responses. Phantom limb pain can also be accompanied by “stump pain” which is a separate, yet interconnected phenomenon, likely resulting from neuroma formation, bone spurs or deep wound infections.(Macrae 2001)

Failed back surgery syndrome (FBSS) is another chronic pain syndrome which results after one or more spinal surgeries have proven unsuccessful in the treatment of chronic lower back pain and/or sciatica. Approximately 10 – 40% of lumbar laminectomies ± spinal fusion will develop chronic pain sequelae, while micro-discectomy reportedly has a lower incidence of progressing to FBSS.(Sebaaly et al. 2018) Pre-operative (eg. psychiatric illness, social stressors), intra-operative (eg. poor technique) and post-

operative (eg. progressive instability, chronic inflammation) factors have all been implicated in the genesis of FBSS.(Chan and Peng 2011) FBSS has also been defined by "the failure of surgical outcomes to meet pre-surgical expectations of the patient and surgeon."(Waguespack et al. 2002) As a result, managing patient expectations pre-operatively and psychosocial strategies to mitigate the aforementioned risk factors are commonly employed to reduce the incidence of FBSS. Despite these preventive measures, the surge in the number of spinal surgeries being performed has made FBSS a significant burden on patients and society. Fortunately, neuromodulation has emerged as an effective option for the treatment of chronic pain in FBSS,(Kallewaard, Nijhuis, et al. 2019) and is a field of active interest for post-surgical pain management more broadly.

1.3.2 *Complex Regional Pain Syndrome*

Complex regional pain syndrome (CRPS) encompasses a group of chronic pain syndromes (reflex sympathetic dystrophy, causalgia, Sudek atrophy) characterized by continuous, spontaneous or evoked, pain in a specific region (most commonly upper limb) of the body. CRPS type 1 is the most common presentation, among patients without evidence of nerve injury, while CRPS type 2, also known as causalgia, is seen in patients with an associated lesion in the peripheral nervous system (PNS). The pain is usually described as "burning" or "stinging" and, based on the Budapest consensus criteria,(Harden et al. 2007), must be accompanied by at least one symptom from the following categories:

- Sensory – Hyperalgesia or allodynia
- Vasomotor – Changes in skin colour, skin colour and/or temperature asymmetry
- Trophic/Motor – Trophic changes in the skin, hair nails, decreased range of motion, motor weakness, tremor or dystonia.
- Sudomotor – oedema, sweating changes or sweating asymmetry

The pathogenesis of CRPS has been characteristically described as “sympathetically-maintained”, as demonstrated by relief of pain and dysesthesia (any abnormal unpleasant sensation) after sympathetic blockade.(Gungor, Aiyer, and Baykoca 2018) However the pathophysiology of CRPS also includes proinflammatory mechanisms,(Üçeyler et al. 2007) genetic predisposition (HLA-DQ1),(Kemler et al. 1999) central sensitization and cortical plasticity.(Marinus et al. 2011)

1.3.3 *Postherpetic Neuralgia*

After primary infection with the varicella-zoster virus (VZV), the virus travels via retrograde axonal transport and integrates its viral DNA into the host genome to establish latency in the dorsal root or cranial nerve ganglia. Herpes zoster (shingles) occurs upon reactivation of the latent virus and tends to occur in older individuals as immune function wanes with age, or among immunodeficient individuals due to HIV, chemotherapy or systemic disease. Acute herpes zoster is characterized by a painful rash which begins as erythematous papules which progress to a vesicular eruption in a dermatomal distribution. The painful acute neuritis which accompanies herpes zoster is usually self-limited, however 18% of patients with shingles, and 33% in persons over 79, will have persistent pain beyond 90 days of rash onset which defines postherpetic neuralgia (PHN).(Yawn et al. 2007)

Allodynia and/or sensory deficits of the affected dermatome have been described to accompany the “burning”, “sharp” or “stabbing” pain of PHN. The pathogenesis of the development of PHN is not clearly understood. However, its emergence among immuno-compromised individuals suggests that altered immune function plays an important role. Additionally, haemorrhagic inflammation affecting the peripheral nerve, DRG and areas of the spinal cord have been observed during acute herpes zoster.(Bennett and Peter 2009) Coupled with histological findings of demyelination, fibrosis and spinal cord atrophy in PHN patients, chronic inflammation also seems to play an important role in the pathogenesis of PHN.(S. M. Zhu et al. 2009)

1.3.4 *Painful Diabetic Neuropathy*

Diabetic neuropathy is the most common neuropathy in the world. The prevalence of diabetes varies by region and ethnicity, affecting between 2 and 22% of the world's adult population.(IDF 2019) The complications of diabetes can range from cranial nerve dysfunction, nerve entrapment, autonomic dysfunction, and sensory dysfunction preferentially affecting the feet.(Said 2007) Length-dependent neuropathy results in significant physical and social morbidity, estimated to affect around 30% of people with diabetes, and more than half of those 60 years or older.(Young et al. 1993) Clinically, small (C, Aδ) and large (Aα, Aβ) fibre damage lead to symptoms of pain, paraesthesia and numbness which can progress to further complications such as neuropathic arthropathy and ulceration. The pathophysiology of diabetic neuropathy involves (i) osmotic stress from polyol accumulation, (ii) endoneurial microangiopathy, (iii) oxidative stress, and (iv) generation of advanced glycation end products which all contribute to nerve damage.

Painful Diabetic Neuropathy (PDN) is a neuropathic pain syndrome, affecting around 26% of people with diabetes, which results in considerable morbidity and impairment in quality of life.(Davies et al. 2006) PDN has escaped categorisation to specific pathomorphological findings, however physiologically it is likely to involve dysfunctional processing at the level of the DRG, central nervous system and autonomic nervous system.(Shillo et al. 2019)

1.3.5 *Post-stroke pain*

Post-stroke pain (PSP) is a type of central neuropathic pain that develops after cerebrovascular insult affecting any part of the pain pathway, most commonly the sensory thalamus. Indeed, the earliest reports of PSP described it as 'le syndrome thalamique" or "thalamic syndrome",(Déjerine and Roussy

1906) a phenomenon which still bears the eponymous title of the original authors (Dejerine-Roussy syndrome).

A large cohort study has estimated that approximately 11% of patients with ischemic stroke will develop chronic PSP.(O'Donnell et al. 2013) Thalamic syndrome is often caused by a lesion of the VPL, VPM or pulvinar of the thalamus and causes pain in the region of hemiplegia/hemi-anaesthesia up to 6 months after the cerebrovascular accident. However, the clinical presentation varies based on the anatomical location of the infract. For example, lesions of the brainstem such as lateral medullary syndrome (Wallenberg syndrome) may produce isolated facial pain ipsilateral to the lesion and sensory deficits in the contralateral limbs which may or may not manifest neuropathic symptoms.(MacGowan et al. 1997)

The pathophysiology which underlies PSP is based largely on theories of disinhibition of the posterolateral inferior thalamus and resultant overactivity in the thalamocortical loop which manifests as pain.(Klit, Finnerup, and Jensen 2009) Deafferentation of the thalamus is likely the inciting factor for central sensitization and ongoing dysfunctional oscillatory activity in thalamic projections to the cerebral cortex.(Gexin Wang and Thompson 2008)

Deep brain stimulation (DBS) has become a popular treatment strategy in PSP patients, with differential effects on pain alleviation depending on the target of choice. DBS targeting the periventricular grey (PVG) and/or sensory thalamus has resulted in significant reductions in both VAS (sensory) and MPQ (sensory/affective) scores in a cohort of PSP patients.(Owen et al. 2006) In contrast, a small randomized controlled crossover trial of DBS targeting the ventral striatum/anterior limb of the internal capsule (VS/ALIC) revealed no difference in sensory-discriminative metrics of pain during stimulation, but had significant improvement in affective metrics of chronic pain – Montgomery-Åsberg Depression Rating

Scale (MADRS) and Beck Depression Inventory (BDI) (Lempka et al. 2017) – which underscores the selectivity of various anatomical targets for modulating the various dimensions of chronic pain.

1.4 Neurophysiology

Despite an abundance of literature describing the epidemiology, clinical features and treatment of chronic pain, the tools used to investigate pain in the human system have had variable degrees of success in demystifying the physiology of pain. In response to this gap in our understanding, a number of neurophysiological techniques have attempted to interrogate these aberrant neuronal impulses on a variety of spatial and temporal scales. Neurophysiologic techniques such as electroencephalography, magnetoencephalography, microneurography and local field potential recordings, facilitated by neuromodulatory therapies, have started to shed some light on the neural encoding of neuropathic pain.

1.4.1 *Microneurography*

The technique of microneurography utilizes a tungsten microelectrode inserted percutaneously into a nerve bundle to facilitate single unit recordings of neurons in humans. This technique is a powerful tool to investigate human systems as it provides neurophysiologic information with the highest spatial and temporal resolution (See Figure 4), but also provides a window into the physiological recordings of myelinated and unmyelinated nerve fibres of the peripheral nervous system.

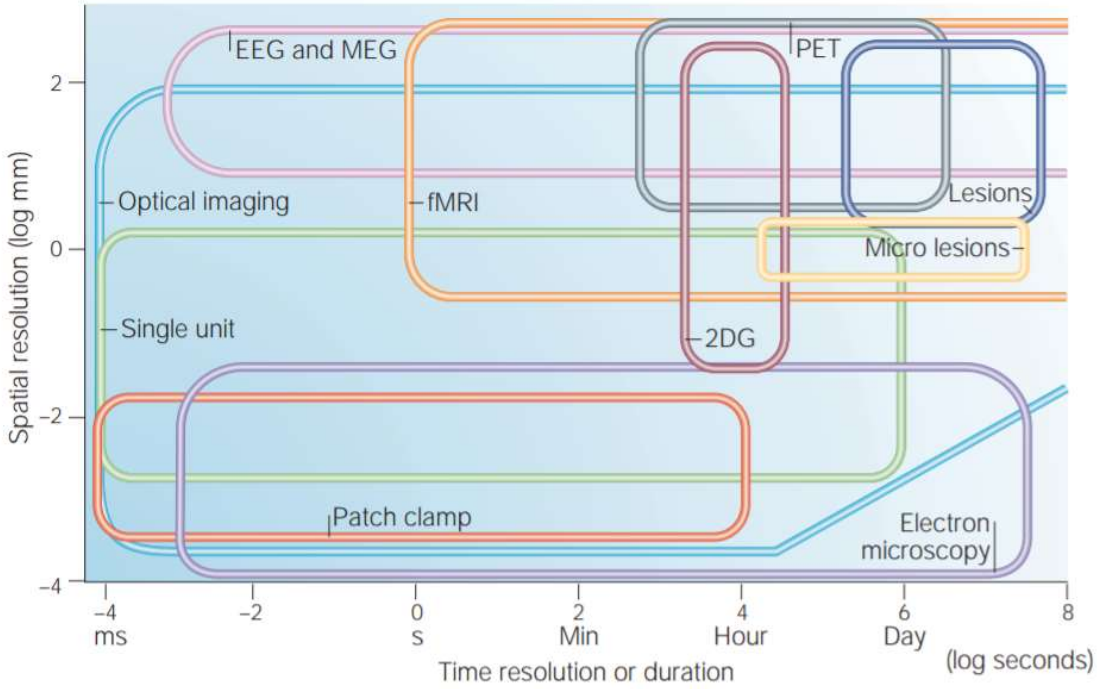

***Figure 4**. Spatio-temporal resolutions of various neurophysiologic studies adapted from Grinvald and Hildesheim 2004*

While microneurography may provide information on both fast (Aδ) and slow conducting (unmyelinated C) fibres, the description of C fibre aberrations among a diverse group of neuropathic pain syndromes has been impressively consistent across the literature. Increased spontaneous C fibre activity (Serra et al. 2012) and pathological changes in the ratio of mechano-insensitive (tonically-active) to mechano-sensitive C fibres (Kleggetveit et al. 2012) have been reported in the chronic pain literature. In addition to this degree of hyperexcitability, recordings of activity-dependent slowing of conduction velocities (Ørstavik et al. 2003) have also been observed and are hypothesized to contribute to the symptoms of stimulus hypersensitivity – allodynia and hyperalgesia – which are characteristic of neuropathic pain.

1.4.2 *Local Field Potentials*

Significant insights into the neurophysiological signals of deep brain nuclei have been made possible due to DBS recordings during surgery and in the immediate post-operative period. These recordings are in the form of local field potentials (LFPs) which represent the extracellular summation of post-synaptic potentials generated by a neural ensemble.

DBS interventions for pain have targeted the ACC,(Boccard et al. 2014) sensory thalamus and/or the periaqueductal/periventricular gray (PAG/PVG) matter (Pereira and Aziz 2014) for effective control of medically refractory neuropathic pain. The dearth of literature regarding deep brain signals in neuropathic pain is reflective of the rarity with which these procedures are performed. Nevertheless, some consensus regarding the features of LFP recordings which are deemed to be representative of the pain experience have been suggested.

Bursts of low threshold spike (LTS) activity in the thalamus seems to result from Aδ and C fibre inputs (Kobayashi et al. 2009) and this resultant neuronal hyperexcitability, as seen in the aforementioned microneurographic recordings, is also a feature of thalamic dysfunction in chronic pain. Patient recordings from neuronal ensembles of both the thalamus and PAG have revealed that low frequency spindle activity (8 – 14Hz) which correlated with subjectively reported pain.(A L Green et al. 2009) The centromedian-parafascicular complex has also been a target believed to modulate cognitive and affective components of pain processing. Neurons of this region have demonstrated spontaneous activity in neuropathic pain as well as responsiveness to noxious stimuli (Weigel and Krauss 2004), affirming its role in the experience of pain.

Furthermore, thalamic LFP recordings may reliably predict pain relief in patients treated with DBS (Huang, Geng, et al. 2016). While theta (4 – 7 Hz) activity has been shown to inversely correlate with

pain relief, alpha (8 – 14Hz) and beta (15 – 30 Hz) activity have demonstrated a positive correlation with pain relief in limited patient series.(Huang, Luo, et al. 2016)

However, as an investigation with very high spatial and temporal resolution of brain structures, LFPs may not provide sufficient insight into the wider brain networks involved in pain – the "pain connectome" – compared to other investigative tools such as electroencephalography (EEG) and magnetoencephalography (MEG).

1.4.3 *Electroencephalography and Magnetoencephalography*

EEG is a widely available and well-validated tool in neuroscience. It can be used to investigate the electric potential changes on the cortical surface as a marker of neuronal activity across large cortical regions. These electric fields, based on the principle of electromagnetic induction, are accompanied by a complimentary magnetic field, which can be detected by MEG. Of the techniques employed to investigate chronic pain, EEG and MEG record signals with the lowest spatial resolution. However, MEG may be able to provide more accurate event-related changes, but remains generally inaccessible, expensive and, consequently, rarely utilized as an investigative tool.

Despite the interest in pain representations on the scale of neurons or nerve bundles, the pain percept is more accurately represented as a matrix of activity across various brain regions. The ability to decipher physiological information of the cortical, and in some cases subcortical, pain matrix is the primary advantage of EEG and MEG over other neuroscientific tools. The characteristics of EEG and MEG which have been most widely used as metrics of pain activity include event-related potentials (ERPs), event-related fields (ERFs) and power spectral density (PSD) estimates. PSD analyses demonstrate power content of a signal across the frequency spectrum. Changes in the activity along

this spectrum (delta [1 – 4Hz], theta [4 – 7Hz], alpha [7 – 13Hz], beta [13 – 30Hz], gamma [> 30Hz]) have been used to identify and correlate different aspects of pain perception.

Many studies have identified a shift in the peak power spectra toward lower frequencies, as well as increased power in theta and alpha frequencies in chronic pain patients when compared to healthy controls (Pinheiro, Queirós, et al. 2016). A study conducted by Sarnthein et al. 2006 has revealed that there is a peak coherence in theta frequency activity between thalamic LFPs and frontal cortex EEG recordings which provides a valuable bridge between the invasive and non-invasive neural signals of pain processing. This aberrant low frequency activity has been described as a putative "thalamocortical dysrhythmia" model of neuropathic pain.

Additionally, analysis of ERPs and ERFs have largely shown that there is a decrease in amplitude of cortical responses to various stimuli among chronic pain patients (Sitges et al. 2010; Vuckovic et al. 2014). This decrease in cortical potential is believed to be contributory to the phenomenon of central sensitization that is seen in many neuropathic patients, whereby repeated noxious stimuli do not result in habituation and adaptation. However, in order to probe the significance of these observed neurophysiologic changes, selective alteration of function can be employed to demonstrate causal relationships. Neuromodulatory interventions provide a unique opportunity to both investigate the neurophysiology of pain and augment therapy for this important patient population.

1.5 Neuromodulation

The delivery of electrical current as a method of therapy has its origins in the treatment of pain. In the era of the Roman empire, Scribonius, a court physician, employed the bioelectricity of the torpedo fish for the treatment of headaches and gout.(Tsoucalas et al. 2014) Many applications of invasive and non-invasive electrical therapies would follow, and expand the application of electrical neuromodulation to

many other conditions – Parkinson's disease,(Brittain and Cagnan 2018) epilepsy(Eastin and Lopez-Gonzalez 2018) and psychiatric conditions(Tracy and David 2015) comprising the most popular. However, modern neuromodulation has increased the variety of devices and targets for pain, simultaneously expanding access to these forms of treatment while providing novel avenues for experimental inquiry into the pain percept.

1.5.1 *Non-invasive stimulation*

Transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS) have surged in popularity over the last decade for a diverse array of clinical and experimental indications. TMS utilizes a figure-of-8 coil to, non-invasively, induce a magnetic field which stimulates the production of action potentials in the underlying layers of cortex. Conversely, tDCS uses electric current passed from anode (positively charged) to cathode (negatively charged) to depolarize or hyperpolarize membrane potentials of neurons and alter their excitability. Both methods have shown beneficial results in alleviating neuropathic pain, though efficacy varies depending on aetiology (Zaghi, Heine, and Fregni 2009).

The most common target for non-invasive brain stimulation in pain, paradoxically, has been the motor cortex (M1), followed by the DLPFC. It is believed that stimulation of the motor cortex can influence the activity of the underlying pain matrix inclusive, but not necessarily limited to, the thalamus, cingulate and insular cortices.(Marcos F. DosSantos et al. 2016) Accordingly, a reliable physiological metric of the response to TMS in pain evaluation has been the motor-evoked potential (MEP) of the corresponding muscle region. The amplitude of this MEP response has been shown to be increased in painful limbs compared to non-painful sites (Lefaucheur et al. 2006), suggestive of an increased corticospinal excitability during chronic pain.

It has also been reported that anodal tDCS targeting the motor cortex is capable of decreasing MEP amplitude and increasing intracortical inhibition as a mechanism of pain relief.(Portilla et al. 2013) It has been postulated therefore, that the stimulation of M1 modulates aberrantly disinhibited regions of the pain connectome in order to produce its analgesic effect.

1.5.2 *Invasive stimulation*

Spinal cord stimulation (SCS) and DBS are the most widely reported invasive neuromodulatory techniques for neuropathic pain. DBS and SCS were first used in the 1960s for the treatment of intractable pain. While DBS would wane in popularity during the subsequent decades, SCS emerged as the prototypical intervention for pain in the field of functional neurosurgery.

SCS has been shown to decrease somatosensensory-evoked potentials (SEPs) (de Andrade et al. 2010) and normalize pathologic low-frequency activity (Schulman et al. 2005) to levels consistent with that of healthy controls based on neurophysiologic studies. Non-invasive stimulation methods have also been employed to investigate the mechanisms of spinal cord stimulation on pain relief. It has been shown that elevated intracortical facilitation seen in neuropathic pain, as mentioned previously, can be rectified in response to spinal cord stimulation revealing the utility of SCS in bottom-up modulation of maladaptive cortical plasticity.(Pahapill and Zhang 2014)

The efficacy of DBS in treating neuropathic pain has been suggested to display frequency-dependent effects in the thalamus and PAG. Previous studies (Nandi et al. 2003) have demonstrated that low frequency stimulation tends to improve pain relief, whereas high frequency stimulation tends to worsen pain. As the majority of neurophysiologic studies have identified aberrancies of the low-frequency spectrum in neuropathic pain, it may be intuitive to assume that low frequency stimulation may target, abolish or restore physiologic low frequency activity in the pain matrix.

Neurophysiologic studies have also made valuable revelations with respect to the mechanism of pain augmentation in novel targets such as the ACC. MEG analysis has shown reduced activity in pre-supplementary motor, medial prefrontal and PAG in response to stimulation of the ACC, and produces long term changes in the activity of the rostral and caudal ACC (Mohseni et al. 2012).

Though the mechanisms underlying the experience of pain and its evolution into chronicity may be multifactorial, the use of a common language in neurophysiology may facilitate more immediate improvement in the delivery of neuromodulatory therapies for those afflicted with refractory neuropathic pain. These insights may in future, not only inform methods to more effectively deliver neuromodulation by, for example utilizing closed-loop stimulation paradigms, but may also illuminate new mechanisms and processes that might objectively identify currently unknown elements of the subjective experience of pain.

1.6 Aims of Thesis

The aim of this thesis is to explore the neurophysiologic representations of pain and how neuromodulatory techniques might bring about pain relief. The three major objectives are:

1. To investigate the impact of Dorsal Root Ganglion Stimulation (DRGS) on the sensory, cognitive and affective domains on chronic pain.
2. To evaluate the supraspinal and autonomic mechanisms of DRGS and whether cortical changes may be augmented by non-invasive brain stimulation.
3. To assess the efficacy of DBS for chronic pain and evaluate the utility of frequency-specific stimulation.

2 METHODS

2.1 Dorsal Root Ganglion Stimulation

2.1.1 *Patient Selection*

Patients were considered candidates for DRGS if they had severe, medically refractory (failed therapy with at least 3 classes of analgesics) neuropathic pain of at least 2 years duration. Each patient had a DRG electrode placed at a pre-determined spinal level depending on the dermatomal distribution and focality of their pain. Based on neuropsychological and multi-disciplinary team assessments, the exclusion criteria for DRGS included opiate dependence, untreated depression or low mood, catastrophization, ongoing litigation, and unrealistic expectations, as these are all poor outcome prognosticators.

***Table 1**. Dorsal Root Ganglion Stimulation patient demographics, electrode location and stimulation parameters.*

Patient	Age	Gender	Diagnosis	Electrode location	Stimulation parameters (Frequency [Hz]/ Amplitude[mA] / Pulse width[µs])
1	52	Male	Post-surgical pain	Right L1	30/0.525/400
2	54	Male	Post-surgical pain	Right L3/L4	20/0.475/360
3	29	Male	Post-traumatic compressive neuropathy	Left L2	20/0.7/250
4	78	Male	Diabetic neuropathy	Bilateral L5	Right – 20/1.025/450 Left – 20/0.775/480

5	46	Male	CRPS	Right L3	20/0.7/410
6	52	Male	Post-surgical Pain	Left L1	28/1.3/250
7	58	Female	CRPS	Right L2/L3	20/2.1/250
8	61	Male	Post-surgical pain	Left L3	20/2.1/140
9	47	Male	CRPS	Left L4	20/6/350
10	55	Male	Nerve entrapment	Right C7/C8	20/0.425/300
11	29	Male	Post-surgical pain	Bilateral L5	Right – 20/2.25/700 Left – 20/650/800
12	52	Female	CRPS	Right L5	30/0.7/500
13	77	Female	Postherpetic neuralgia	Right T1	30/0.4/300
14	22	Female	Dystonic pain	Right L2/L3	20/2.4/300
15	49	Female	Postherpetic neuralgia	Right L5	20/1.6/400
16	53	Female	Meralgia paresthetica	Right L2	20/0.6/300
14	52	F	CRPS	Left L5	20/1.6/500
15	48	M	CRPS	Right C6/C8	C6 – 20/1.1/450 C8 – 20/1.1/750

16	22	M	Post-traumatic compressive neuropathy	Right L5	40/2.475/370
17	43	F	Post-surgical pain	Left L5	20/0.55/270
18	28	F	Post-traumatic compressive neuropathy	Left C6/C8	C6 – 28/1.125/440 C8 – 20/1.225/410
19	34	M	CRPS	Left L3/L4	20/0.974/410
20	44	M	Post-surgical pain	Right L1	20/2.675/200
21	70	M	Post-surgical pain	Left L5	40/1.8/200
22	48	M	Post-operative peripheral neuropathy	Right L1	20/0.5/190
23	39	M	Post-traumatic compressive neuropathy	Right C8/T1	20/0.475/ 300
24	61	M	Phantom limb pain	Left L4/L5	20/1.0/270
25	53	F	Post-surgical pain	Right T12/L1	20/0.275/220

2.1.2 *Implantable Neurostimulator*

The Axium Neurostimulator System [See Table 2] includes the Implantable Neurostimulator (INS) device, a trial neurostimulator (TNS) device, a clinical and patient programmer [See Figure 5], one or more leads which may be used in combination with a lead extension and the accessories used for implanting the system.(Abbott Neuromodulation 2016)

***Table 2**. DRG Stimulation Device Specifications*

Descriptor	**Axium Neurostimulator System**
Connector	Quadrapolar, in-line
Center to Center Connector Spacing	3.3 mm (0.130”)
Diameter	1.0 mm (0.040”)
Length	50 cm (20”) or 90 cm (35”)
Number of Electrodes	4
Electrode Shape	Cylindrical
Electrode Length	1.25 mm (0.050”)
Edge to Edge Spacing	5 mm (0.200”)
Center to Center Spacing	6.25 mm (0.250”)
Array Length	20 mm (0.790”)
Ball Tip Diameter	1.0 - 1.5 mm (0.040” - 0.060”)
Stylet Wire Diameter	0.25 mm (0.010”)

DC Lead Impedance (50cm / 90cm / Extension)	<20Ω / <35Ω / <60Ω

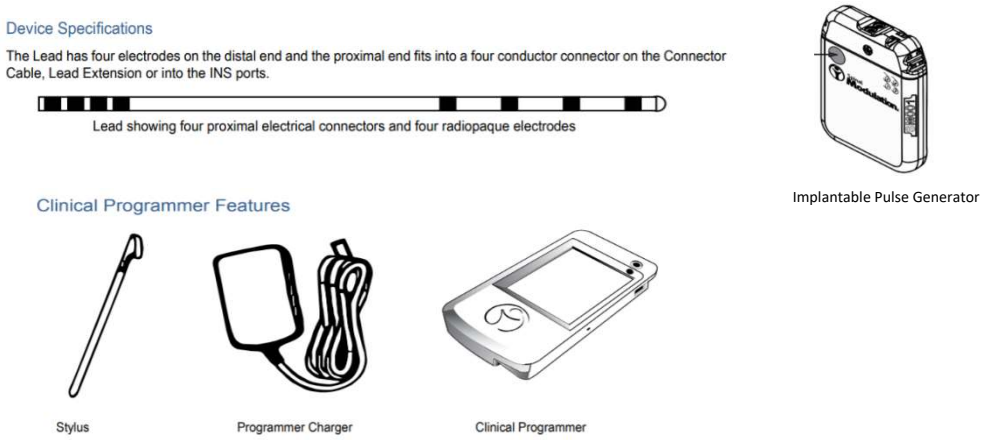

Figure 5. *Illustration depicting the components of Axium neurostimulator*

2.1.3 *Surgical Procedure*

Patients who meet the inclusion criteria first undergo a temporary trial period using the TNS to ascertain clinical efficacy, then undergo permanent implantation with the INS device. The DRG stimulators were implanted under local anaesthetic with light sedation (propofol) in the prone position. Under fluoroscopic control, the delivery sheath was used to enter the epidural space and a DRG Axium® lead (Abbott Laboratories, Sunnyvale, CA, USA) was introduced, under X-ray guidance, into the appropriate nerve root exit foramen, so that the electrode contacts were positioned over the dorsum of the DRG in the dorsal part of the foramen. Sedation was weaned and the leads were tested for efficacy prior to re-sedation. After anteroposterior and lateral X-rays had confirmed satisfactory position, [See

Figure 6] a strain-relief loop was fashioned in the spinal canal, and the wires were tunnelled to an implantable pulse generator (IPG) that was placed subcutaneously remote from the spine.

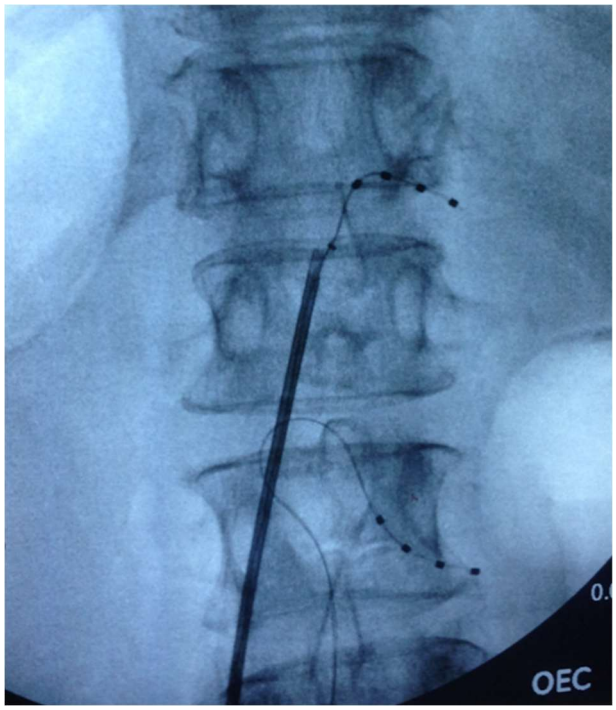

***Figure 6**. Fluoroscopic image of intra-operative dorsal root ganglion (DRG) lead placement at T12 and L2 on the right side.*

2.2 Ethics

The "Cerebral Signature of Chronic Pain" protocol (Protocol record – 13/SC/0298) was approved by the South-Central Oxford Research Ethics Committee (REC) in September 2013 for the investigation of neurophysiologic indicators of pain in the cerebral cortex. Ethical approval was initially obtained to conduct quantitative sensory testing, muscle sympathetic nerve activity and LFP recordings in chronic pain patients with implanted neurostimulation devices. Two substantial amendments to the protocol were approved in order to facilitate this research. The first amendment included the use of MEG recordings in neuropathic pain patients receiving DRG, SCS and DBS therapy. This amendment was approved by the Clinical Trials Research Group (CTRG) in February 2017 and ethical approval was granted by the REC and Health Research Authority (HRA) in May 2017, after which experimental planning and patient recruitment was commenced. The second amendment was submitted in January

2018 and included the use of non-invasive brain stimulation in DRG/SCS patients and expanded recruitment to include healthy participants. REC and HRA approval for this amendment was received in June 2018. All experiments were conducted in accordance with the Declaration of Helsinki.

2.3 Pain Assessment

A variety of pain assessment tools have been employed to generate objective measurements for the subjective experience of pain. Chapters 3, 4, 5 and 8 employed the Numerical Rating Scale (NRS) which requires patients to select a number on a 21-point scale between 0 and 10 which they believe reflects the severity of their pain at a given timepoint. In contrast, the VAS presents a line of a fixed length (10 cm) which a patient uses to indicate the severity of their pain from no pain to the worst pain imaginable. In Chapters 6 and 9, patients' responses were measured and recorded using the VAS as a numerical indicator of their subjective pain intensity. [See Appendix A] NRS and VAS measurements have demonstrated significant correlations in the evaluation of chronic pain,(M. P. Jensen, Karoly, and Braver 1986) and a 20% change in these indicators has been suggested to reflect a clinically meaningful therapeutic effect on pain.(Farrar et al. 2000)

While these indices are useful in evaluating the sensory-discriminative dimension of pain intensity, the affective dimension of pain is not sufficiently well-represented by these metrics. The Verbal Rating Scale and Pain-O-Meter are tools that have been infrequently used to quantify pain unpleasantness,(Haefeli and Elfering 2006) in large part due to the popularity of the MPQ as a metric of pain affect. MPQ scores were previously recorded for the DBS patients described in Chapter 9 and consists of 78 words across 20 groups for patients to select whether they describe or apply to the pain they feel. These groups are divided into descriptors which assess the sensory (10 sets), affective (5 sets), evaluative (1 set), and miscellaneous (4 sets) dimensions of ongoing pain. The Short Form McGill Pain Questionnaire (SF-MPQ) was subsequently developed by selecting the most commonly used

descriptors from the MPQ and compared to the standard form.(Melzack 1987) This revealed that a shortened version of sensory and affective descriptors was sufficiently sensitive to evaluate chronic pain in a diverse cohort and, hence, was employed in the characterization of the affective dimension of pain in our DRGS cohorts.[See Appendix A]

2.4 Magnetoencephalography

Magnetoencephalography, like EEG, is used as a non-invasive neurophysiologic tool for the investigation of brain activity. However, instead of electric fields, MEG detects the underlying magnetic fields using a superconducting quantum interference device (SQUIDs) in a helmet-shaped array to convert the magnetic fields into electric signals. In particular, MEG is sensitive to tangential magnetic fields located within the brain sulci,[See Figure 7] as opposed to radial fields emanating from brain gyri, as an indicator of underlying postsynaptic potentials in the cortex.

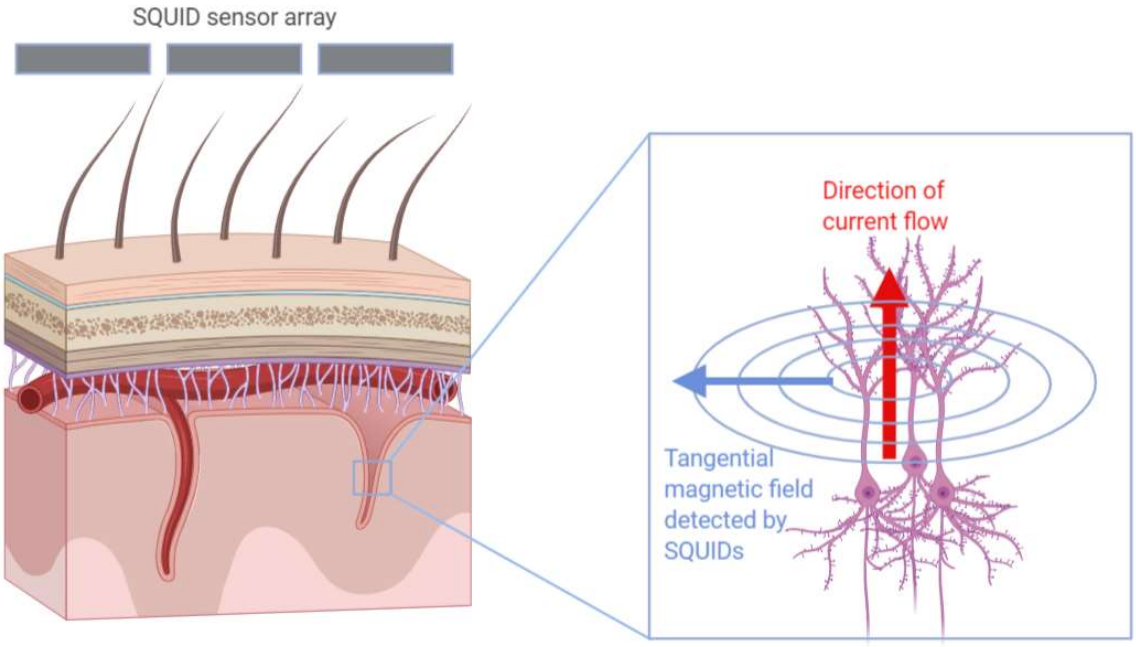

***Figure 7**. Illustration of the electromagnetic changes in the sulci of the cerebral cortex which are captured by magnetoencephalography*

Cortical magnetic fields are small and difficult to detect through the scalp due to the abundance of magnetic fields in our environment which can cause interference. As such, all MEG recordings were performed at the Oxford Centre for Human Brain Activity (OHBA) in a magnetically shielded room to limit external influences on recordings. All ferromagnetic objects, phones and clothing with metallic components were not allowed within the room during MEG recording sessions. Additionally, sources of electromagnetic activity within the body (heart and muscle activity) need to be recorded and subsequently removed from recorded signals to ensure MEG signals are only representative of neural activity. As a result, electrocardiographic (ECG) recordings were monitored by applying bilateral electrodes to the volar aspect of the wrists and, simultaneously, electro-oculographic (EOG) traces were recorded by two electrodes, placed above and below the left eye. The OHBA uses a 306-channel Elekta Neuromag MEG system comprised of 102 magnetometers and 204 planar gradiometers and samples signals at a rate of 1000 Hz. The head shape of each participant was manually digitized using a

Polhemus tracker. The MEG recording protocol [See Figure 8] was used for the experiments detailed in Chapters 3 and 4. Coin toss randomization was chosen as the method for simple randomization during this experimental protocol due to its simplicity and adequacy in generating balanced allocation to different groups. Although this method might introduce bias for intervention allocations in the context of a randomized controlled trial, this method was considered satisfactory for the purposes of randomizing patients in an observational recording session.

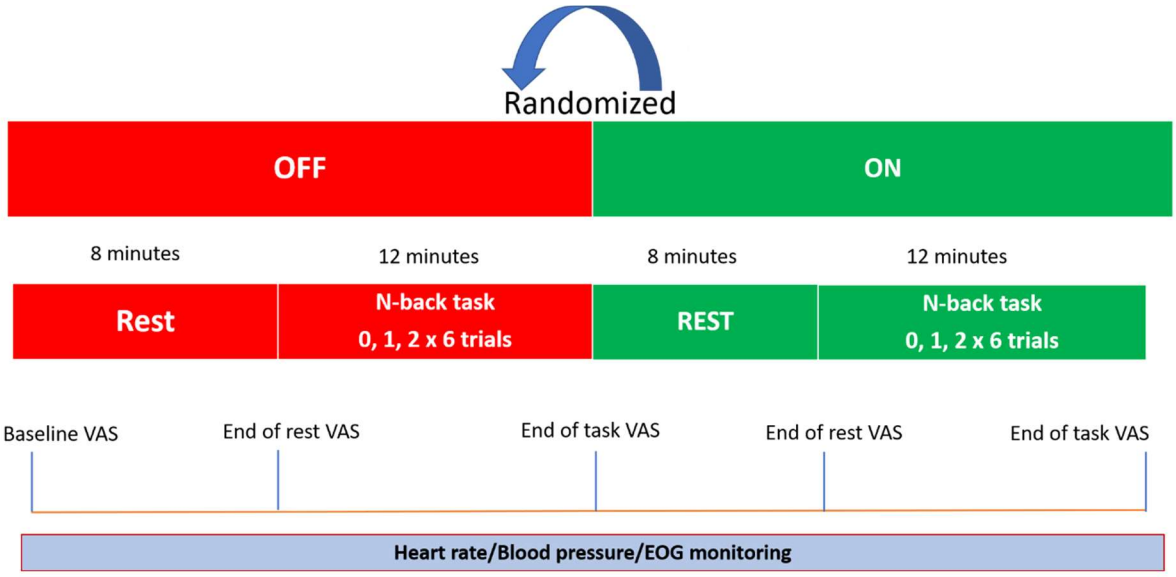

Figure 8. *Illustration of DRGS-MEG experimental protocol*

2.5 Electroencephalography

Electroencephalography is a widely available non-invasive tool to detect and record neurophysiologic activity of the brain. EEG uses scalp electrodes to detect electric fields generated from the underlying cerebral cortex. Like MEG, EEG cannot record the activity of individual neurons, but represents the summation of dendritic postsynaptic potentials among groups of pyramidal neurons approximately 6cm

beneath the scalp.(Binnie and Prior 1994) EEG is particularly sensitive to radially-oriented neuronal activity of cortical gyri, as opposed to the tangentially-oriented cortical activity recorded by MEG.

For recordings, scalp electrodes may be individually placed, or multi-channel recordings may be facilitated by using an electrode cap. The electrodes are usually made of Ag/AgCl disks with a conductive gel placed between the scalp and electrodes to lower the impedance and improve the quality of recordings. The electrode positions have been standardized by the International Federation in Electroencephalography and Clinical Neurophysiology, commonly known as the 10/20 system. The recorded signals are transmitted via electrodes to an amplifier which records signals for analyses to be conducted offline. Our experiments utilized the TMSi Refa amplifier (TMSi, Enschede, The Netherlands) recording from 20 scalp electrodes. This EEG recording protocol [See Figure 9] was used for the experiments detailed in Chapter 5.

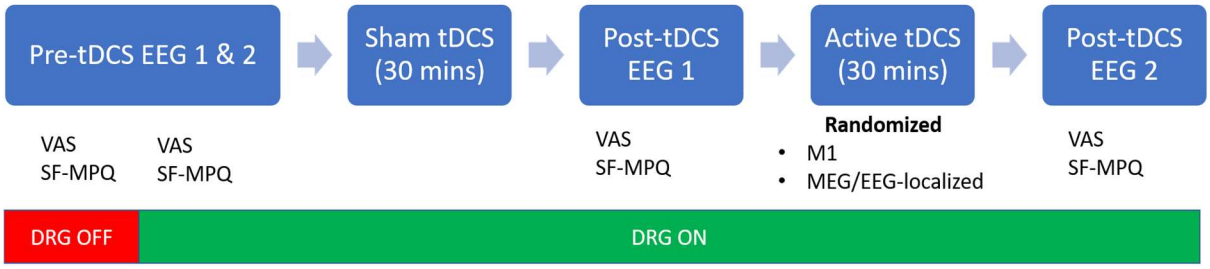

Figure 9. *Illustration of Paired Acute Invasive/Non-invasive stimulation experimental protocol*

2.6 Signals Analysis

There are innumerable methods that have been employed over the decades, and many others in active development, to analyze and interpret EEG/MEG signals to decode human neurophysiology. The methods used, however, should be appropriate with respect to the experimental conditions and the hypotheses being tested. For example, the most commonly used metrics are ERPs for EEG and ERFs for

MEG. These metrics represent averaged changes in recorded potential (ERP) or field strength (ERF) which is typically time-locked to a stereotyped stimulus (auditory, visual, tactile).(Sur and Sinha 2009) While useful for the interpretation of event-related neuronal changes, our experiments did not involve time-locked stimuli and so, negated the utility of this well-validated method.

Our interest in pain necessitated a focus on the dynamic whole-brain changes during different pain states, with varying conditions/interventions. As a result, we used power spectral density (PSD) analyses which could reflect the changes in frequency components of neural oscillations, namely – theta [4 – 7Hz], alpha [7 – 13Hz], beta [13 – 30Hz] and gamma [> 30Hz] – in order to appreciate the differences in neural dynamics during different experimental conditions.

We were also interested in identifying regions of cortex which were significantly contributory to the changes in power spectra observed during MEG recordings. For this type of analysis, source localization techniques, both at the sensor level (2D) and based on source reconstruction techniques (3D) have been used. While the sensor level analyses are useful in identifying general regions of cortex which may reflect increased/decreased neural oscillatory activity, 3D source reconstruction offers greater detail and specificity of localized cortical activity. However, a limitation to the applicability of 3D reconstruction is the requirement of head/brain MRIs of each individual, which proved challenging to acquire prospectively as most participants were already implanted with MRI-incompatible neurostimulators. This obstacle was overcome by warping open source MRI templates to digitized head shapes acquired during MEG recordings to substitute for individual scans.(Fleischmann et al. 2020) Many techniques have been used for 3D source reconstruction.(Wendel et al. 2009) We employed the inverse modelling technique, which uses pre-processed MEG fields to fit individual dipoles to co-registered head models (based on warped template MRIs) by a process known as beamforming. Additional details relevant to the signal analysis conducted are provided in Chapters 3 and 4.

2.7 Deep Brain Stimulation

2.7.1 *Patient Selection*

Patients with chronic, intractable (pharmaco-resistant) neuropathic pain, particularly those with post-stroke pain, atypical facial pain, brachial plexus injury or failed SCS, are evaluated for DBS. A multi-disciplinary team including neuropsychologist, pain specialist, neurosurgeon evaluate the aetiology of pain to rule out psychogenic or factitious disorders and the patient completes a 12-day pain diary to characterize their baseline pain intensity.

2.7.2 *DBS leads and targeting*

Once patient selection is completed, the choice of intra-cranial target is guided by evidence-based best practice and clinical experience. Based on recent literature, PAG/PVG is the preferred target.(Frizon et al. 2020) However, depending on the therapeutic response to awake intra-operative stimulation, a trial of stimulation/co-stimulation targeting the sensory thalamus (VPL and VPM) may be warranted. The VPM is usually effective for facial pain, while the VPL is traditionally targeted for patients with arm and/or leg pain. Targeting is performed on fused stereotactic magnetic resonance imaging (MRI)/computed tomography (CT) scans using Radionics Image Fusion and Stereoplan (Radionics, Burlington, Massachusetts). The thalamic targets are planned based on their coordinates relative to the midcommissural point (MCP). The VPM is traditionally located 10 – 12 mm lateral, 5 – 8 mm posterior at the level of the posterior commissure which define the x, y and z coordinates respectively. The VPL is also targeted at the level of the posterior commissure, just lateral to the VPM (x = 12 – 14 mm) and medial to the posterior limb of the internal capsule. The PAG/PVG is targeted at the level of the superior colliculus, less than 10mm below the AC-PC line, 3 – 5 mm from the midline, just anterior to

the cerebral aqueduct. The final location for DBS lead [See Table 3] placement is guided by awake intra-operative somesthetic response to stimulation, and so, may vary by several mm between patients.

***Table 3**. DBS lead specifications*

Description	**Model 3387**
Connector	Quadrapolar, in-line
Diameter	1.27 mm
Length	10 – 50 cm
Shape	Straight
Conductor resistance	<100Ω
Distal End	
Number of electrodes	4
Electrode shape	Cylindrical
Electrode Length	1.5 mm
Electrode spacing	1.5 mm
Electrode distance	10.5 mm
Distal tip distance	1.5 mm
Proximal End	
Lead contact length	2.3 mm
Lead contact spacing	4.3 mm

Lead contact distance	16.6 mm
Stylet handle length	40.1 mm

2.7.3 *Surgical procedure*

Written informed consent is obtained after a detailed discussion regarding the risks and benefits of DBS are explained. Locations of the targets for DBS electrodes (model 3387, Medtronic Inc, Minneapolis, Minnesota) were determined using pre-operative scans. For surgery, a Cosman-Roberts-Wells (CRW) base ring is applied to the patient's head under local anaesthesia and a stereotactic CT is performed. The CT is volumetrically fused to the pre-operative T1-weighted MRI scan and coordinates for the intended target are calculated. A frontal trajectory avoiding the lateral ventricle is preferred to limit unintended haemorrhage from vascular structures and potential lead deflection on traversing the ependymal surface. A 3cm parasagittal scalp incision and 2.7mm twist drill craniotomy is performed under local anaesthesia to facilitate lead insertion. Bipolar stimulation at 5 – 50 Hz, pulse width 100 – 450 μs, amplitude 0.1 – 3 V is performed intra-operatively to evaluate subjective clinical effect. Thalamic stimulation usually produces paraesthesia, while a feeling of warmth is usually reported during PAG/PVG stimulation. The DBS electrodes are fixed to the skull by a miniplate and the lead(s) externalized for one week of trial stimulation before permanent implantation. Post-operative CT scans are performed and fused with pre-operative MRI scans to confirm final lead placement [See Figure 10]. After successful trial stimulation, permanent implantation is done at a second operation under general anaesthesia and leads are connected to a subcutaneously implanted IPG, usually in the infraclavicular region.

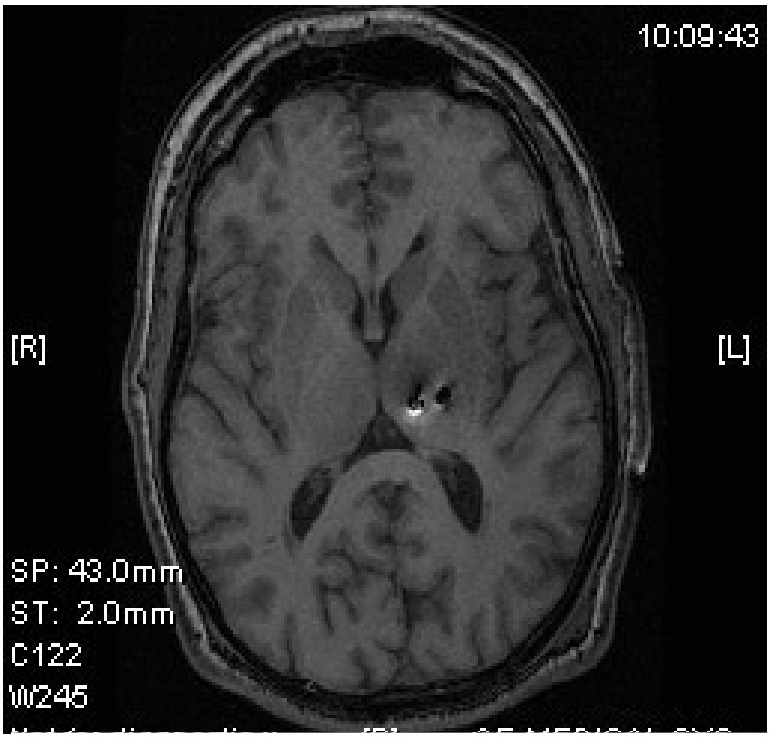

Figure 10. *Representative post-operative MRI of a patient with implanted left thalamic DBS leads*

3 QUANTIFYING THE CLINICAL EFFECTS AND WASHOUT PERIOD OF DORSAL ROOT GANGLION STIMULATION

3.1 Summary

The washout period of a drug or intervention is a necessary variable to quantify prior to implementing a crossover study design. The washout period is necessary to ensure that sufficient time has elapsed between interventions to ensure that no carryover effects are present when evaluating their effects on a population. Unfortunately, the field of neuromodulation has not reliably quantified the time period during which the effects of neurostimulation dissipate, nor has a standardised method for quantifying these effects been regularly employed.

We sought to quantify the wash-in and washout period of acute DRG stimulation by quantifying the changes in pain score over time in 16 chronic pain patients. The variability in pain scores was used as a metric of the acute effects of neurostimulation and cessation of this variability taken to be the wash-in or washout period of acute DRG stimulation.

The greatest variability in reported pain scores occurred within sixty seconds of turning OFF/ON the DRG stimulation. Maximal improvement and worsening of pain scores occurred between 360 and 480 seconds. The change in pain scores were not found to be significantly different from subsequent pain ratings after 300 seconds (5 minutes) for both ON and OFF stimulation conditions.

Our study has demonstrated that in the context of DRG stimulation for pain, five minutes is an appropriate washout period to prevent carryover effects in a crossover study design.

3.2 Introduction

Crossover designs are useful in clinical trials where the disease population is limited, or the intervention applied is uncommon. Participants in a crossover design are exposed to each intervention (e.g. placebo and target drug), and outcomes are compared at the end of each period. This design facilitates the use of smaller sample sizes, as each participant acts as their own control and limits between-subject variability in statistical comparisons while increasing statistical power. A critical element in crossover designs is the implementation of an adequate washout period to prevent carryover effects between each intervention.

For pharmaceutical studies, washout periods are well-established and depend on the drug half-life in the participant's circulation. For clinical trials involving neuromodulation, however, washout periods have not been characterized or standardized with the same degree of rigour. Pre-clinical animal studies of dorsal root ganglion stimulation (DRGS) suggest that neuronal activity diminishes within an order of minutes (Pawela, Kramer, and Hogan 2017). Additionally, clinical studies of electrical neuromodulation have reported both immediate (within minutes) (Barolat-Romana et al. 1985) and long term (over months) effects (Deer et al. 2017) on symptom severity. We hypothesized that majority of the clinical effects on pain suppression occur immediately after onset and cessation of neurostimulation. Therefore, it was necessary to measure the wash-in and washout periods of acute DRG stimulation in chronic pain and evaluate its suitability for the intended crossover designs employed in this thesis.

3.3 Methods

Sixteen patients with diagnosed chronic pain syndromes and who had undergone permanent implantation of a DRG stimulator (DRGS) at the John Radcliffe Hospital were recruited for this study. Participants were assigned to begin the study in the OFF stimulation (n=8) condition or the ON

stimulation (n=8) condition by block randomization. Each DRG stimulator was then switched 'on' or 'off' respectively while pain scores were recorded every 30 seconds.

Statistical analysis was conducted in GraphPad Prism software version 8.0 (La Jolla California USA, www.graphpad.com). We identified the mean increase (MI) and mean decrease (MD) for each condition and identified the time to achieve 75% (MI_{75}/MD_{75}) and 90% (MI_{90}/MD_{90}) of effect on pain scores. D'Agostino test was used to confirm that the data was normally distributed. Student's t-tests were used for pairwise comparisons and repeated measures ANOVA used to identify significant differences in pain scores between each timepoint. Tukey's posthoc test was applied to correct for multiple comparisons.

3.4 Results

The mean age of participants was 51 years ± 16.5 (mean ± SD) - ten (10) men, six (6) women. Mean baseline pain score before turning DRG stimulation 'on' was found to be 6.68 ± 2.75 and resulted in a statistically significant reduction in pain scores (Percentage suppression of pain = 40% ± 2.88, $t(7)=3.503$, $p=0.01$) over the 10-minute period. Prior to turning 'off' DRG stimulation, the mean baseline pain score was found to be 4.37 ± 2.88 (mean± SD) and upon cessation of stimulation resulted in a statistically significant increase in pain scores (Percentage increase in pain = 53% ± 1.180, $t(7)=4.549$, $p=0.0026$) [See Figure 11].

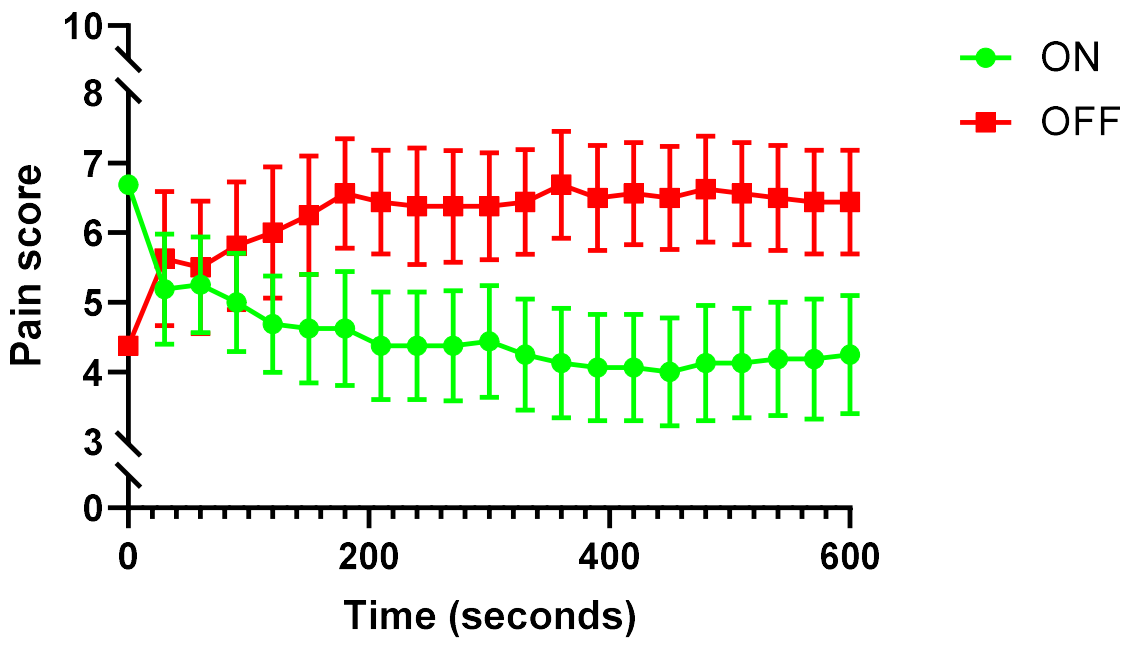

Figure 11. *Line graph depicting change in pain scores with time when turning Dorsal Root Ganglion stimulation 'on" (green) or 'off' (red). At 5 minutes (300 s) (grey dotted line) after turning DRGS 'on' or 'off', there is no statistically significant change in reported pain scores (Mean ± SEM)*

The greatest variability in reported pain scores occurred within sixty seconds of turning OFF/ON the DRGS (range +2 to -2.5). While maximal improvement and worsening of pain scores occurred between 360 and 480 seconds, the change in pain scores were not found to be significantly different ($F(2, 18) = 4.32$, $p > 0.05$) from subsequent pain ratings after 300 seconds (5 minutes) for both ON and OFF stimulation conditions. Immediate effects on pain suppression occurred more quickly (MI_{75} reached within the first 30 seconds) compared to the carryover effects upon cessation of stimulation (MD_{75} reached between 90 and 120 seconds). In contrast, 90% of the mean effect on pain from wash-in and washout (MI_{90} and MD_{90}) occurred between 180 and 240 seconds.

3.5 Discussion

Our findings represent the first systematic approach to evaluate the acute effects of DRG stimulation and its washout period in chronic pain patients. Unfortunately, there is no consistency in the literature to methodologically quantify the acute effects of neurostimulation. Therefore, we employed a similar technique to that used for estimating the effects of DBS in alleviating the motor symptoms of Parkinson's disease, and the return of symptoms during DBS washout (Temperli et al. 2003). Similarly, our findings reflect that 1) the majority of clinical improvement/worsening occurs within the first few minutes of onset/cessation of neurostimulation, 2) the rate of improvement occurs more rapidly during stimulation than the rate of symptom exacerbation during washout and 3) there is a plateau period, after which, any increase/decrease in clinical severity during long-term stimulation does not vary significantly.

While these acute effects of neurostimulation on chronic pain do not display significant variability after 5 minutes, it is possible that chronic DRG stimulation will produce additional long-term effects. Our findings of acute DRGS represents a 40% reduction in pain, while pain suppression during long-term evaluations of DRG stimulation tend to report improvements > 50% (Kallewaard, Edelbroek, et al. 2019). This added effect on pain relief may reflect chronic neuroplastic changes, alterations in gene expression or cortical reorganization during long-term DRG stimulation.

Nevertheless, our estimate of acute DRG washout (10 minutes) resulted in pain exacerbation > 50%. In concert with the negligible variability in pain scores during the latter half of this period, our evidence suggests that 10 minutes is a sufficient washout period for crossover studies investigating the acute effects of DRG stimulation. This evidence facilitates the ease of utilizing multi-phase crossover designs (N-of-1 trials) (Alexander L. Green et al. 2004) in evaluating the effects of neuromodulation, and can decrease the reliance on randomized controlled trials for surgical interventions.

Predominance of fast-decay effects or slow-decay effects during neurostimulation is seemingly dependent on the site of stimulation (Cooper et al. 2014) and longevity of the disease (Cooper et al. 2013). Our methodology may be employed for different neurologic targets and disease cohorts to evaluate the temporal progression of clinical effects during electrical stimulation. Additionally, the incorporation of neurophysiologic recordings and/or neuroimaging during wash-in and washout evaluations would add substantially to our understanding of the acute and chronic effects of electrical stimulation on the human nervous system.

4 SUPRASPINAL EFFECTS OF DORSAL ROOT GANGLION STIMULATION

4.1 Summary

DRGS has become a popular neuromodulatory treatment for neuropathic pain. We used MEG to explore the cortical changes that occur in response to DRGS at rest and how these patterns reflect the pain experience.

Thirteen patients with chronic pain and implanted DRG stimulators were included in the MEG analysis. MEG Recordings were performed at rest while the stimulator was turned ON or OFF. Numerical rating scale (NRS) scores were recorded before and after onset of DRGS. Power spectral and source localization analyses were performed on pre-processed MEG recordings.

At rest, patients in severe pain with DRGS-OFF had significantly increased theta (4-7 Hz) power and decreased alpha (7-13 Hz) power compared patients reporting less pain. This shift towards lower frequencies was contrasted by a shift towards higher frequency power distribution (low beta 13-20 Hz) when DRGS was turned ON. A significant correlation was found between the increase in low beta activity and the degree of reported pain relief.

Our results demonstrate increased low frequency power spectral activity in chronic pain patients with DRGS-OFF which shifts towards higher frequency power spectral activity in response to therapeutic DRGS. These neurophysiologic changes in response to DRGS provides support for the use of neuroimaging in the search for potential biomarkers of pain.

4.2 Introduction

The dorsal root ganglion (DRG) is a component of the PNS located lateral to the spinal cord at each segmental level. It contains the pseudounipolar cell bodies of primary sensory afferents of each spinal nerve. These afferents synapse with secondary neurons in the nucleus proprius and substantia gelatinosa of the spinal cord to give rise to the ascending spinothalamic tract of the pain pathway.(Haberberger et al. 2019)

As an important component of pain transduction, the DRG has been targeted for the treatment of neuropathic pain by ganglionectomy (Acar et al. 2008), intrathecal medications (Wolff, Groen, and Crul 2001) and radiofrequency ablation.(Shanthanna et al. 2014) Lying in the lateral epidural space, with dura terminating distal to the ganglion, it is anatomically suited for the placement of epidural electrical leads. DRGS was first approved for use in Europe in 2011 and subsequently was approved for use by the FDA in February 2016. Since its introduction, DRGS has been shown to produce comparable efficacy to conventional SCS for many intractable pain syndromes, with less postural variability during stimulation(Kramer et al. 2015) and greater selectivity for painful dermatomes in CRPS and causalgia.(Deer et al. 2017)

Many mechanisms of pain relief during DRGS have been hypothesized including 1) the inhibition or filtering of aberrant neuronal impulses from propagation at the DRG t-junction, 2) anti-inflammatory effects and changes in gene expression at the DRG,(R. Y. North et al. 2019) 3) autonomic changes via sympathetic synapses or 4) ascending effects on the supraspinal neuraxis.(Bremer et al. 2016) The possibility of supraspinal effects has been investigated in rodents with functional magnetic resonance imaging (fMRI), indicating modulatory effects of DRGS on cortical and subcortical structures.(Pawela, Kramer, and Hogan 2017) Human studies have explored the central neurophysiologic effects of DBS revealing normalization of elevated power spectral activity in chronic pain patients.(A L Green et al.

2009; Huang, Luo, et al. 2016) Studies of SCS in humans have also demonstrated substantial evidence of supraspinal effects in treating pain,(Schlaier et al. 2007; Sivanesan et al. 2019) for example, inhibition of cortical somato-sensory evoked potentials.(de Andrade et al. 2010; Poláček et al. 2007)

The exploration of the neurophysiologic indicators underlying chronic pain have revealed overlapping power spectral findings, particularly with regards to changes in theta (4 – 7 Hz), peak alpha (8 – 13 Hz) and low beta (13 – 20 Hz) frequencies.(Pinheiro, Queirós, et al. 2016) Thalamocortical dysrhythmia (TCD) has been postulated to represent a common central pathophysiologic mechanism in patients suffering from neuropathic pain. Studies have demonstrated a shift towards lower peak frequency activity in patients suffering from chronic pain compared to healthy controls.(Walton, Dubois, and Llinás 2010) MEG recordings have been shown to demonstrate the optimal spatial and temporal resolution with which to capture and investigate these thalamocortical dynamics experimentally.(Ribary et al. 1991) We hypothesize that neuromodulation of this key structure in the PNS, the dorsal root ganglion, can modulate power spectra in the theta, alpha and low beta bands at rest as potential biomarkers of pain relief.

4.3 Materials and Methods

4.3.1 *Participants and study design*

The study was conducted with approval from the South-Central Oxford Research Ethics Committee in accordance with the Declaration of Helsinki. Sixteen patients were recruited between September 1, 2017 and February 1, 2019 for this cross-sectional study who had undergone surgical implantation of DRG stimulators at the John Radcliffe Hospital for medically refractory chronic pain syndromes (see Table 1). Informed consent was obtained, and participants were randomized by flipping a coin to begin MEG recordings in the *ON*-stimulation condition or *OFF*-stimulation condition to prevent order effects.

4.3.2 *Pain rating*

Baseline pre-operative pain scores were calculated based on an average of the morning and afternoon pain scores from each patient's pain diary kept over the course of a week prior to DRGS implantation. Pain ratings were also recorded before each MEG recording session. Patients were asked to rate their pain from 0 (no pain) to 10 (worst pain imaginable) while DRGS was *ON* and while DRGS was *OFF*, based on the NRS. The SF-MPQ was also used to measure the sensory and affective subscales of each patients reported pain. Patients were then categorized as having no pain (NRS = 0), mild pain (NRS ≤ 5), moderate pain (NRS = 5-8) or severe pain (NRS > 8).(Boonstra et al. 2016)

After switching from DRGS-OFF to DRGS-ON, patients who experienced > 50% reduction in pain scores were considered to have "substantial pain relief", while those with < 50% pain relief were considered to exhibit only adequate pain relief. Those patients who reported an increase in pain score despite the onset of DRGS, were categorized into a "worsening pain" group and those without pain categorized as "no pain".

4.3.3 *MEG Recordings*

Patients were sat upright in a magnetically shielded room and scanned at rest for 8 minutes. Participants were instructed to keep their eyes open and fixed on a projected cross during both DRGS-ON and DRGS-OFF conditions, separated by a pre-defined washout period (10 minutes) to prevent carryover effects.(Parker, Green, and Aziz 2019)

4.3.4 *MEG Analysis*

To remove artefacts of stimulation, raw MEG magnetometer recordings were filtered offline using the temporal extension of Signal Space Separation (tSSS) via the MaxFilter software (Elekta Neuromag v2.2) with a subspace correlation limit of 0.9. The automated bad channel selection was then followed by

visual inspection to remove saturated data or those exhibiting spurious artefact. The resultant MEG data was analyzed with MATLAB using the Fieldtrip and Brainstorm toolboxes. The raw MEG data was filtered between 1 - 100 Hz and a notch filter of 48-52 Hz was also applied, before recordings were resampled to 300 Hz. Independent Component Analysis (ICA) was used to decompose the MEG data, identify and subsequently remove EOG and ECG artefact. A multi-taper frequency transformation approach was used with a Hanning time window of 2 s and overlap of 1 s to produce time-frequency topographic representations of each recording. The power spectra were estimated using Welch's method with a Hanning window of 2 seconds with a 50% overlap. Power spectral densities were then normalized by dividing by the integral power between 1 Hz and 50 Hz to control for inherent differences within each participant and the average power spectra binned according to frequencies of interest – theta (4-7 Hz), alpha (7- 13 Hz) and low beta (13-20 Hz). Peak alpha frequency was identified by visual inspection of each individual power spectral density estimate.

The ICB152 MRI template in Brainstorm(Tadel et al. 2011) (http://neuroimage.usc.edu/brainstorm) was warped to fit the head model of each participant by co-registering the nasion, left and right pre-auricular fixed points acquired during head shape digitization (Gohel et al. 2017). Each subject-specific template was then used to calculate a lead field matrix based on a single shell model. The subsequent head model was co-registered with MEG data and source localization performed using the dynamical imaging of coherent sources (DICS) beamformer technique based on the frequency domain of the processed MEG signals.

4.3.5 *Statistical Analyses*

Statistical analyses to determine differences between ON and OFF stimulation was based on the non-parametric cluster-based permutation tests in the Fieldtrip toolbox.(Maris and Oostenveld 2007) A cluster was defined as two or more adjacent sensors reaching the pre-determined level of significance

(t-statistic < 0.05). Statistical significance was determined using cluster correction in the "Monte Carlo" Fieldtrip function (p value < 0.05, two-tailed) in order to correct for multiple comparisons. Other statistical analyses presented were conducted using the GraphPad Prism software. D'Agostino normality testing was conducted on each data set to confirm Gaussian distribution and mixed effects ANOVA were used with Tukey's posthoc tests applied for multiple comparisons. Comparisons of relative power in the ON and OFF-stimulation conditions were calculated by finding the difference in the relative power between the two conditions and normalizing to the OFF-condition baseline power to correct for inter-subject variability. P values <0.05 were regarded as statistically significant. Geisser-Greenhouse corrections were applied where tests for sphericity were found to be significant (p < 0.05).

4.4 Results

Of the sixteen participants recruited, there were 10 males and 6 females, with an average age of 51 years (SD 16.5). Two participants exhibited postural/mobility-associated pain and, as such, experienced no pain during MEG recordings. Two participants reported an increase in pain scores during the ON stimulation condition. Three MEG recordings were excluded from analysis due to unacceptable artefact or missing channels in the dataset. Seven patients began the MEG recording session in the ON-stimulation condition, while nine patients started in the OFF-stimulation condition. Based on baseline pain scores, the thirteen patients included in MEG analysis were categorized into no pain (n=2), mild pain (n=4), moderate pain (n=4) and severe pain groups (n=3).

The mean percentage change in pain score in response to acute DRG stimulation was 21% (SD 30%, p= .0068). In contrast, mean percentage change from pre-operative pain scores during chronic DRG stimulation was 46% (SD 37% p= .0001),[See Figure 12A] with 8/16 of participants experiencing >50% reduction from pre-operative baseline pain. Acute DRG stimulation resulted in a reduction in the

sensory domain measures of the SF-MPQ (t=2.31, p=.039), but did not have a significant effect on terms reflecting the affective dimension of pain (t=1.44, p=.17).[See Figure 12B]

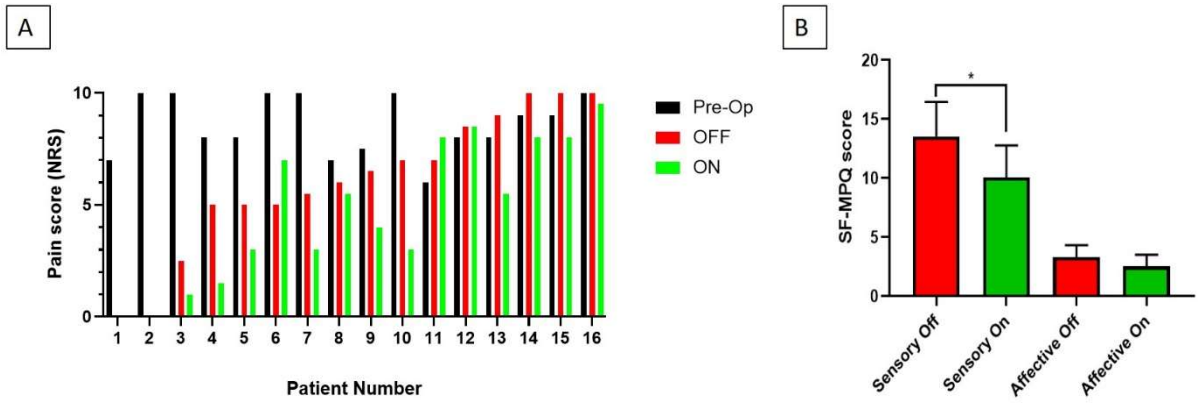

Figure 12. (A) *Grouped column graph depicting reported pain scores at baseline pre-operatively (black), OFF stimulation (red) and ON stimulation (green)* ***(B)*** *Column graph illustrating changes in the Short Form McGill Pain Questionnaire (SF-MPQ) in response to acute DRGS (Mean ± SEM). * p < 0.05*

4.4.1 *Mean Spectral Energy in Pain*

Participants who only experienced mobility-associated pain (Patients 1 and 2) served as a control group for the exploration of the effect of dorsal root ganglion stimulation in the pain-free state. In the DRGS-OFF condition, mean theta band power (4-7 Hz) was significantly higher among those patients in the severe pain category ($F_{(3, 35)} = 6.117$, $p = 0.0086$) compared to those in mild pain. [See Figure 13A] Mean alpha band power (7-13 Hz) was significantly higher among those patients reporting no pain ($F_{(3, 117)} = 3.871$, $p = .011$) compared to those experiencing moderate-to-severe pain,[See Figure 13B] reflected by a significant negative correlation between pain scores and mean alpha power in the in the DRGS-OFF condition (Pearson's correlation, $r = -0.51$, $p = 0.03$). [See Figure 13C] This finding was further supported

by the significant increase in peak alpha power when DRGS was turned *ON* compared to DRGS-*OFF* (t=2.37, p=.035). [See Figure 13D]

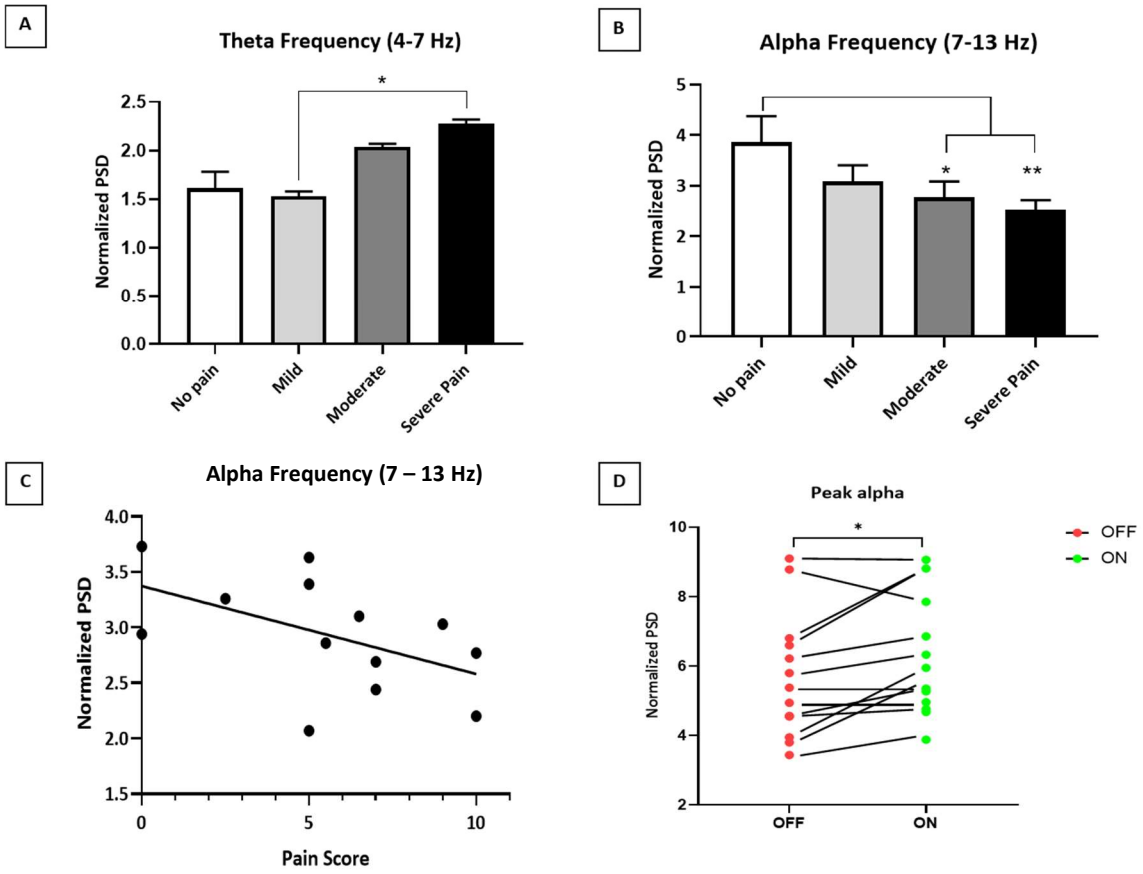

Figure 13. *Column graphs portraying average normalized* ***(A)*** *theta and* ***(B)*** *alpha band power across no pain (n=2), mild pain (n=4), moderate pain (n=4) and severe pain groups (n=3) (Mean ± SEM).* ***(C)*** *Pearson correlation of average normalized alpha range PSD with reported pain scores.* ***(D)*** *Peak alpha frequency of DRGS patients during OFF stimulation (red) and ON stimulation (green) demonstrating an increase in peak alpha power in response to DRGS-mediated pain relief. * p < 0.05, ** p < 0.01*

4.4.2 *Changes in MSE during DRGS*

In response to DRGS, the 'pain-free control' patients demonstrated spectral changes that were in direct contrast to the observed changes during therapeutic DRGS (subjects in whom pain was present at baseline and whose pain reduced with stimulation). In the pain-free state, DRGS resulted in a significant increase in theta band power ($F_{(3, 63)} = 5.922$, $p = .013$) [See Figure 14A], while all other DRGS patients experienced a decrease in theta power localized to the underlying centro-parietal cortex [See Figure 14B]. Pain-free participants also demonstrated a decrease in the low beta band power ($F_{(3, 135)} = 15.84$ p

< .0001), [See Figure 14C] when compared to the substantial pain relief group (> 50% reduction in pain scores).

Furthermore, during DRG stimulation, patients who reported pain relief, demonstrated a significant shift towards higher frequency power, represented by an increase in the mean low beta (13- 20 Hz) power compared to those with adequate pain relief (< 50% reduction in pain scores) or worsening pain scores ($F_{(3, 95)}$ = 12.17, p < .0001).[See Figure 14C] This shift towards higher frequency MSE was also reflected by a significant positive correlation between pain relief and change in low beta power (Pearson's correlation, r = 0.6984, p = .016).[See Figure 14D]

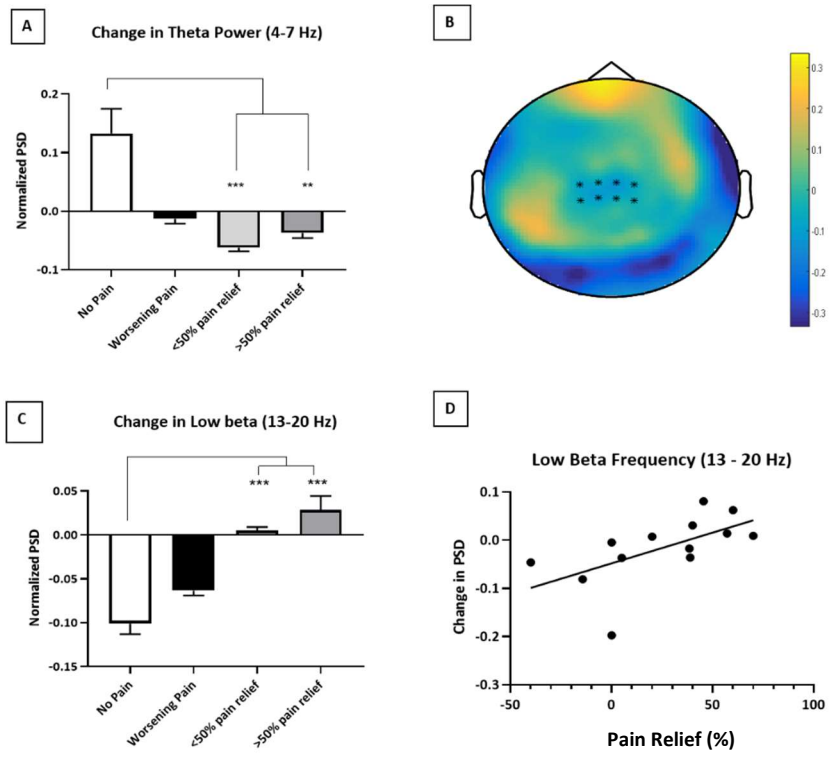

Figure 14. *Column graph depicting the changes in normalized power spectral density (PSD) in the* ***(A)*** *average theta band power.* ***(B)*** *Topographic plot demonstrating reduction in theta power over the centro-parietal cortex during DRG stimulation across all pain patients.* ***(C)*** *Column graph depicting augmented low beta band power during DRGS-mediated pain relief.* ***(D)*** *Pearson correlation of the change in normalized low beta range PSD with percentage reduction in pain scores.*

4.4.3 *Source Localization*

DRG stimulation was observed to produce a statistically significant ($p < .05$) reduction in low frequency activity in the central and medial parietal cortical regions.[See Figure 16D] Significant heterogeneity in the distribution of cortical activation during DRGS was observed across the participants.[See Appendix C] However, a similar observation of statistically significant ($p < .05$) depression in theta/alpha activity over the cortical sensors contralateral to the site of pain,[See Figure 15A & B] accompanied by ipsilateral increase in alpha/low beta activity in the cortical sensors ipsilateral to the site of pain [See Figure 15B & C] was observed among 7 of 13 DRG patients included in the analyses. 3D source reconstruction also revealed significant reductions in low frequency theta activity were observed in the contralateral somatosensory cortices, dorsolateral pre-frontal cortex (DLPFC), cingulate cortex and thalamus in patients that reported pain relief [See Figure 15D].

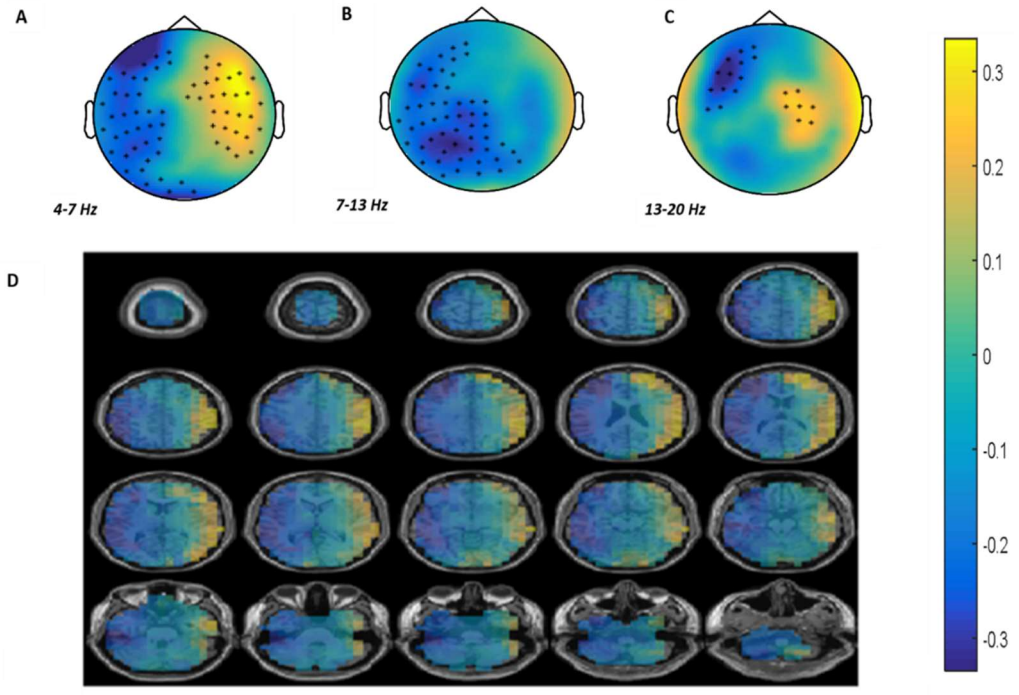

Figure 15*. Topographic plots showing significant changes in power spectral activity detected across magnetometers in a representative patient depicting contralateral reductions in* ***(A)*** *theta (4-7Hz),* ***(B)*** *alpha (7-13 Hz) and* ***(C)*** *low beta (13-20 Hz) activity, accompanied by increases in power spectral activity in alpha and low beta in the underlying cortex, ipsilateral to the region of pain.* ***(D)*** *3D source reconstruction showing ipsilateral cortical activation and contralateral cortical depression in response to DRGS-mediated pain relief.*

4.5 Discussion

Among the hypotheses for the neurophysiological basis of neuropathic pain, is the phenomenon of thalamocortical dysrhythmia (TCD), which hypothesizes that abnormal thalamocortical activity could underly a variety of neurologic disorders.(Llinás et al. 1999) TCD has been reported to demonstrate a shift towards augmented lower frequency activity in neurogenic pain, which can be normalized by thalamotomy(Sarnthein et al. 2006) to the levels of healthy controls. Findings observed during spinal cord stimulation(Schulman et al. 2005) have suggested that patients with features of thalamocortical dysrhythmia were likely to fail a trial of SCS due to its inability to modulate thalamic activity. However, a more recent study using intra-operative EEGs, has provided evidence that supports the utility of theta-alpha interactions in evaluating SCS-induced pain relief.(Telkes et al. 2020)

Our findings provide novel human evidence that neuromodulation directed towards the DRG can produce pain relief via a supraspinal mechanism, likely by modulating the TCD generator of central pain. Our findings further support the hypothesis of TCD as a common feature of neuropathic pain, as we demonstrate increased low frequency (4-7 Hz) activity with increasing severity of pain, an inverse relationship between resting state alpha power (7-13 Hz) and the severity of pain, and a shift towards high frequency (13-20 Hz) activity in response to therapeutic neurostimulation in a mixed cohort of chronic pain patients.

It has been postulated that deafferentation is central to production of the pathological thalamocortical theta activity observed in TCD.(G. Wang and Thompson 2008) Dorsal root ganglion stimulation may simulate these afferent transmissions(Matthias Hubert Morgalla et al. 2019) by modulating primary sensory neuronal activity to generate excitatory ascending inputs to the thalamus which are lost during the phenomenon of TCD.

Neurophysiologic studies have reported increased activity across all frequency bands in chronic pain and, as such, consensus remains elusive. This is likely due to variability in study designs and methods of reporting. Based on a recent systematic review,(Pinheiro, Queirós, et al. 2016) seven of eleven case-controlled studies which reported PSD estimates from neurophysiologic studies of pain have observed similar results to those presented in our series. However, the dynamism of the pain experience makes measurement of its neurophysiologic signature with an appropriate temporal resolution more challenging. Therefore, our study has capitalized on the superior temporal resolution of MEG to capture the dynamic changes in the pain state.

This observed shift in power to lower frequencies (increased theta activity and decreased alpha activity) with increasing pain could be a promising biomarker of neurogenic pain. Also, based on our findings, a corrective shift towards higher frequencies (increased low beta activity and normalized alpha activity) is indicative of the adequacy of pain relief. These neurophysiologic effects could also underly the efficacy of 20 - 30 Hz stimulation in relieving chronic pain symptoms during thalamic DBS.(Pereira and Aziz 2014) Pre-clinical studies of dorsal column stimulation have shown its potential to abolish pathologic low frequency synchronization in corticostriatal networks.(Fuentes et al. 2009) DRGS, and low frequency DBS, may target and abolish these pathologic theta oscillations and restore physiologic oscillatory activity in the thalamocortical network.

Paraesthesias in the distribution of the targeted dermatome are commonly observed during DRGS, and are likely produced as an epiphenomenon, independent of the neuromodulatory effect on pain relief.(Verrills et al. 2019) We postulate that the divergent activity observed in the pain-free state (increased cortical theta and decreased cortical beta during DRGS) [See Figure 14] may represent the percept of paraesthesia due to DRGS in the absence of pain-related cortical signatures among these control participants. Additionally, we have been able to identify cortical activity changes during DRGS in

brain regions known to be involved in the pain connectome.(Legrain et al. 2011) Of note, decreased cortical activity in the hemisphere contralateral to the site of pain was a significant finding among patients reporting DRGS-mediated pain relief. The regions involved included the thalamus, somatosensory, insular and cingulate cortices.[See Figure 15D] Pre-clinical studies have investigated the regional cortical activity of DRGS and have similarly found attenuation of activity in both somatosensory cortex and thalamus but did not identify insular cortex or cingulate cortices as regions responsive to DRG stimulation. These differences may be due to a more evolutionarily complex pain network involving the insular and cingulate cortex in humans, and their roles in generation of the affective dimension of pain,(Lu et al. 2016) which may be attenuated in animals.

Interestingly, the depressions in cortical activity observed could also be accompanied by cortical activation in the parietal cortex ipsilateral to the site of pain, which may represent interhemispheric disinhibition during pain relief, and signify the presence of neuroplastic adaptations of the ascending lemniscal structures as has been previously reported in patients suffering from chronic pain.(Fallon et al. 2013) However, the variation in patterns of increased activity, and the degree of cortical deactivation throughout the pain network, suggested that a personalized approach to interpretation and utilization of these results was required. This led to the conception of using tDCS to probe causality using these individualized patterns of cortical activity. Hence, the first clinical trial using Paired Acute Invasive/Non-invasive Stimulation (PAINS) (ClinicalTrials.gov: NCT03954093) was conceived to disambiguate this cortical activity as a true reflection of the pain experience and pain relief or conclude its representation as purely epiphenomenal.

As neuroimaging studies have shown, the effects of neuromodulation can result in cortical re-organization,(Pahapill and Zhang 2014) an effect which could account for the long-term effects of neurostimulation on pain relief. Most studies which have evaluated the efficacy of DRG stimulation,

tend to evaluate pain reduction over chronic timescales (3 - 12 months post-operatively). These chronic effects of neuromodulation may reflect the difference between the acute reduction of pain scores seen in our study (mean reduction in NRS - 21%), compared to a 60 – 80% reduction in pain scores from baseline seen over a 3 month follow-up period.(Deer et al. 2017; Piedade et al. 2019) The assessment of the degree to which pain relief is "clinically significant" is controversial, likely owing to the variability of cut-off points that have been applied across the literature. We chose to designate >50% pain relief as "substantial" as this degree of pain reduction is widely used and accepted as a beneficial outcome in the setting of neuromodulation for pain.(Deer et al. 2020) Nevertheless, studies which have sought to identify the minimal clinically significant difference in pain alleviation have shown that, on average, a decrease of 7 – 13% in pain scores has proven to be a meaningful difference for different chronic pain cohorts.(Todd et al. 1996; Singer and Thode 1998) Therefore, those patients experiencing <50% pain relief are likely to fall within the "adequate pain relief" category we have defined, especially when considering the dimensions of the pain experience which cannot be fully captured and appreciated with conventional pain intensity scores.

Unfortunately, in this experiment, the potential effects of DRG stimulation on the affective dimension of chronic pain (based on SF-MPQ scores), was not found to be significantly decreased by acute DRG stimulation. Re-organization in the limbic-cortical network has been reported to contribute to the chronification of pain.(McCarberg and Peppin 2019) Therefore, cortical neuroplasticity induced by chronic neurostimulation in these affective regions could be contributory to the additional pain reduction seen in long-term follow-up of DRGS cohorts.

A common limitation of neuromodulation studies is the inability to properly control for the presence of an implanted device in healthy controls. Our study benefited from the inclusion of chronic pain participants, with implanted DRG stimulators, in a pain-free state. This provided a rare opportunity to

disambiguate the effects of DRG stimulation on the human nervous system, from its effect on pain relief. In contrast to the theta suppression and increase in low beta power that was observed during pain relief, DRG stimulation produced an increase in theta activity and suppression of low beta power in the pain-free state. Additionally, the use of coin toss randomisation, while controversial,(Kang, Ragan, and Park 2008) resulted in a balanced allocation of patients to begin MEG recordings. Random sequence generation would be an improvement on this method of simple randomisation for future experiments which seeks to remove the potential for human manipulation in the process of flipping a coin.(M. P. A. Clark and Westerberg 2009) Nevertheless, coin toss randomisation, in this instance, was successful in producing balanced groups to begin the experimental protocol and did not influence the analyses thereafter. Despite the limitation of a relatively small study population (n=13), the utility of a crossover design, increases statistical power by reducing of within-subject variability. Similar designs are useful for rare conditions/interventions encountered in clinical research, particularly in the field of neuromodulation.

The identification of these potential supraspinal effects of DRG stimulation compounds observations from existing pre-clinical and clinical neuromodulation literature, while underscoring the importance of neurophysiologic tools like MEG to assess chronic pain and objectively stratify patients in the determination of therapeutic efficacy. Future directions of this type of research would ideally include larger patient cohorts investigated with pre-operative and post-operative neuroimaging (fMRI, PET scanning) combined with similar neurophysiologic techniques (EEG, MEG) to achieve a more robust demonstration of these effects of neuromodulation in pain.

5 COGNITIVE DIMENSION OF CHRONIC PAIN IN DORSAL ROOT GANGLION STIMULATION

5.1 Summary

A cognitive task, the n-back task, was used to interrogate the cognitive dimension of pain in patients with implanted dorsal root ganglion stimulators.

MEG signals from thirteen patients with implanted DRGS were recorded at rest and while performing the n-back task at 3 increasing working memory loads with DRGS-OFF and the task repeated with DRGS-ON. MEG recordings were pre-processed, then power spectral analysis and source localization was conducted.

During DRGS, a significant reduction in reported pain scores (mean 23%) and increased gamma (30 – 45 Hz) oscillatory activity was observed during task performance. DRGS-induced pain relief also resulted in a significantly reduced reaction time during this high working memory load condition ($p=0.011$). A significant increase in average gamma power was observed during task performance compared to the resting state. However, patients who reported exacerbations of pain, demonstrated a significantly elevated gamma power compared to those who reported pain relief during the task.

Our findings demonstrate that gamma oscillatory activity is differentially modulated by cognitive load in the presence of pain, and this activity is predominantly localized to the prefrontal and anterior cingulate cortices in a chronic pain cohort.

5.2 Introduction

Pain is a multi-dimensional experience, traditionally described as consisting of sensory, affective and cognitive domains (Melzack, R., & Casey 1968). Each domain can contribute to the modulation, and at times the propagation, of chronic pain. The cognitive dimension of pain has been demonstrated by investigating the roles that attention, distraction and memory play in augmenting pain (Bushnell, Čeko, and Low 2013; Torta et al. 2017). Studies have shown that engaging attentional networks with cognitive loads can attenuate perceived pain for a given stimulus – a distraction mechanism of pain relief (Schreiber et al. 2014; Valet et al. 2004). Conversely, it has also been demonstrated that pain can have a detrimental effect on attentional task performance – a disruptive effect of pain on cognition (Berryman et al. 2013; Chris Eccleston and Crombez 1999); suggestive of an integrated network involving prefrontal, somatosensory and limbic cortices, and a complex interplay between pain and cognition among these regions.

The role of neurophysiology in these processes has revealed a similarly overlapping feature of pain and cognition - cortical gamma oscillations. High frequency gamma activity has long been associated with cognition and attention (Gruber et al. 1999; Tallon-Baudry et al. 2005), but has also been shown to encode ongoing pain (De Pascalis, Cacace, and Massicolle 2004; Tan et al. 2019). Moreover, surgically implanted devices such as spinal cord stimulation have shown the potential to modulate cortical gamma [30-45 Hz] activity (Bai et al. 2017), supporting the hypothesis of supraspinal mechanisms of action for spinal, and potentially peripheral, neuromodulation.

A key structure of the peripheral nervous system, the DRG, contains a collection of primary afferent cell bodies in the lateral epidural space which synapse within the spinal cord laminae to convey nociceptive inputs which form the ascending STT. DRGS is a technique that has gained popularity over the past decade as an effective target of neuromodulation in chronic neuropathic pain and has

demonstrated the potential to improve the cognitive-affective dimensions of pain (Deer et al. 2017). Neuroimaging has been an invaluable tool to corroborate the effects of cognitive modulation in pain research (Bantick et al. 2002; Seminowicz and Davis 2007; Sprenger et al. 2012; Tracey et al. 2002). As such, we have employed the technique of MEG, coupled with a well-validated working memory task, the *n-back task* (Attridge et al. 2015; D. J. Moore, Keogh, and Eccleston 2013b), to investigate the effect of DRGS-mediated pain relief on cognitive performance, the effect of increasing attentional load on the pain percept and the neurophysiologic representation of gamma band oscillations in a cohort of chronic pain patients.

5.3 Materials & Methods

5.3.1 *Attentional task*

A numerical n-back task was used which consisted of integers ranging from 1 to 4 flashing on a display for 500 msec. Participants were instructed that three working memory loads of increasing difficulty would be cycled for the duration of the task: 0-back, 1-back and 2-back conditions. During the 0-back (low working memory) condition, participants were to immediately respond with a button press corresponding to the number flashed on screen. During the 1-back condition (low-to-intermediate working memory), participants were only to button press if the number flashing on screen corresponded to the number that flashed previously (one back). In the 2-back condition (high working memory), participants were only to button press if the number that flashed on-screen corresponded to the number that appeared two sequences before (two back).

Six trials of each condition would cycle sequentially for a total duration of twelve minutes while MEG signals were recorded. Participants were trained until they were comfortable with the paradigm and randomized to start the task in the ON or OFF stimulation condition. The possible outcomes of the task

would be a "hit" (correctly identifying a target for the relevant task condition), an error of omission (failure to identify a target for the relevant task condition), an error of commission (incorrectly identifying a non-target as a target in the relevant condition) or no button press (correctly omitting a non-target) [See Figure 16].

Average reaction time (RT) and accuracy (number of hits/total number of targets) for each condition were calculated and evaluated for statistical differences.

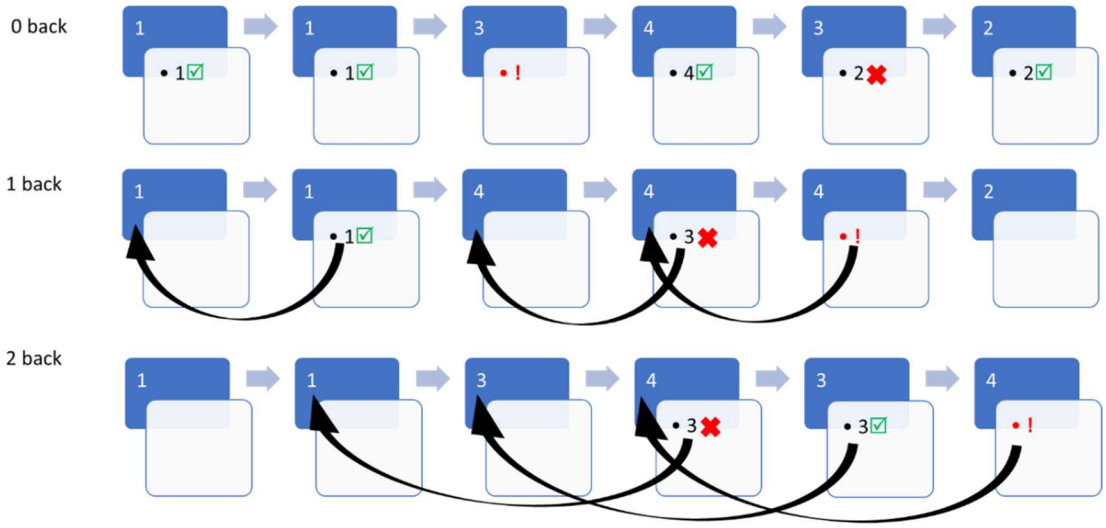

Figure 16 *Diagrammatic illustration of numerical n-back task, depicting hits (☑), errors of omission (!) and errors of commission(X) at three working memory loads (0-back, 1-back and 2-back).*

5.3.2 *Spectral and Source Analysis*

MEG Recordings were conducted as outlined previously [See Methods] during 12 minutes of task performance, with pain scores recorded before and after the task. Data was visually inspected and artefacts such as flats and jumps were detected in each channel and marked. The strong magnetic artefacts in the raw data, such as the artefacts of stimulation, were suppressed by the spatiotemporal signal space separation (tSSS) method (Taulu and Simola 2006) with a subspace correlation limit of 0.9 (Carrette et al. 2011; Medvedovsky et al. 2009) using MaxFilter software (Elekta Neuromag, version 2.2).

Additionally, the automatic detection of saturated and bad MEG channels was also applied in the software. The bad channels detected were excluded from tSSS analysis to prevent artefacts spreading. The resultant MEG data was analysed with MATLAB R2019a using the Fieldtrip (Oostenveld et al. 2011) and Brainstorm (Tadel et al. 2011) toolboxes. The raw MEG data was filtered between 1 - 100 Hz and a bandstop filter of 48-52 Hz was also applied, before recordings were resampled to 300 Hz. ICA was used to decompose the MEG data, identify and subsequently remove eye-blink and cardiac artefacts. The components related to eye-blink and cardiac activity were identified by comparing ICA component with EOG and ECG recordings.

The power spectra were estimated using Welch's method with a Hanning window of 3 seconds with a 50% overlap. The relevant epochs were then extracted for each working memory load condition and power spectral density (PSD) estimates averaged across all MEG channels. PSDs were then normalized by dividing by the integral power between 1 Hz and 50 Hz to control for inherent differences within each participant and the average power spectra binned to the frequency of interest - gamma band activity (30 - 45Hz).

The ICB152 MRI template in Brainstorm was warped to fit the head model of each participant by co-registering the nasion, left and right pre-auricular fixed points acquired during head shape digitization (Gohel et al. 2017). Each subject-specific template was then used to calculate a lead field matrix based on a single shell model. The subsequent head model was co-registered with MEG data and source localization performed using the dynamical imaging of coherent sources (DICS) beamformer technique based on the frequency of interest (30-45 Hz) of the processed MEG signals.

5.3.3 *Statistical Analysis*

Statistical analyses of MEG data to determine normalized PSD differences between *ON* and *OFF* stimulation was based on the non-parametric cluster-based permutation tests in the Fieldtrip toolbox

(Maris and Oostenveld 2007). A cluster was defined as two or more adjacent sensors reaching the pre-determined level of significance (t-statistic < 0.05). Statistical significance determined using the Monte Carlo method (p value < 0.05, two-tailed) in order to correct for multiple comparisons. Comparisons of relative power between resting state and task performance conditions were calculated by finding the difference in the relative power between the two conditions and normalizing to the baseline power of the resting state condition to correct for inter-subject variability. The GraphPad Prism software version 8.1 (La Jolla California USA, www.graphpad.com) was used for other figures and statistical analyses presented. D'Agostino normality testing was conducted on each data set to confirm Gaussian distribution and the corresponding parametric test - Student' t-test or mixed effects ANOVA (for comparisons of three or more groups) were utilized for analyses respectively. P values <0.05 were regarded as statistically significant.

5.3.4 *Mediation Analysis*

A two-tailed Pearson correlation was performed to identify the relationship between gamma band activity and patients' reported pain scores and task reaction times. Mediation analysis was conducted using SPSS (version 26) to assess whether there was a mediating effect between pain-related and cognition-related gamma activity in the frontal cortex, somatosensory cortex and dorsolateral prefrontal cortex. Mediation was tested by means of the joint significance test (MacKinnon et al. 2002).

5.4 Results

Sixteen participants were recruited (10 males, 6 females) with an average age of 51 years (SD 16.5), however, only thirteen patients were included in MEG analysis after excluding data with unacceptable artefact/missing MEG channels. Contrary to expectation, only three of the sixteen participants reported alleviation of pain during task performance during the *DRGS-OFF* condition. The majority reported either

worsening of pain scores (n=7), or no change in pain (n=3) during task performance compared to rest [see Figure 17]. Our cohort also included patients with posture-dependent/mobility-associated chronic pain syndromes (n=2), which meant they did not report any pain at rest or during the task performance.

However, there was a significant reduction in reported pain scores (mean reduction- 23% (SD 0.27), $F(2, 30) = 10.33$, $p < 0.001$) when DRGS was switched *ON* during the task, compared to *DRGS-OFF* during rest ($p = 0.01$) and task conditions ($p = 0.005$) [See Figure 17].

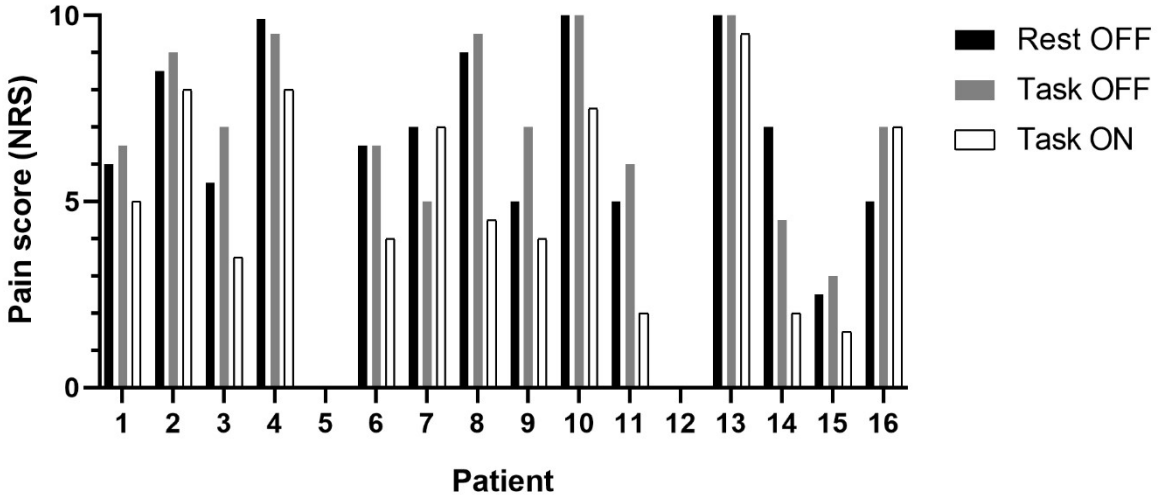

Figure 17. *Grouped column graph depicting change from baseline pain scores at rest (black) and during n-back task performance (grey) with DRGS turned off, as well as during task performance with DRGS turned on (white) among the sixteen participants. Of note, patients 5 and 12 had mobility-associated/posture-dependent pain and served as a unique "no-pain control" for the study.*

5.4.1 *Task Performance*

There was a significant reduction in task accuracy ($F (2, 24) = 36.25$, $p < 0.0001$) [See Figure 18A] and prolongation of RT ($F (2, 24) = 14.59$, $p < 0.0001$) [See Figure 18B] in response to increasing attentional loads. There was no significant difference in RTs between 0-back and 1-back conditions, regardless of

stimulation condition (OFF stimulation, p = 0.98, ON stimulation p = 0.73). However, the effect of working memory load on RT was driven by differences between the two lower working memory loads (0-back/1-back) and high working memory load (2-back) for both OFF (p < 0.001) and ON (p = 0.004) stimulation conditions [See Figure 18B].

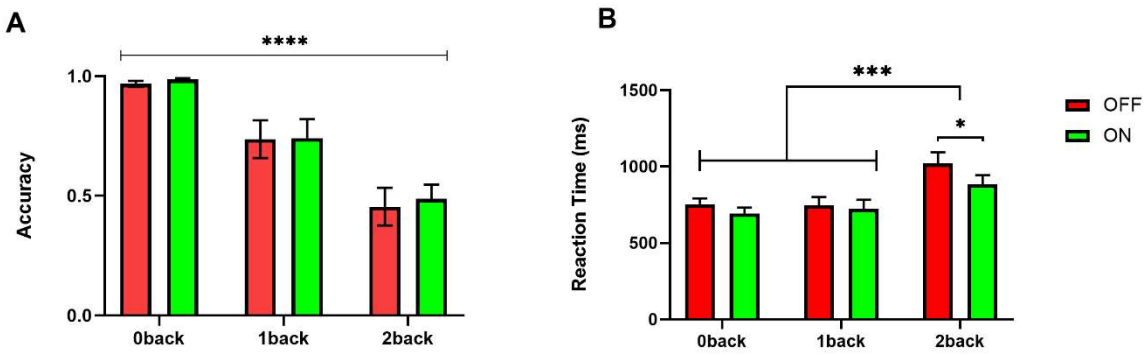

Figure 18. *Bar graphs illustrating (A) task accuracy (proportion of correctly identified hits of all targets presented) and (B) reaction time with DRGS OFF (red) and ON (green) over increasing working memory loads. p < 0.0001 - ****; p < 0.001 - ***; p < 0.05 - *.*

DRG stimulation was associated with a significant reduction in reaction time (F (1, 12) = 6.516, p = 0.025), with post-hoc tests confirming the statistical difference occurred within the highest working memory load (2-back) condition (p = 0.011) [See Figure 18B]. In contrast, there was no significant difference in task accuracy in response to DRGS across any working memory load condition (F (1,12) = 0.722, p = 0.41) [See Figure 18A].

5.4.2 *Gamma Band Activity*

Of the patients included in MEG analysis experiencing pain during the study (n=11), five reported 50% or greater reduction in reported pain scores with DRGS, while one reported worsening of pain. DRGS-mediated pain relief was associated with a significant reduction in gamma activity [30 - 45 Hz] across all

MEG sensors during task performance (t=2.27, p= 0.036) [See Figure 19A]. The observed reduction in gamma band activity during pain relief was predominantly localized to the prefrontal cortex based on source-space analyses, but also revealed reductions in gamma activity in both somatosensory and anterior cingulate cortices after 3D source reconstruction [See Figure 19B].

There were significant differences in gamma band fluctuations, dependent on the interaction of distraction and pain scores ($F(3, 80) = 65.01$, $p < 0.001$). All groups exhibited increased gamma oscillatory activity during task performance compared to resting state. There was significantly greater gamma activity during task performance among those patients experiencing pain compared to pain-free controls ($p < 0.001$).[See Figure 19C] Furthermore, among those in the pain-state, there was a significantly greater change in gamma oscillatory activity in patients that reported worsening pain during the task compared to those that exhibited pain relief during the attentional task (p=0.01).[See Figure 19C] This increased gamma activity was also localized to the prefrontal and anterior cingulate cortices.[See Figure 19D]

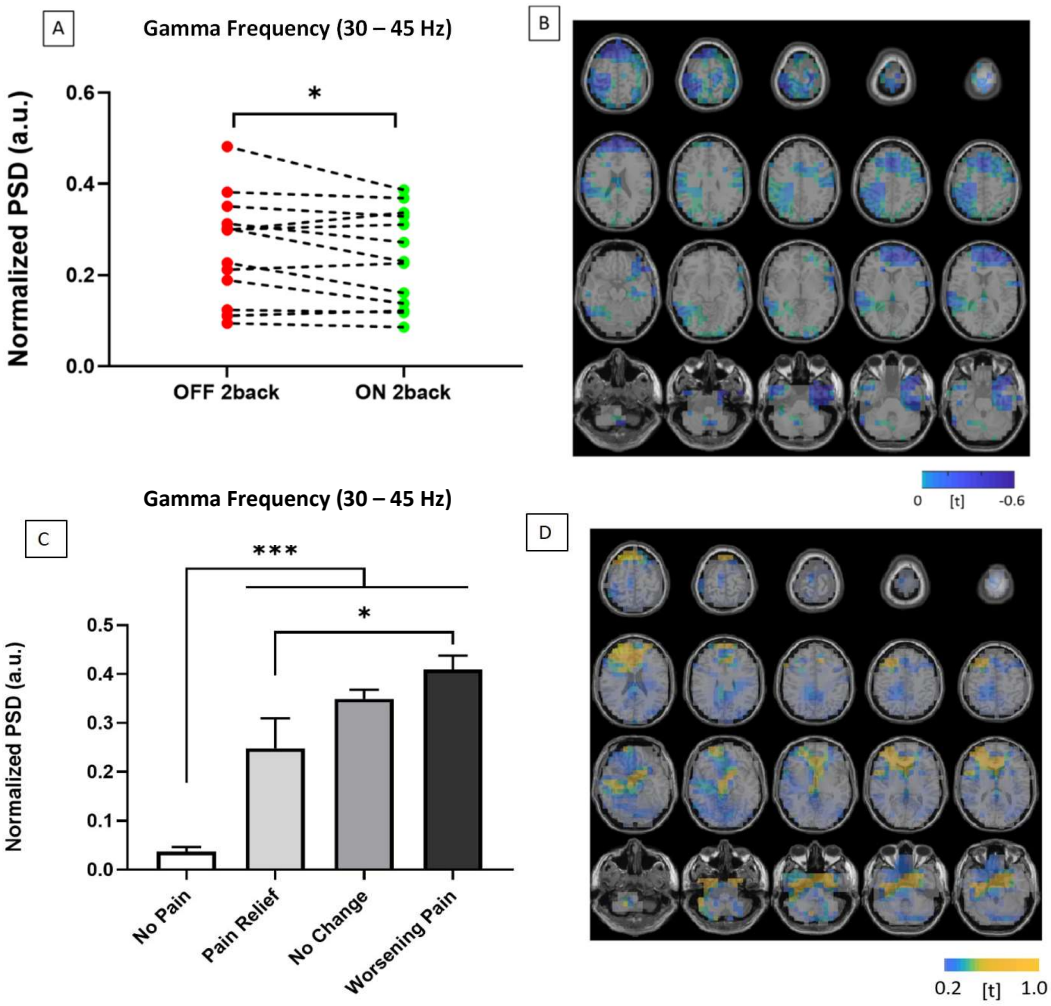

Figure 19. *(A) Graph illustrating change in normalized gamma power spectral density (PSD) between OFF (red) and ON (green) DRGS during high cognitive load (2-back condition). (B) 3-D source localization of a representative participant demonstrating t-statistic maps of significant reductions in gamma cortical activity across the prefrontal, anterior cingulate and somatosensory cortices during DRGS-mediated pain relief. (C) Column graph illustrating change in normalized power spectral density (PSD) with DRGS OFF, during high working memory load (2-back condition) compared to resting state grouped according to pain response during working memory load - no pain (n=2), pain relief (n=2), no change (n=3) and worsening pain (n=6) groups [Total of 13 patients included in MEG analysis]. (D) 3-D source localization of a*

representative participant demonstrating t-maps, as before, of significant increases in cortical activity across the prefrontal and anterior cingulate cortices during task performance.

Significant correlations were found between gamma band activity and subjectively reported pain scores in the frontal cortex [r= 0.4, p = 0.04], while significant correlations between gamma band activity and reaction times were found in both frontal and somatosensory cortex.[See Figure 20] However, further analysis did not reveal a mediating effect of pain on cognition, or vice-versa [See Table 4].

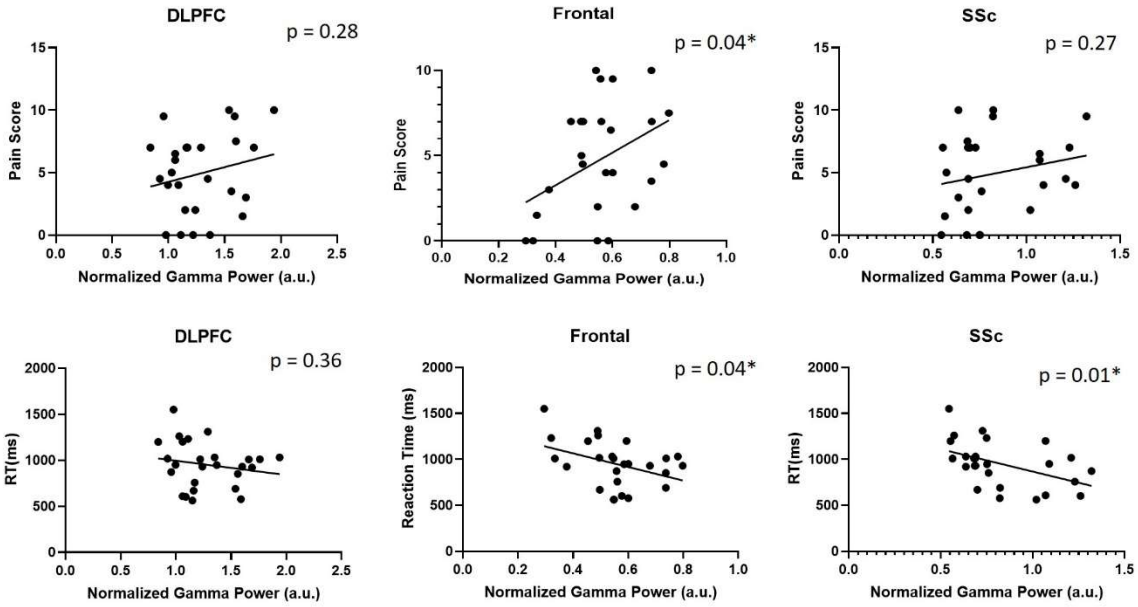

Figure 20*. Graphs depicting correlations between reported pain scores and normalized gamma activity (top row) as well as correlations between reaction time and 2-back reaction times (bottom row) in the dorsolateral prefrontal cortex, frontal cortex and somatosensory cortex (SSc).*

Table 4*. Mediation effects between pain-related gamma activity and cognition-related gamma activity in frontal, somatosensory and dorsolateral prefrontal cortices.*

	Standardized β	Standard Error	p-value
Frontal			
Pain → Gamma	0.398	0.008	0.044

Cognition → Gamma	-0.332	0.00	0.082
Somatosensoy cortex			
Pain → Gamma	0.93	0.014	0.63
Cognition → Gamma	-0.447	0.00	0.028
Dorsolateral Prefrontal cortex			
Pain → Gamma	0.179	0.019	0.4
Cognition → Gamma	-0.134	0.00	0.53

5.5 Discussion

Our findings demonstrate the efficacy of DRGS in alleviating the disruptive effect of pain on cognition and supports the use of neurophysiologic signals, in particular, gamma band activity, to investigate the cognitive dimension of pain. We further demonstrate that while increased cognitive load is reflected by enhanced gamma oscillatory activity, the effect of pain, and pain relief, can modulate gamma activity in the human prefrontal and anterior cingulate cortices. Furthermore, our findings demonstrate that there was no mediating effect of pain on cognition, or vice-versa, which suggests that the potential for pain and cognition to modulate cortical gamma activity occur independently.

An inverse relationship is to be expected between task accuracy and reaction time with increasing cognitive load (Meule 2017). Accordingly, the n-back task results in our chronic pain cohort showed a significant reduction in task accuracy and concomitant increase in reaction times with increasing working memory loads. However, cognitive loading (working memory) did not alleviate pain in the majority of our participants. The phenomenon of distraction-induced analgesia is equivocal, having demonstrated mixed

results across the pain literature. While there are studies which suggest that selective attention can mitigate the sensation of pain (Bantick et al. 2002; Buhle and Wager 2010), there are also studies which have found that distraction can also exacerbate the perception of pain (Goubert et al. 2004), as was seen in seven of the sixteen participants recruited in this study. Interestingly, the studies which demonstrate the phenomenon of distraction-mediated analgesia have been performed in healthy adults with the application of experimentally-induced pain. However, the initial report of worsened post-distraction pain(Goubert et al. 2004), was performed in a cohort of chronic back pain patients which, taken together with our findings, suggests that this mechanism of pain alleviation may not be as applicable in chronic pain as previously thought.

It is classically believed that attention processing has a limited capacity, and by re-directing a portion of attentional reserves towards a cognitively demanding exercise, such as the n-back task, the accessibility of pain processing to this attentional network is decreased (Abercrombie 1966; Kahneman 1973; McCaul and Malott 1984). However, this mechanism of attentional switching, seems to be sensitive to the degree of pain and the demands of the task on central attention (Christopher Eccleston 1995; Roa Romero et al. 2013). A pleasant, moderately engaging task might produce the intended alleviation of the pain percept by gating the accessibility of salient noxious stimuli to conscious processing. However, it seems similarly plausible that the challenge of a difficult, cognitively demanding task can become frustrating and potentially exacerbate pain perception.

The disruptive effect of pain on task performance (accuracy) was not found to be significant in our cohort, despite marginal increases in accuracy during therapeutic DRGS. However, participants' reaction times were significantly reduced for a given level of accuracy, particularly in the high working memory load (2-back) condition. This suggests that with the alleviation of chronic pain, reduced response latency can be achieved without sacrificing task performance. Pain is a well-known interruptive factor in cognitive performance (Attridge, Keogh, and Eccleston 2016; Keogh et al. 2014; D. J. Moore, Keogh, and Eccleston

2013a), and, persons suffering from chronic pain have been shown to exhibit deficits in various aspects of cognitive function including attention and memory (Moriarty et al. 2017; Nadar, Jasem, and Manee 2016). The impact of pain on cognition seems to be dependent on the attentional load required of the task (D. J. Moore, Eccleston, and Keogh 2017; D. J. Moore, Keogh, and Eccleston 2012), which has similarly been demonstrated by our findings. The majority of these studies have been conducted with experimentally-induced pain in healthy adult participants. However, our study benefited from the ability to investigate the effect of acute pain relief, through neuromodulation, within the chronic pain phenotype and demonstrated its ability to improve performance on a cognitive task.

Our findings are bolstered by incorporating a well-established neurophysiologic signature, gamma oscillatory activity, as an objective metric of pain and attention. The neurophysiologic importance of gamma band activity in the attentional modulation of pain has been previously demonstrated in healthy controls (Hauck, Lorenz, and Engel 2007). While our findings support the academic consensus which describes increased gamma activity in response to increased attentional demands (O. Jensen, Kaiser, and Lachaux 2007; S. Ray et al. 2008), we further delineate the potential for pain to modulate this gamma activity.

DRGS-induced pain relief was associated with significantly reduced gamma activity during task performance [See Figure 19A]. While a previous MEG study of SCS has hypothesized about the potential for increased cortical gamma activity in chronic pain (Schulman et al. 2005), our findings have provided further support for this proposed mechanism of thalamocortical dysrhythmia. Our study also benefitted from a "no-pain control" group in this chronic pain cohort. Interestingly, in the *DRGS-OFF* condition, the "no-change" and "no-pain" groups also showed a significant disparity in gamma activity despite neither group having reported benefit from distraction-mediated analgesia [See Figure 19C]. This observation suggests that this increased gamma activity is representative of ongoing pain in the chronic pain cortical network of the "no-change" group. Furthermore, we observed significantly lower gamma activity among

participants reporting pain relief during task performance, compared to those reporting worsening pain. Taken altogether, our results suggest that the blunted increase in gamma activity we observed during task performance is a consequence of pain alleviation from distraction. However, it is also possible that pain relief in this group occurred in response to distraction-mediated analgesia and this dampened gamma activity may represent the diversion of limited attentional resources. Further studies are required to conclusively disambiguate the causal relationship between these two possibilities.

The results of MEG source localization revealed gamma activation in brain regions which are known to be involved in the overlapping network of pain and attention, including somatosensory cortex (Petrovic et al. 1999, 2000) and cingulate cortices (Davis et al. 1997; Schmidt-Wilcke et al. 2014). However, the observed changes in gamma activity were predominantly localized to the prefrontal cortex, which has been implicated in the top-down attentional modulation of painful stimuli (Legrain et al. 2009) and has also been identified as a region that encodes ongoing pain among chronic pain patients and healthy adults (E. S. May et al. 2019; Schulz et al. 2015). Similar findings of attenuated cortical activity in cortico-limbic networks during DRG stimulation has been demonstrated in pre-clinical studies(Pawela, Kramer, and Hogan 2017) and EEG studies of SCS (De Ridder et al. 2013). Coupled with our findings of increased gamma activity during cognitive loads, and decreased gamma activity during pain relief in the prefrontal cortex, this represents further supportive evidence of the supraspinal effects of DRG stimulation.

While acknowledging the study limitations of a small sample size, resulting from the novelty of DRGS as an intervention for chronic pain, the crossover study design was chosen in order to overcome this limitation and increase statistical power. It should also be recognised that such an overlap in cortical networks between pain-related and attention-related activities may still be represented by more functionally distinct anatomical regions than the areas described in our analysis. Further elucidation of these anatomical differences might be achieved by combining techniques such as fMRI which can resolve deeper anatomical structures involved in the pain network (insular cortex, thalamus) with greater

sensitivity and spatial resolution. These limitations notwithstanding, this study offers novel evidence for the supraspinal effects of DRGS in chronic pain and demonstrates the neurophysiologic representation of pain and cognition by gamma oscillatory activity, in the human prefrontal cortex.

6 PAIRED ACUTE INVASIVE/NON-INVASIVE STIMULATION (PAINS) TRIAL

6.1 Summary

DRG stimulation, an invasive method of modulating sensory input, and tDCS, a non-invasive method of altering cortical excitability, have both been shown to relieve chronic pain through neuromodulation at various levels of the nervous system. We employed a randomized, sham-controlled crossover study design to investigate whether single-session tDCS would have an additive therapeutic effect alongside DRG stimulation in the treatment of chronic pain.

Sixteen neuropathic pain patients with implanted DRG stimulators were recruited. Baseline pain scores were established with DRGS-OFF. Pain scores were then recorded with DRGS-ON, after paired sham tDCS stimulation, and after paired active anodal tDCS stimulation. For active tDCS, patients were randomized to 'MEG-localized' tDCS or contralateral M1 tDCS for 30 minutes. EEG recordings and evaluations of tDCS adverse effects were also collected.

Participants tolerated both sham and active tDCS with no significant adverse effects. Paired DRGS/active tDCS resulted in a reduction in pain scores compared to DRGS/sham tDCS or DRGS alone. There was no significant difference in the additive effect of M1 vs. MEG-localized tDCS over DRGS alone.

A single session of tDCS alongside DRGS is safe and can significantly reduce pain acutely in neuropathic pain patients. Paired invasive/non-invasive neuromodulation is a promising new strategy for pain management.

6.2 Introduction

6.2.1 *Background*

Clinicians have used neuromodulation, targeted at a variety of structures in the CNS and PNS, in an effort to alleviate chronic pain. Invasive strategies have generally targeted the CNS via thalamic(Abreu et al. 2017; Pereira, Boccard, et al. 2013) or PAG/PVG (Hosobuchi et al. 1979; Sims-Williams et al. 2017) DBS as well as SCS.(R. B. North et al. 2005) However, more recently, dorsal root ganglion stimulation, modulating the PNS, has emerged as a promising invasive neurostimulation technique (Deer et al. 2017; Matthias H. Morgalla et al. 2018). Historically, non-invasive techniques such as transcutaneous electrical nerve stimulation (TENS) (Gibson et al. 2019; Nnoaham and Kumbang 2008) and electroacupuncture (Seo et al. 2017; K. M. Shin et al. 2018) have targeted the PNS to treat chronic pain, with mixed and often disappointing results. Perhaps more effective in modulating chronic pain have been non-invasive methods targeting the CNS, most notably repetitive transcranial magnetic stimulation (rTMS) (Galhardoni et al. 2015) and tDCS (Ngernyam and Jensen 2014). These techniques have demonstrated the potential to amplify pain reduction in tandem with conventional therapy. (Goudra et al. 2017)

It is well established that a variety of pathophysiologic processes (both central and peripheral) are contributory to the generation and propagation of chronic neuropathic pain. (Meacham et al. 2017) Although clinically, DRGS is in its infancy, mechanisms of pain relief have been investigated, and likely include modulation of pathological DRG excitability,(Koopmeiners et al. 2013) as well as supraspinal effects.(Parker et al. 2020) Previous findings have observed inverse trends between cortical beta activity and pain intensity,(M. Jensen et al. 2013) which our MEG findings [See Chapter 4] have corroborated as a potential indicator of DRGS-mediated pain relief.

Among available techniques for non-invasive brain stimulation, tDCS is widely considered safer than TMS, (Rosen et al. 2009) and anodal tDCS targeting M1 has consistently been shown to be an efficacious target in relieving chronic neuropathic pain.(Fregni, Gimenes, et al. 2006) While DRGS and tDCS in isolation have demonstrated therapeutic efficacy for patients who no longer derive benefit from standard medical management, their efficacy in combination remains to be investigated.

6.2.2 *Objective*

We hypothesized that paired invasive/non-invasive neuromodulation of both the PNS and CNS respectively would result in an additive therapeutic benefit. To this end, we evaluated the safety and efficacy of paired DRGS alongside a single session tDCS in the treatment of chronic neuropathic pain. We also investigated whether individualised, neurophysiologically guided tDCS would provide a superior therapeutic benefit to anodal tDCS targeting M1.

6.3 Materials & Methods

6.3.1 *Trial design*

Ethical approval was obtained by the South-Central Oxford Research Ethics Committee (REF: 13/SC/0298) and conducted in accordance with the Declarations of Helsinki. The trial was prospectively registered on ClinicalTrials.gov (NCT03954093). The study was a Phase I/II randomized, single-blind, sham-controlled crossover trial, evaluating the safety and efficacy of a single-session of paired invasive (DRGS) and non-invasive (tDCS) neurostimulation for neuropathic pain. Outcomes were recorded i) at baseline with DRGS-OFF, then ii) DRGS-ON, iii) during paired DRGS-ON + sham tDCS, and finally iv) with paired DRGS-ON + active tDCS. Regarding the active tDCS treatment, patients were allocated by simple randomization to receive anodal tDCS delivered to the motor cortex contralateral to the site of pain, or localized tDCS based on previously conducted patient-specific MEG recordings of DRGS-mediated pain

relief. Allocation concealment was achieved by using sequentially numbered opaque sealed envelopes containing intervention groups.

6.3.2 *Participants*

Patients with diagnosed intractable chronic pain syndromes were contacted for recruitment in this study. Inclusion criteria were age > 18 and > 6 months post-implantation of a functional DRG stimulator which was proven effective based on intra-operative trial stimulation. Exclusion criteria were previous treatment with non-invasive brain stimulation (tDCS/TMS), non-functional DRG stimulator, a personal or family history of seizure disorder/epilepsy, presence of metallic implants/devices in the head, history of alcohol abuse or sleep deprivation.

6.3.3 *Interventions*

6.3.3.1 Surgical Procedure

DRG stimulators were implanted as previously described [See Methods].

6.3.3.2 Direct Current Stimulation

A pair of surface electrodes (35 cm^2) covered with saline-soaked sponges was used to deliver direct current via a battery-driven stimulator (Neuroconn) for 30 minutes. During sham stimulation, electrodes were placed in the same positions planned for active stimulation, however stimulation was automatically turned off after 30 seconds.(Knotkova and Rasche 2014) During active stimulation of M1, the anode was placed over the C3/C4 position (electroencephalogram 10/20 system) and the cathode was placed on the contralateral supraorbital area. The location of the anode was applied to the hemisphere contralateral to the site of the patient's pain and stimulated at a constant current of 2 mA for 30 minutes. This protocol of motor cortex stimulation has been previously shown to be effective in relieving pain (David et al. 2018) and was used as a positive control intervention. MEG-localized tDCS

was delivered at 2 mA for 30 minutes based on source-localized activity during DRGS-mediated pain relief.[See Appendix C] The anode was placed on a region of cortex which demonstrated increased beta oscillatory activity during DRGS-mediated pain relief, while the cathode was placed on the contralateral supraorbital region during DRGS-mediated pain relief [See Figure 21A].

6.3.4 *Outcomes*

The primary outcome was change in VAS after each intervention, while the secondary outcomes included changes in the SF-MPQ, power spectral changes on continuous EEG recordings, evaluations of safety, tolerability and blinding to tDCS.

6.3.4.1 Pain Rating

A standardized pain questionnaire with VAS and SF-MPQ was presented at the end of each intervention phase. The VAS was rated 0 (no pain) to 10 (worst pain imaginable) and patients allowed to indicate their pain rating at each time point. The SF-MPQ consisted of 15 words (11 sensory descriptors, 4 affective descriptors) and the patients allowed to indicate whether these words described their current sensation of pain (none – 0 points, mild – 1 point, moderate – 2 points, severe – 3 points)

6.3.4.2 Continuous EEG

During each intervention, EEG recordings were undertaken with the patient seated at rest, eyes closed (EC) for a duration of five minutes. EEG was recorded from 20 electrodes (Fp1, Fp2, F3, F4, FC5, FC1, FC2, FC6, C3, Cz, C4, CP5, CP1, CP2, CP6, P3, Pz, P4, O1 and O2) using a TMSi REFA amplifier and an EEG cap recording from Ag/AgCl electrodes (TMSi, Enschede, The Netherlands). The EEG sensors were placed according to the international 10/20 system [See Figure 21 B-C], with the ground placed on the right wrist. Recordings were performed at a sampling rate of 2048 Hz and impedance was kept below 1KΩ.

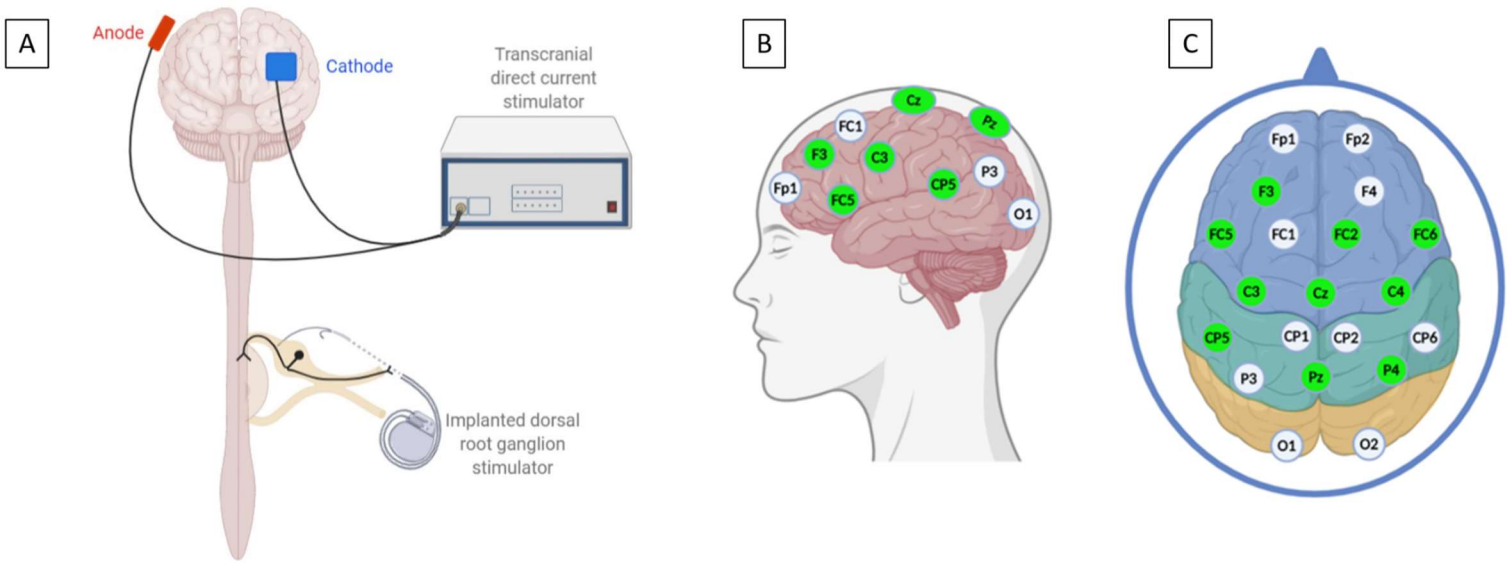

Figure 21 *(A) Illustration of paired invasive/non-ivasive stimulation acting at central and peripheral elements of the nervous system. Illustrations depicting scalp electrode locations used for recordings from (B) lateral and (C) vertical views. (**grey** electrodes were excluded due to missing data/artefact across some trials; **green** electrodes were included for Power Spectral Density analysis)*

Data were pre-processed offline in a custom MATLAB (R2019a) script using the Fieldtrip toolbox. Power spectral density estimates were produced using a multi-taper frequency transformation approach with a Hanning time window of 4s and overlap of 0.9s. Power spectral densities were then normalized by dividing by the integral power between 1 Hz and 90 Hz to control for inherent differences within each participant and the average power spectra binned according to frequencies of interest – low (13-20 Hz) and high (20-30 Hz) beta frequencies.

6.3.4.3 Adverse Effects and Blinding

A standardized questionnaire (http://www.neurologie.uni-goettingen.de/downloads.html) [See Appendix D] was presented to each participant after each tDCS intervention to evaluate the presence/absence of the most commonly reported side effects (itching, pain, burning, warmth, fatigue,

metallic taste) or to report any other symptom experienced. These symptoms were rated as none, mild, moderate or severe, along with their subjective assessments of whether they considered the intervention to be real, placebo or unsure to evaluate blinding, and how much the intervention affected their general state (not at all, slightly, considerably, much, very much).

6.3.5 *Sample Size*

The sample size required to detect a comparable improvement was calculated using an online calculator from (http://hedwig.mgh.harvard.edu/sample_size/js/js_crossover_quant.html). Based on previous studies of paired neurostimulation for chronic pain,(Boggio et al. 2009) which reported a mean VAS reduction of 36.5% (±10.7%), we estimated that for an effect size of 18% (10.7%) a sample size of 16 patients with a power of 99%, at an α level of 0.05 would be required to detect the effect of paired DRGS/tDCS .

6.3.6 *Statistical analysis*

GraphPad Prism software version 8.1 (La Jolla California USA, www.graphpad.com) was used for all other statistical analyses. D'Agostino omnibus tests were used to assess the Gaussian distribution of the data. Pain scores were compared using repeated measures one-way ANOVA with Greenhouse-Geisser correction to adjust for sphericity. Repeated measures two-way ANOVA (two within-subject factors: Condition [DRGS-OFF, DRGS-ON, DRGS-ON/sham tDCS, DRGS-ON/active tDCS] and Frequency) used to compare power spectral densities with multiple comparisons correction (Tukey).

6.4 Results

Sixteen patients (eleven males, five females) with a median age of 52.5 years (IQR 44.3 – 60.5) were recruited for a single session of paired invasive/non-invasive stimulation. Recruitment rate was 80% and retention rate was 100% [See Figure 22] at a median follow up of 39.5 months (IQR 14.8 – 54).

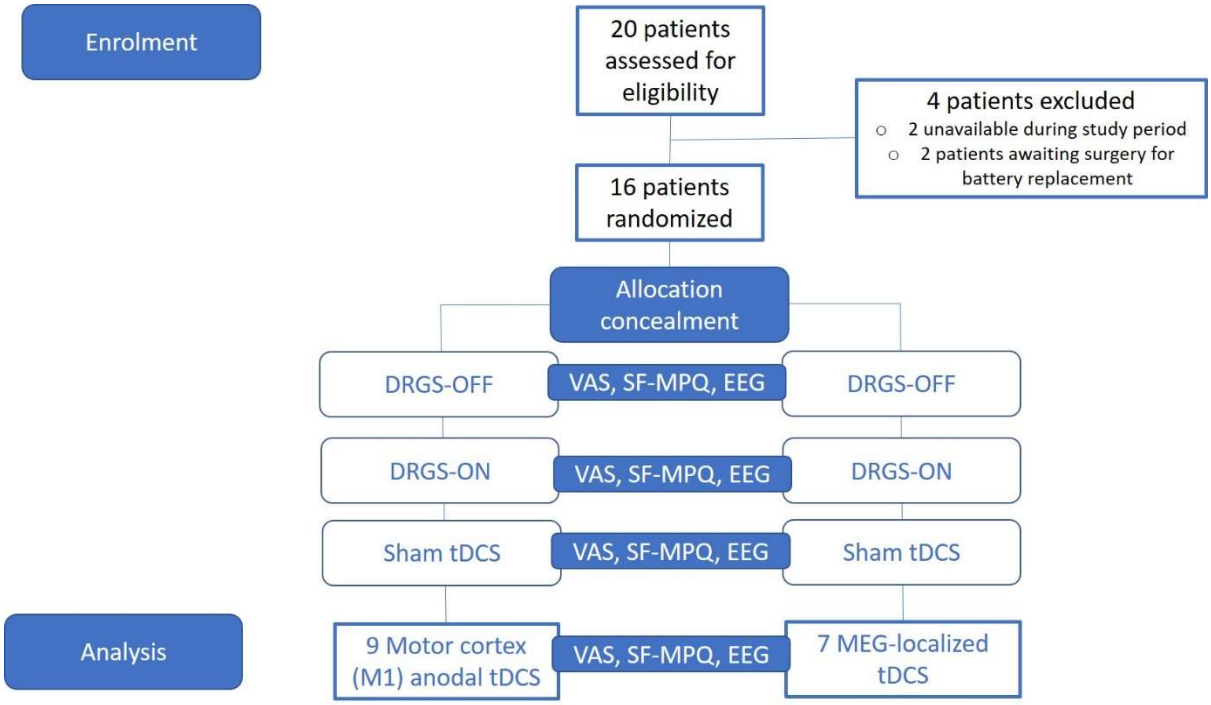

Figure 22. *Flow diagram illustrating patients assessed for eligibility (n=20), reasons for exclusion and those recruited for trial randomization (n=16)*

6.4.1 *Primary Outcome*

There was a significant reduction in VAS from baseline (DRGS-OFF) compared to all stimulation conditions [F (1.55, 23.31) = 22.81, p < .001]. While there was no significant difference in reported pain scores after pairing DRGS-ON with sham tDCS (p= .98), there was a statistically significant reduction in VAS with paired DRGS-ON and active (M1 and MEG-localized) tDCS (p = .005) [See Figure 23A].

DRGS-ON alone resulted in a 37% mean reduction in pain (95% CI, 15 – 54% ;p < .001), while DRGS-ON paired with active tDCS resulted in a 57% mean reduction in pain (95% CI, 25 – 73%; p < .001)

compared to DRGS-OFF. There was no statistically significant difference between the additional pain relief observed based on randomized tDCS target. M1 anodal tDCS provided an additional 39% improvement pain relief, while MEG-localized tDCS produced an additional 30% improvement in pain relief over DRGS alone (t = .5, p = .62) [See Figure 23B].

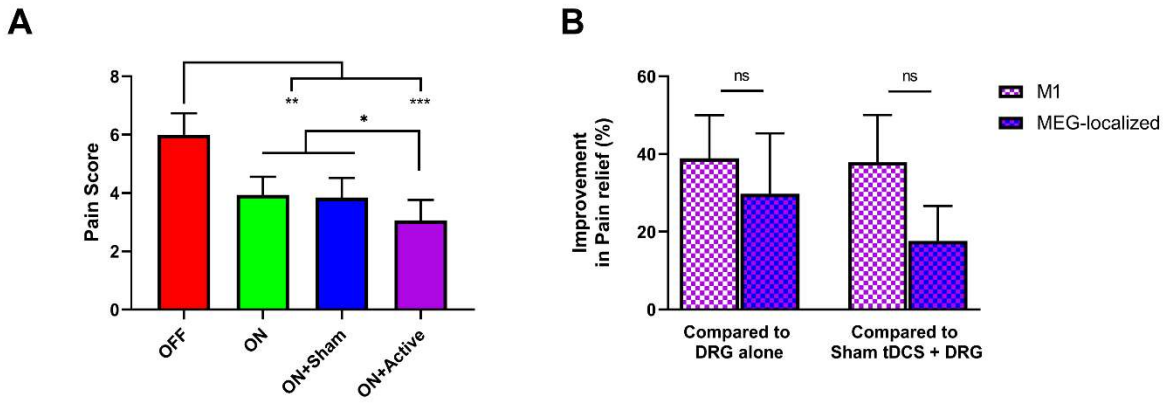

Figure 23. *Column graphs depicting (A) reported pain scores in the DRGS-OFF, DRGS-ON, DRGS-ON/Sham tDCS and DRGS-ON/Active tDCS conditions and (B) Relative improvement in pain relief in M1 group vs MEG-localized groups*

6.4.2 *Secondary Outcomes*

6.4.2.1 Power Spectral Density

Significant augmentation of beta activity (13 – 30 Hz) was observed between DRGS-OFF and DRGS-ON across frontal (FC5 [F (2.106, 31.59) = 1.664; p = .003], FC6 [F (2.144, 32.15) = 0.8547; p = .001]), central (C3 [F (2.148, 32.23) = 0.7561; p = .002], Cz [F (1.731, 25.96) = 0.9728, p = .002]) and parietal (Pz [F (2.037, 30.56) = 1.522, p = .002]) electrodes [See Figure 24 B, D, E, F, I]. Significant increases in low beta (13 – 20 Hz) were also observed in frontal electrodes (FC5 [F (2.407, 36.10) = 1.369; p = .005], FC6 [F (2.323, 34.84) = 2.143; p = .0001]) between DRGS-OFF and paired DRGS-ON/active tDCS[See Figure 25 B & D].

Of note, significant differences in beta oscillatory activity were observed between the sham tDCS and active tDCS conditions in parietal regions (Pz [F (2.037, 30.56) = 1.522; p = .0063], P4 [F (2.100, 31.50) = 1.063; p = .0015])[See Figure 24 I & J]

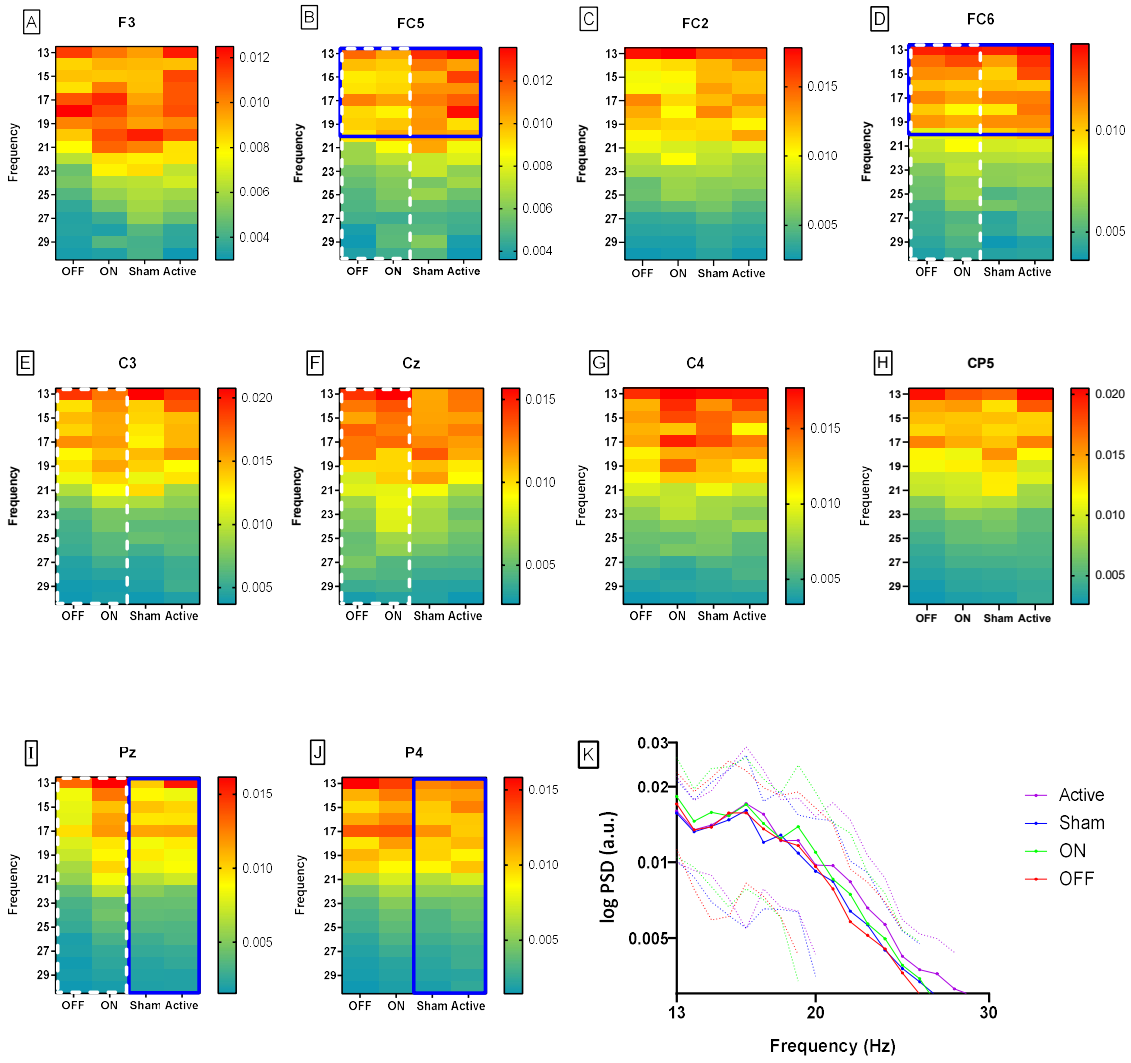

Figure 24 *(A-J) Heat maps illustrating changes in beta activity across scalp EEG electrodes and (K) line graph depicting average changes (n=16) in Power Spectral density across DRGS-OFF, DRGS-ON, DRGS-ON/Sham tDCS and DRGS-ON/Active tDCS conditions*

6.4.2.2 Short Form - McGill Pain Questionnaire

There was a significant reduction in pain from baseline in both the sensory ($F(3, 45) = 18.1$, $p < .001$) and affective ($F(3, 45) = 4.6$, $p = .007$) dimensions of the SF-MPQ during DRGS alone and both paired invasive/non-invasive stimulation conditions (i.e both sham and active)[See Figure 25]. While the

greatest pain reduction was observed during paired DRGS/active tDCS (sensory – 54%; affective – 63%), the observed reduction in pain was not significantly different in the active tDCS group compared to sham tDCS (p = .89) or DRGS alone (p = .46).

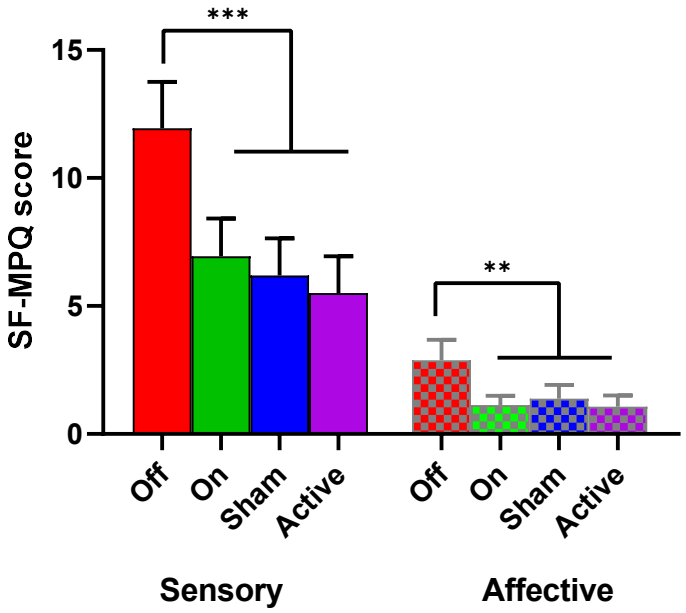

Figure 25. *Column graphs illustrating changes in the Sensory and Affective dimensions of the Short Form McGill Pain Questionnaire during DRGS-OFF, DRGS-ON, DRGS-ON/Sham tDCS and DRGS-ON/Active tDCS*

6.4.2.3 Safety and Tolerability

All participants were effectively blinded to the interventions ($\chi^2_{[2,\ n=16]} = 0.267$, p = .87) [See Table 5].

Table 5*. Illustrating results of adequacy in blinding based on patient perceptions of tDCS interventions as real stimulation or placebo*

	Real	**Placebo**	**Not sure**
Sham tDCS	7	3	6
Active tDCS	8	2	6

Pairing of tDCS along with DRGS was well-tolerated. All patients reported the interventions either affected their general state slightly (sham[n=7]; active[n=8]) or not at all (sham[n=9]; active[n=8]). The

most commonly reported adverse effect was itching near the electrode site (sham[n=10], active[n=10]), followed by burning (sham[n=5], active[n=4]), warmth (sham[n=4], active[n=4]) and tingling (sham[n=5], active[n=1])[See Figure 26]. However, all patients reported that these sensations were tolerable and did not warrant termination of the experimental protocol.

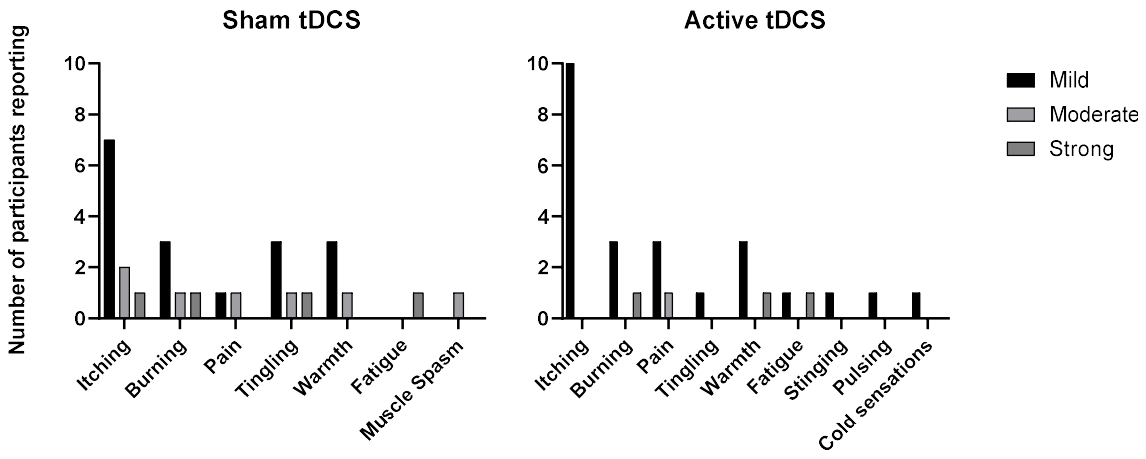

Figure 26. *Patient reported incidence of adverse effects during sham and active tDCS conditions.*

6.5 Discussion

Our study provides novel evidence of the safety and efficacy of paired invasive/non-invasive neuromodulation for the treatment of chronic neuropathic pain. Thirty minutes of single-session anodal tDCS coupled with DRGS resulted in a significant acute improvement in chronic pain symptoms when compared to sham stimulation. Sham tDCS resulted in an average pain reduction of 7% in addition to that achieved by DRGS alone, while active tDCS produced a 20% reduction in pain compared to DRGS alone. This additive effect of paired invasive/non-invasive stimulation may well be due to either recruitment of other central pain relief networks or the amplification of previously identified supraspinal mechanisms associated with DRGS.(Parker et al. 2020)

The clinical implications of our results raise new questions regarding the longevity of this additive effect, as long-term pain relief from single-session tDCS was not evaluated. However, the paired non-invasive/invasive approach could conceivably be used as a rescue therapy to ameliorate intermittent exacerbations of pain in DRGS patients. Such fluctuations are typical of chronic pain syndromes. The optimal therapeutic benefits of tDCS on pain have been reported to aggregate after repeated sessions of stimulation (Castillo-Saavedra et al. 2016). Therefore, a multiple session approach of combined neurostimulation could be an option for chronic pain patients with implanted DRGS systems. Practically, the integration of combined central and peripheral neuromodulation can be on an outpatient basis. At-home patient-delivered tDCS has been attempted (O'Neill et al. 2018) and, while feasible, may benefit from supervised administration via, for example, tele-medicine, (Pérez-Borrego et al. 2014) to ensure appropriate use and maximal therapeutic benefit.

Targeting patient-specific, MEG-localized cortical activity related to DRGS-mediated pain relief, was not superior to standard M1 anodal tDCS in pain relief efficacy. This finding supports the renewed interest in motor cortex stimulation as a therapeutic target in the treatment of neuropathic pain. Unfortunately, over several decades of investigation, invasive motor cortex stimulation has demonstrated significant variability in its efficacy and tolerability in alleviating chronic pain. There have been reports of long-lasting therapeutic effect in some patients treated with invasive motor cortex stimulation, particularly those suffering from post-stroke pain.(Carroll et al. 2000; Pereira et al. 2015) However, this modality has also demonstrated disappointing rates of success in some cohorts,(Nandi et al. 2002) which has led to a shift in the field towards exploring alternative strategies, like DBS, which have been more reliable and well-tolerated in the treatment of neuropathic pain. Nevertheless, the best available evidence has still provided justification for both the use of invasive and non-invasive stimulation of the motor cortex in well-selected chronic pain cohorts.(Rasche et al. 2006; Lima and Fregni 2008; Mo et al. 2019) When

considering different electrode montages convergent mechanisms of action have been found, for example comparing tDCS targeting M1 or DLPFC, both resulted in augmented functional connectivity between thalamus and sensori-motor cortices.(Sankarasubramanian et al. 2017) While we expected individualised tDCS to be superior, it is possible that a similar convergence phenomenon is at play. Other mechanisms reported to underlie the efficacy of anodal tDCS include reductions in cortical GABA concentration,(Kim et al. 2014) increased levels of both cortical glutamate and glutamine(V. P. Clark et al. 2011) and NMDA-mediated neuroplasticity.(Nitsche et al. 2003)

Our findings demonstrate that both DRGS alone and active tDCS significantly augmented cortical beta activity in both frontal (FC5, FC6) and parietal (Pz, P4) electrodes during acute pain relief. Based on EEG studies, anodal tDCS has been shown to increase cortical beta oscillatory activity,(Mangia, Pirini, and Cappello 2014) and supports an analgesic mechanism involving reversal of cortical beta suppression observed while experiencing pain.(Misra et al. 2016) Diminished cortical beta activity in pain patients compared to healthy controls (Boord et al. 2008; Sitges et al. 2010) has been observed in the pain literature, with some neuromodulatory techniques targeting upregulation of low beta oscillations to achieve pain relief.(Heathcote et al. 2019) In contrast, while MEG-localized tDCS did not demonstrate superior efficacy to M1 stimulation, the evaluation of transcranial alternating current stimulation (tACS) in a similar paradigm may yield more promising results due to its propensity to modulate neuronal activity in a frequency-dependent manner. (Kanai, Paulus, and Walsh 2010)

Our findings also represent novel evidence demonstrating both safety and tolerability of externally applied direct current in patients with implanted neurostimulators. While safety concerns have traditionally prompted exclusion of patients with implanted devices,(Bikson et al. 2016) our patient cohort represents a unique subset of participants in which the distance of the implanted DRGS system from the origin of direct current, likely obviates any deleterious effects of the intervention. However,

the evidence of scalp tDCS- (Chhatbar et al. 2018) and TMS-induced electric fields (Magsood et al. 2020) recorded from implanted DBS electrodes will very likely limit the extrapolation of this type of combination treatment to patients with head/brain implants.

A potential limitation of the study design was the lack of randomization for the order of stimulation. This was done to prevent carryover effects due to the potential long-lasting neurophysiologic changes after a single session of active tDCS.(Marcos Fabio DosSantos et al. 2012; Portilla et al. 2013) In future studies, a larger cohort could better control for order effects by implementing a multiple-session design and evaluation of a randomized sequence of interventions over a longer trial period. This design was not employed in this proof-of-principle study due to concerns of participant attrition.

The effect of tDCS alone in our chronic pain cohort was not evaluated due to the likelihood of carryover effects from this intervention and incompatibility with our single session study design. However, a plethora of studies have already established the utility of active tDCS in chronic neuropathic pain patients.(Antal et al. 2010; Fregni, Boggio, et al. 2006) To our knowledge, a comparative efficacy study of invasive and non-invasive stimulation remains unexplored, and if so, is certainly warranted.

This study provides novel evidence for the potential to combine non-invasive and invasive neuromodulation therapies, to safely amplify pain relief in chronic intractable pain. Targeting elements of both the central and peripheral nervous systems simultaneously is likely to be important for maximising pain relief.

7 AFFECTIVE DIMENSION OF PAIN IN DORSAL ROOT GANGLION STIMULATION

7.1 Summary

The Facial Expression Recognition Task (FERT), is a well-validated tool used which presents various emotional stimuli (neutral, angry, happy, sad, surprised, disgusted and fearful faces) to investigate the effects of treatments on disorders of mood such as Major Depressive Disorder and Bipolar Disorder. We hypothesized that DRGS-mediated pain relief would alter perception of emotional faces and demonstrate its potential to modulate the affective dimension of chronic pain.

Ten chronic pain patients with implanted DRG stimulators and ten age-matched healthy controls were recruited to perform the FERT. Chronic pain patients performed the FERT while DRGS was ON and while DRGS was OFF in a randomized order. Participant's reaction times and accuracy in categorizing each facial expression were analysed and compared.

All participants correctly identified positive emotions more readily compared to negative emotions. There were no significant differences in reaction times to FERT stimuli across healthy controls or DRGS conditions (DRGS-OFF and DRGS-ON). Chronic pain patients were more likely to correctly classify angry and happy faces compared to healthy controls, while healthy controls were more likely to correctly identify sad faces compared to chronic pain participants.

These results demonstrate the differences in positive and negative attentional biases between people suffering from chronic pain and healthy controls. However, we were unable to demonstrate an effect of acute DRGS on this metric of the affective dimension of chronic pain.

7.2 Introduction

The affective dimension of chronic pain refers to the emotional responses which are elicited in response to pain, and which can influence one's perception of the pain experience. There are six distinct emotions that are broadly recognizable across populations – anger, disgust, fear, sadness, happiness and surprise.(Ekman 1992) The ability to distinguish these various emotions has been linked to neural processing in the limbic regions of the brain and has been used to assess affective processing in a variety of psychiatric conditions.(Douglas and Porter 2010; Harmer, Grayson, and Goodwin 2002) Patients with chronic pain have also demonstrated deficits in facial emotion recognition, thought to result from deficits in the affective dimension of pain (N. Y. Shin et al. 2013) or a contribution of pain-related motor deficits in task performance. (von Piekartz et al. 2015)

DRGS, while beneficial in the treatment of the sensory dimension of chronic pain, has also demonstrated superiority to SCS in improving total mood disturbance, depression, tension and confusion based on the Profile of Mood States (POMS) scale.(Deer et al. 2017) We hypothesized that chronic pain patients would exhibit differences in facial expression recognition compared to healthy controls, and that therapeutic DRGS could modulate this effect on the affective dimension of chronic pain.

7.3 Materials & Methods

7.3.1 *Participants*

Ten chronic pain patients with previously implanted DRG stimulators and ten age-matched healthy controls (HC) were recruited for this study. Written informed consent was obtained from all participants prior to the task.

7.3.2 *Stimuli*

The Facial Expression Recognition Task (FERT) presented six basic emotions – anger, happy, sad, fearful, surprised and disgust – along with neutral faces. Each emotional face was presented with variable expressivity from neutral (0%) to full emotion (100%) [See Figure 27] with 10% increments in a randomized order. These 10 variations of each emotion were presented to each participant four times along with 10 neutral faces resulting in 250 facial stimuli presented over a 12-minute session. Happy and surprised faces were considered positive emotions, while angry, sad, fearful and disgusted faces were considered negative emotions.

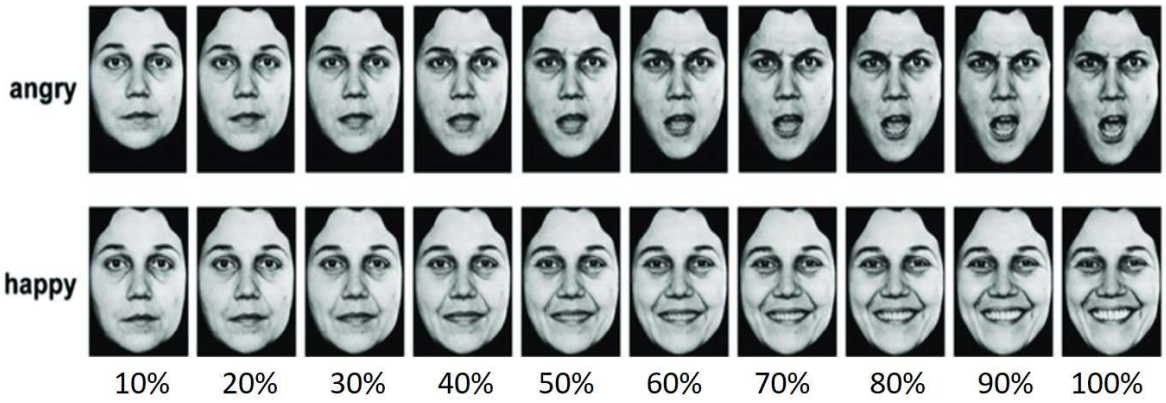

Figure 27 *Representative variations in degree of emotional expressivity in angry and happy faces*

7.3.3 *Task Performance*

Each participant was seated in a room at ambient temperature and told to identify the faces as quickly and as accurately as possible by pressing the appropriately labelled key on a keyboard. Stimuli were presented on the screen for 500 msec and would not proceed to the following stimulus until the participant selected a category of the presented emotion. An untimed rest period was allowed halfway into each session to prevent participant fatigue. For DRGS participants, the task was presented twice – once in the DRGS-OFF condition and in the DRGS-ON condition, with the starting condition randomized across the participants to prevent order effects. At least one hour was allowed to elapse between these

sessions to allow for DRGS washout (ON-to-OFF) or to allow time for full therapeutic effect (OFF-to-ON), while mitigating the effects of participant familiarity with the task. The percentage of each emotion correctly identified as well as the reaction time from stimulus presentation to categorization of each emotion were extracted offline from the recorded data file and used for analysis.

7.3.4 *Statistical Analysis*

The GraphPad Prism software version 8.1 (La Jolla California USA, www.graphpad.com) was used to perform all statistical analyses. One-way ANOVA with Tukey's post hoc multiple comparisons test was used to compare performances of healthy controls, DRGS-OFF and DRGS-ON conditions. p-values > 0.05 were considered statistically significant.

7.4 Results

The mean age (± SD) of enrolled patients and healthy controls was 54 (± 13) and 53 (± 19) years respectively. All participants were able to more easily identify positive emotions compared to negative emotions (HC [t = 8.9, p < .0001], DRGS-OFF [t=5.9, p = .0002], DRGS-ON [t = 3.9, p = .0039]). There were no significant differences in reaction time across all patients based on stimulus presented(neutral [F (2, 27) = 1.9, p= .17], happy [F (2, 27) = 0.06, p =0.94], angry [F (2, 27) = 0.1, p= .86], disgust [F (2, 27) = 0.05, p= .95], sad [F (2, 27) = 0.07, p = .93], fear [F (2, 27) = 0.01, p > .99]). [See Figure 28]

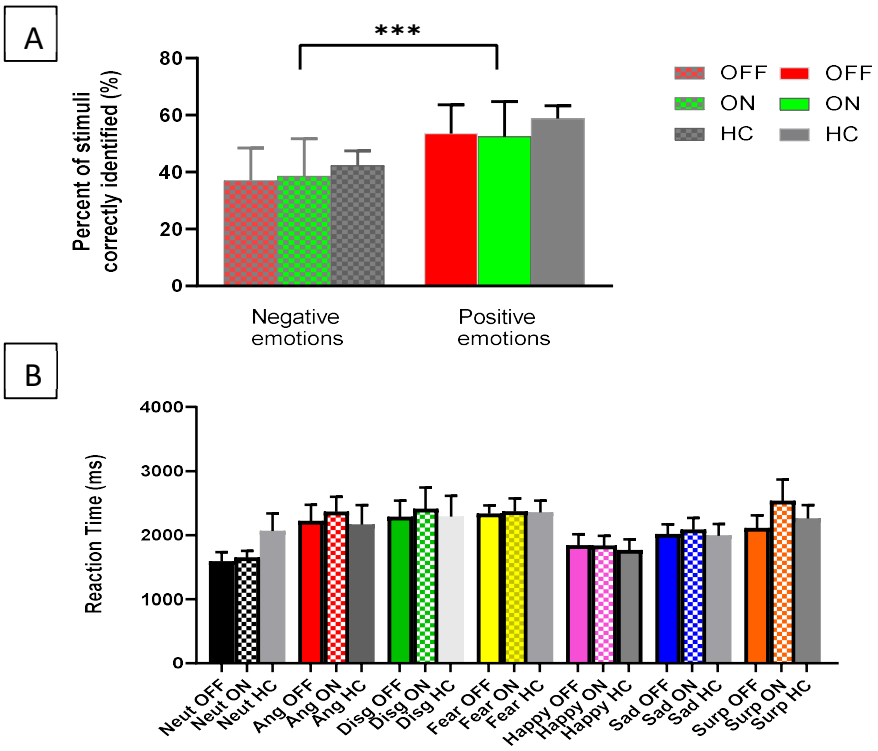

Figure 28. *(A) Percentage of correctly identified positive (happy, surprised) and negative (angry, sad, fearful, disgusted) emotional stimuli (B) Reaction times in correctly identifying each emotional face among chronic pain participants (DRGS-OFF and DRGS-ON) and healthy controls*

Compared to healthy controls, DRGS patients were more likely to correctly classify angry [F (2,27) = 7.5, p = .003] and happy faces [F (2,27) = 10.0, p < .001]. By contrast, healthy controls were more likely to correctly identify sad [F (2,27) = 7.7, p = .002] faces compared to chronic pain participants. There were no differences identified across participants' recognition of fearful [F (2,27) = 3.2, p = .06], disgusted [F (2,27) = 0.46, p = .63], surprised[F (2,27) = 0.04, p = .96] or neutral [F (2,27) = 0.06, p = .95] faces. Interestingly, DRGS did not significantly alter patient's perception of any emotional stimuli [See Figure 29].

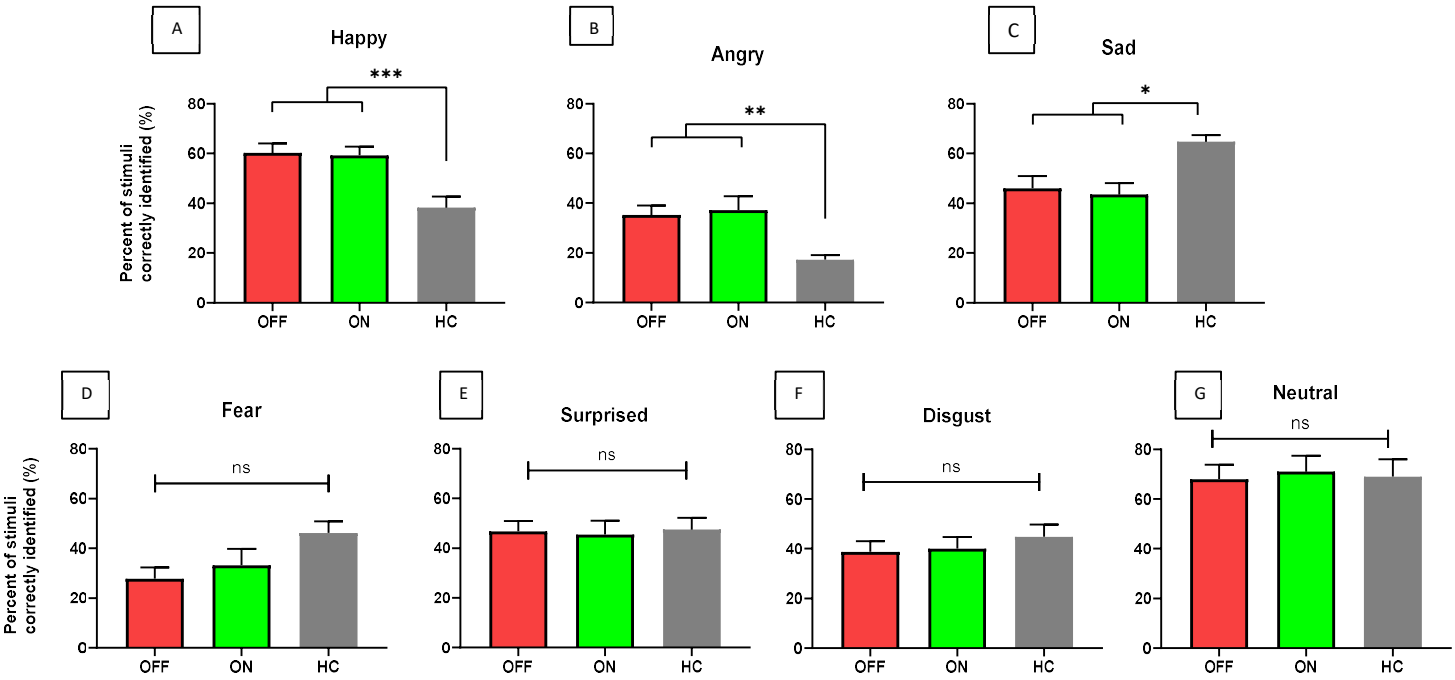

Figure 29*. Column graphs depicting the percentage of emotional stimuli correctly identified among (A) happy, (B) angry, (C) sad, (D) fearful, (E) surprised and (F) disgusted faces*

7.5 Discussion

This study demonstrates differential emotional face recognition between patients with chronic pain and healthy controls particularly for happy, angry and sad faces. These results, though peculiar at face value, has been recognized in the literature regarding stress resilience. Thoern et al. (2016) described

an attentional bias towards positive stimuli (happy faces) in participants who reported a resilience to stress. However, this bias was only observed in participants who also demonstrated an attentional bias towards negative stimuli (angry faces). This phenomenon is postulated to be an adaptive response to threat stimuli. A person likely must first be sensitized to an aversive stimulus in order to produce a compensatory bias towards positive stimuli as a protective mechanism. This process is plausible in chronic pain patients as the chronicity of nociceptive/neuropathic stimuli are known to produce neuroplastic changes associated with attention and cognition (Moriarty, McGuire, and Finn 2011)

The findings of an attenuated responsiveness to sad faces is also supported by previous literature among patients with Major Depressive Disorder treated with antidepressants. (Bamford et al. 2015; Fu et al. 2004; Victor et al. 2013) While it is well-known that many patients with chronic pain also have co-morbid depression (Fishbain et al. 1997; Sheng et al. 2017) a variety of antidepressants including TCAs, SNRIs and selective serotonin reuptake inhibitors (SSRIs) have been used as useful adjuncts in the treatment of chronic pain. This experimental design could not unfortunately control for the use of these types of medications for ethical reasons and it is therefore likely that concomitant administration of this drug class may have resulted in the observed reduction in sad face recognition.

Our study is also a unique application of the test-retest reliability of the Facial Expression Recognition Task. It has been shown that repeat testing of the FERT is possible (Adams et al. 2015) and can be used to facilitate longitudinal studies. However, the limitation of patient participation to a single session required a significantly reduced time period (one hour vs. one week) between first test and repeat testing. We did not observe any significant differences in reaction times or emotion recognition across DRGS-OFF and DRGS-ON, which suggests that either there was no difference in performance between initial test and subsequent tests, or the effect of order randomization successfully attenuated the impact of learning on task performance. These findings while supportive of the use of FERT in single

session repeat testing, also suggests that acute pain relief from DRGS does not have a significant impact on affective processing. As previously discussed, acute DRGS also did not seem to have a significant impact on cognitive task performance but revealed differences in reaction time at higher cognitive loads. (See Chapter 5) This may allude to varying sensitivities between cognitive/affective tasks and may warrant more comprehensive evaluation with the emotional test battery (ETB) to make conclusive statements about the effect of acute DRGS on affective processing. Additionally, differences in emotional processing could likely be more sensitive to longer term testing paradigms (pre-operative vs. 6-week post-operative) and might evaluate the effect of chronic DRGS on altering limbic cortical neuroplasticity.(Biggio et al. 2009)

There has been contradictory evidence in the literature regarding age-related attentional biases. While some portend that a negativity bias may develop as an individual gets older,(Vesker et al. 2018) there is a larger body of evidence that advancing age produces an attentional bias towards positive stimuli (Mather and Carstensen 2003; Reed, Chan, and Mikels 2014) or attenuates the negativity bias observed in younger adults.(Tomaszczyk and Fernandes 2014) Our cohort was generally older, which likely explains the significant bias for positive emotion recognition, an effect which was not different between chronic pain participants and healthy controls.

It has also been reported that the duration of stimulus presentation may affect the outcomes of emotion recognition tasks.(Fox et al. 2000; Pazderski and Mcbride 2018) While these inherent methodological flaws are valid, the ETB, and the FERT by extension, remain the most frequently used and easily accessible tests of affective function/dysfunction. The application of FERT has provided supportive evidence regarding the affective processing of chronic pain, but was unable to demonstrate an acute effect of DRGS on the affective dimension of chronic pain.

8 DORSAL ROOT GANGLION STIMULATION AND AUTONOMIC NEUROMODULATION

8.1 Summary

Neurosurgical techniques targeting multiple sites of the central and peripheral nervous system have shown the potential to modulate autonomic nervous system (ANS) activity for therapeutic benefit. Heart rate variability (HRV) is a well-established indicator of cardiac autonomic activity and has been used to demonstrate the changes in autonomic activity during neuromodulation. We investigated the use of DRGS as a new site for autonomic neuromodulation by using a crossover design to compare the effect of stimulation on HRV in a cohort of neuropathic pain patients.

Blood pressure and resting state ECG recordings were undertaken for 8 minutes in twenty-three patients with diagnosed neuropathic pain syndromes. Eighteen patients were ultimately included in the analysis after exclusion of ectopics and artefact. Frequency-domain indicators of HRV – normalized low frequency (LF) power, high frequency (HF) power and the ratio of low frequency to high frequency power (LF/HF ratio) – were conducted and compared between OFF and ON DRG stimulation conditions.

Significant reductions in blood pressure, normalized LF power and LF/HF ratio, along with a significant increase in the normalized HF power - indicators of sympatho-vagal balance - were observed in response to acute DRG stimulation. These significant changes in HRV parameters were not correlated with changes in reported pain scores. Based on the metrics of HRV, DRG stimulation has the capacity to reduce sympatho-vagal balance independent of its effect on pain reduction. Therefore, DRG stimulation may represent a novel, minimally-invasive site for autonomic neuromodulation in other painful and non-painful dysautonomic disorders.

8.2 Introduction

Dysautonomias are typified by aberrant output of either the sympathetic or parasympathetic nervous systems resulting in an array of manifestations across multiple body systems. Our understanding of autonomic dysfunction of the cardiovascular (essential hypertension, orthostatic hypotension), gastrointestinal (irritable bowel syndrome, gastroparesis) and genitourinary (urinary incontinence, neurogenic bladder) systems has served as the impetus for the development of both medical and surgical interventions which target the ANS for therapeutic benefit.

Neuromodulation of the ANS has demonstrated the potential to relieve the symptoms of a range of disorders which either have a primary or secondary dysautonomic component. Conventional forms of functional neurosurgery such as DBS (Alexander L. Green et al. 2010), and SCS (Anselmino et al. 2009; R. Moore et al. 2004) have both been evaluated for their utility in cardiovascular disease based on their capacity to modulate changes in HRV.

HRV is a well-established indicator of balance between the sympathetic and parasympathetic nervous systems(Electrophysiology 1996). Both the time-domain (for example - standard deviation of the inter-beat intervals in normal sinus beats [SDNN]) and frequency-domain measures of heart rate variability have been used as surrogate markers of autonomic activity(Kleiger, Stein, and Bigger 2005; Reyes del Paso et al. 2013). Frequency domain indicators namely, low frequency ([LF] 0.04 – 0.15 Hz) and high frequency ([HF] 0.15 - 0.4 Hz) power are purportedly more sensitive and representative of parasympathetic nervous system activity, while the LF/HF ratio is thought to represent a marker of sympatho-vagal balance (Shaffer and Ginsberg 2017).

The DRG represents a cluster of sensory afferent somata and is also known to be a source of inter-ganglionic collaterals between the autonomic and somatic nervous systems. We hypothesized that the

superior efficacy of DRG stimulation in sympathetically-mediated disorders like CRPS is due to its mechanistic role in modulating autonomic outflow and investigated its effect on HRV in a diverse cohort of chronic neuropathic pain patients. We report on the efficacy of DRGS as a site for autonomic neuromodulation and provide an overview of the various techniques, approved and experimental, used in autonomic neurosurgery.

8.3 Materials & Methods

8.3.1 *Study Setting & Design*

Patients with previously diagnosed neuropathic pain syndromes who had undergone DRGS implantation at the John Radcliffe Hospital, Oxford were recruited to participate in a single-session, randomized crossover study between September 1, 2017 and March 31, 2020. Patients that met the inclusion criteria underwent ECG recordings during the OFF stimulation and ON stimulation conditions while pain scores (NRS) were recorded for each condition. Pre-operative baseline pain scores were also included to identify long-term responders to DRGS therapy.

8.3.2 *ECG Recording and Analysis*

Informed consent was obtained from each participant prior to commencement of recordings. A 3-lead ECG was recorded by placing two electrodes on the right and left arms, along with one reference electrode while patients were seated in an isolated room at a temperature of approximately 22°C. Patients were randomized to begin recordings in the OFF or ON stimulation condition to prevent order effects and a 10-minute period elapsed between each condition to limit carryover effects of stimulation(Parker, Green, and Aziz 2019). The mean arterial pressure was recorded before and after DRGS, along with eight minutes of resting state ECG recorded in both conditions at a sampling rate of 1000 Hz and stored offline for subsequent analysis.

HRV analysis was conducted in MATLAB R2019b (The MathWorks Inc, Natick, MA, USA) using a custom script along with the Pan Tompkins ECG QRS detector toolbox (Sedghamiz 2014). All recordings were visually inspected for ectopic beats and artefact. RR intervals were detected and the RR interval time series were resampled to 4Hz and analysed using a Fast-Fourier transform (FFT) method as previously described(Ernst 2017). Heart rate and SDNN were calculated from R-R intervals, while absolute values for low frequency (0.04 -0.15 Hz) and high frequency (0.15-0.4Hz) power were obtained from power spectral density analysis and were then normalized to the total power (0.04- 0.4 Hz) [See Figure 30] in order to minimize within- and across-subject variability(Burr 2007).

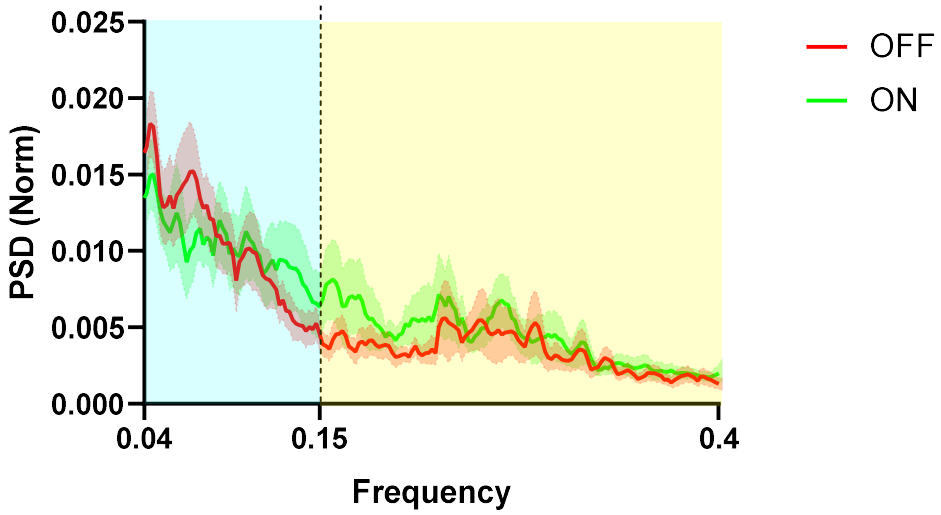

Figure 30 *Average normalized power spectral density (PSD) during OFF and ON DRG stimulation (n=13). Blue area – Low frequency (LF 0.04 – 0.15 Hz) power representative of sympathetic activity. Yellow area – High frequency (HF 0.15 – 0.4 Hz) power, representative of parasympathetic activity. (Bold line represents the mean while the shaded area represents the SEM)*

8.3.3 *Study size*

Sample size was calculated by digitally extracting the mean HF power from previously published literature(Kalmár et al. 2013) using the online WebPlotDigitizer version 4.2 software (San Francisco, California, USA)(Rohatgi 2011) and applying methods in the G*Power 3.1 (Düsseldorf, Germany) software. A minimum sample size of 15 patients would be required to provide a 90% probability of detecting a treatment difference at a two-sided 0.05 significance level.

8.3.4 *Statistical Analysis*

As the presence of irremovable artefact/ectopic beats would generate misleading results of HRV analyses, these patients were also excluded from final statistical analyses. Graphpad Prism software version 8.1.1 (La Jolla California USA, www.graphpad.com) was used to conduct statistical analyses. The Kolmogorov-Smirnov test was used to confirm Gaussian distribution of the data and paired sample t-tests were used to compare OFF and ON stimulation conditions. A two-tailed Pearson's correlation coefficient was used to identify the relationship between change in subjective pain score and change in HRV frequency domain measures to identify whether changes in HRV were pain-dependent. p-values less than .05 were considered significant.

8.4 Results

8.4.1 *Participants – Descriptive data*

Four patients declined to participate, and five patients were subsequently excluded due to the presence of ectopic beats/abnormal ECG artefact that precluded further signal interpretation [See Figure 31]. Eighteen patients (ten males and eight females) were ultimately included in the analysis with mean age of 47 (SD=15.8) at a mean follow-up of 29 months (SD= 20) post-operatively.

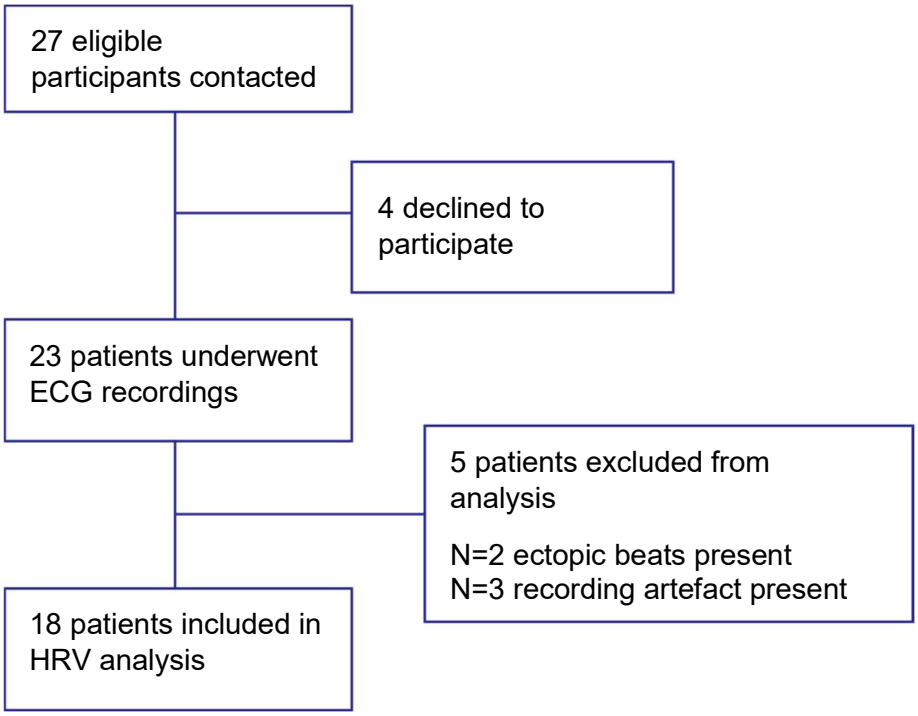

Figure 31. *Flowchart illustrating the inclusion/exclusion during recruitment of DRGS study participants.*

8.4.2 *Outcome data*

Two patients were known to have posture-dependent/mobility-associated pain, and as such did not report any pain during the recording period (OFF or ON stimulation). Two patients reported worsening pain scores during DRGS, while the other participants (n=14) demonstrated a significant mean reduction in pain of 38.1% (SEM= 7.9%) ($t= 4.85$, $p= .0003$) in response to acute DRGS. Eight of the eighteen participants maintained a greater than 50% reduction in their average pain score compared to their pre-operative baseline (mean reduction 46% [SEM = 8.4], n=18) ($t = 5.53$, $p < .0001$).

8.4.3 *Main Results*

There was a reduction in mean heart rate (mean reduction 0.76 bpm, SD= 3.48) and small increase in SDNN (mean increase 0.005, SD= 0.02) in response to DRGS, but neither were found to be statistically significant ($t=0.93$, $p = .37$; $t=0.92$, $p = .37$ respectively). However, a statistically significant reduction in

mean arterial pressure (-8.9 mmHg, SD = 12.1) (t=3.13, p = .0061) was observed between DRGS-OFF and DRGS-ON conditions [See Figure 32].

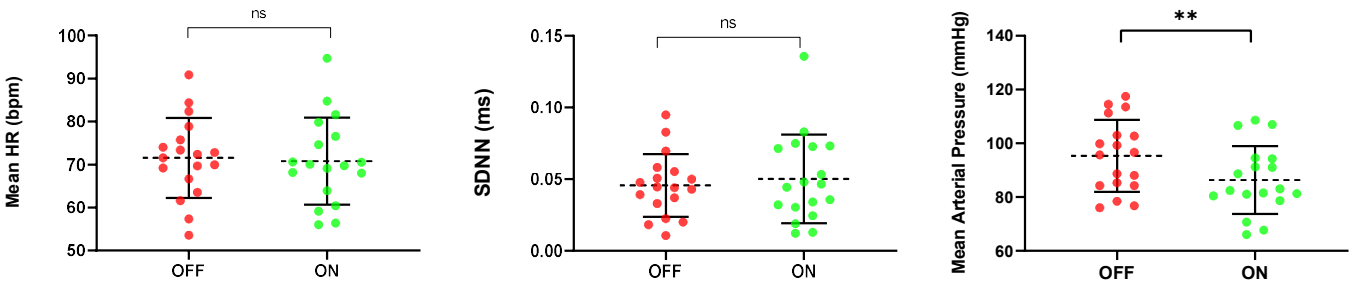

Figure 32. *Scattered dot plots showing changes in mean heart rate, SDNN and mean arterial pressure while DRGS was OFF and when DRGS was ON*

In the frequency-domain, a significant reduction in the normalized LF power (t = 2.58, p = .0195) and a significant increase in normalized HF power (t = 2.58, p = .0195) in response to acute DRGS was observed [See Figures 33 A & B]. These changes were also reflected in a statistically significant reduction in the LF/HF ratio (mean reduction -0.7438 [SD 1.03] t=3.228, p = .0049) [See Figure 33C], demonstrating a significant effect of DRGS on modulating sympatho-vagal balance. However, the changes described in LF power (two-tailed Pearson's correlation, r = 0.0028, p = .91), HF power (two-tailed Pearson's correlation, r= -0.11, p = .67) and LF/HF ratio (two-tailed Pearson's correlation, r = -0.017, p = .95) [See Figures 33 D-F] were not correlated with changes in the reported pain scores during DRGS, suggestive that these effects on autonomic modulation were independent of pain relief.

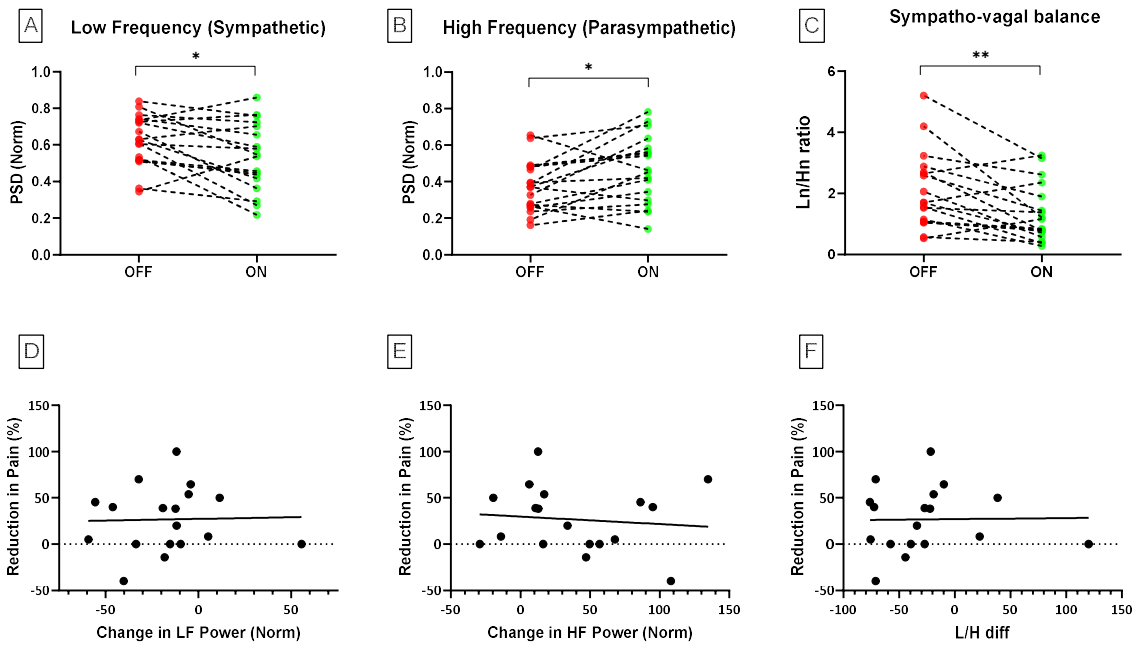

Figure 33. *Normalized power spectral densities (PSD) showing statistically significant* ***(A)*** *reduction in normalized low frequency (LF) power,* ***(B)*** *increase in normalized high frequency (HF) power and* ***(C)*** *reduction in low frequency/high frequency (LF/HF) ratio in response to acute DRG stimulation. (****D-F)*** *Scatter plots showing no correlation between change in pain scores and change in LF, HF or LF/HF ratio.*

8.5 Discussion

Our findings present novel evidence that DRGS modulates sympatho-vagal balance, with a resulting reduction in blood pressure, independent of its effect on pain relief. Dysregulation of the ANS is well-known to underlie the pathology seen in a number of painful (complex regional pain syndrome, painful diabetic neuropathy) and non-painful (orthostatic hypertension, multiple system atrophy) disorders(Mathias 2003). Pain is a well-known evolutionary stimulus for increased adrenergic activity, and alleviation of acute noxious stimuli will therefore be accompanied by a diminution of sympathetic

outflow. The James-Lange theory of emotion purports that “feelings”, like pain, arise as a direct result of a physiologic/autonomic response, like HRV, to affective stimuli.(Friedman 2010) Although the theory is heavily debated, our findings provide new insights into the potential for dissociation of these two phenomena (pain and autonomic activity) that have long been intimately intertwined.

DBS and SCS (Goudman et al. 2019)have both shown their potential to modulate HRV. However, both these effects were seemingly based on their capacity to relieve pain. (Goudman et al. 2019; Pereira et al. 2010) DRGS is known to inhibit neuronal hyperexcitability as a mechanism of pain relief, and based on the evidence provided, this inhibitory effect may also extend to sympathetic nervous system activity. DRGS is likely exploiting the normal anatomical connectivity between the DRG and sympathetic ganglia in order to produce the sympatholytic effects we have observed. This inhibitory autonomic mechanism may occur (i) at postganglionic synaptic collaterals within the DRG, (ii) by modulating the afferent limb of the autonomic reflex arc (Strong, Zhang, and Schaible 2018) or (iii) via antidromic transmission along visceral afferent collaterals in sympathetic ganglia(Matthews and Cuello 1982) [See Figure 34].

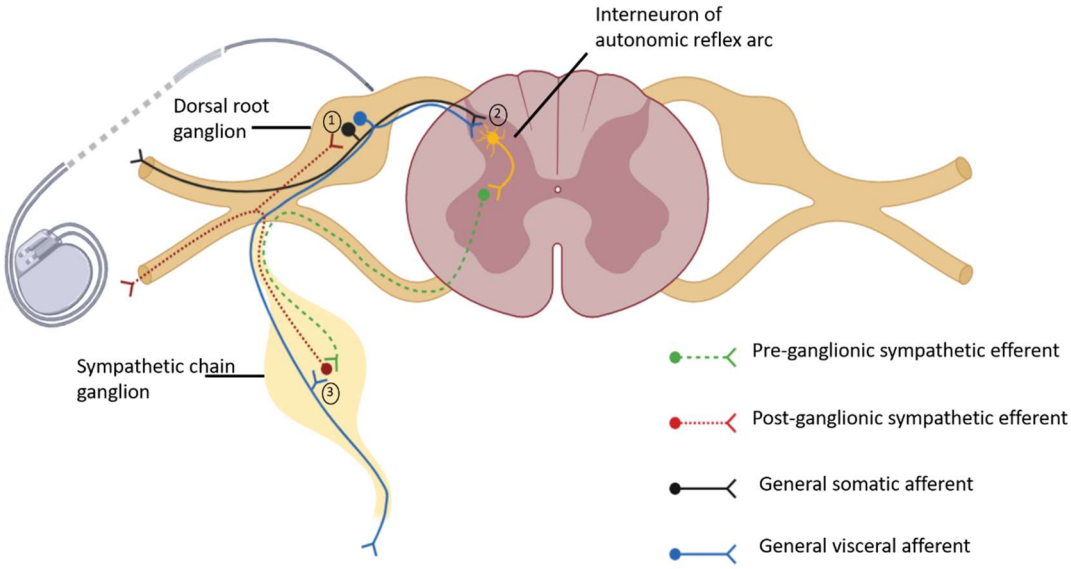

Figure 34. *Schematic illustration of normal anatomic connectivity between the dorsal root ganglion and sympathetic ganglia, and potential mechanistic sites of autonomic neuromodulation*

Furthermore, sympathetic sprouting in the DRG after peripheral nerve injury has been reported as a well-recognized pathophysiologic mechanism in sympathetically-mediated and maintained pain syndromes such as CRPS (Chung et al. 1996). It seems intuitive, therefore, that neuromodulation of this site would demonstrate superior efficacy in dysautonomic pain syndromes compared to SCS, as has become evident from the ACCURATE trial (Deer et al. 2017). This combined effect on somatic and autonomic neuromodulation is a putative mechanism in the management of trigeminal autonomic cephalgias such as cluster headaches with occipital nerve stimulation (Magis et al. 2007) and posterior hypothalamus DBS (Franzini et al. 2003). An autonomic mechanism of pain relief during DRGS could offer additional benefits in similar painful autonomic neuropathies, for example painful diabetic neuropathy (Eldabe et al. 2018; Gandhi et al. 2010) and irritable bowel syndrome (Di Giovangiulio et al. 2015; Salvioli et al. 2015).

In addition to its effects on the cardiovascular system presented here, sacral DRGS has been shown experimentally in animals to activate reflex bladder responses (Bruns, Weber, and Gaunt 2015), alleviate signs of joint inflammation (Pan et al. 2018) and increase bladder capacity in models of overactive bladder syndrome (Z. Wang et al. 2018). The somato-autonomic integration at the DRG presents a unique advantage for targeted stimulation of the ANS to address disorders based on discrete segmental innervation. This evidence supports the use of DRGS as a novel site in the therapeutic armamentarium for autonomic neurosurgery.

8.5.1 *Autonomic Neuromodulation*

The concept of autonomic neurosurgery likely began a century ago when Kotzareff performed the first thoracic sympathectomy for hyperhidrosis(Kotzareff A 1920). Despite the numerous advancements of the procedure (C. K. Chen et al. 2013; Doolabh et al. 2004; L.-H. Zhu et al. 2015), and modest therapeutic efficacy in other disorders of sympathetic aetiology, its applications remain limited to its original indication. Hence, the exploration and evaluation of various new targets to augment dysautonomic symptoms has flourished.

Neuromodulation of the ANS still remains largely in the domain of experimental research. With the exception of SCS for refractory angina and peripheral vascular disease (Erdek and Staats 2003), consensus is yet to be established regarding most implantable systems to modulate autonomic outflow. SCS has also been evaluated with modest benefit in other cardiovascular disorders including heart failure(Tse et al. 2015), ventricular arrhythmias (Grimaldi et al. 2012; Lai, Yu, and Jiang 2019) and atrial fibrillation(Ardell et al. 2014). However, its potential as a therapeutic target for the ANS has also included the genito-urinary systems (urge incontinence (Yakovlev and Resch 2010), neurogenic bladder (Schieferdecker et al. 2019)), gastro-intestinal (irritable bowel syndrome(Lind et al. 2015)) and endocrine systems (insulin sensitivity (Kapural et al. 2004)). Pre-clinical literature has demonstrated

that the sympatholytic mechanism of SCS may be diminished, but not abolished, by total sympathectomy(B Linderoth, Gunasekera, and Meyerson 1991), which suggests that the autonomic mechanism of SCS may also occur partly via the aforementioned somato-autonomic connectivity(Bengt Linderoth, Herregodts, and Meyerson 1994).

DBS has also been reported to produce changes in autonomic function(Basiago and Binder 2016; Hyam, Kringelbach, et al. 2012; Sverrisdóttir et al. 2014) targeting a number of sites including the subthalamic nucleus (S.-Y. Chen et al. 2011), thalamus (Thornton et al. 2002), PAG/PVG,(Alexander L. Green et al. 2005, 2006) and pedunculopontine nucleus (Hyam et al. 2019). However site-specific effects of DBS are still investigational (Hyam, Brittain, et al. 2012) and suffer from insufficient knowledge of appropriate control targets to adequately evaluate the added benefits. Vagus nerve stimulation, though more commonly used as a treatment for refractory epilepsy and depression(Milby, Halpern, and Baltuch 2008) has also demonstrated the ability to improve NYHA class and quality of life in heart failure (Schwartz et al. 2008), however does seem not alter long term mortality based on randomized controlled trials (Gold et al. 2016).

The vast array of other targeted neuromodulatory procedures are under investigation to treat severe and debilitating dysautonomic syndromes. Randomized controlled trials have demonstrated that refractory hypertension (blood pressure >140/90 despite 3 or more anti-hypertensive medications) can been effectively treated with implanted baroreflex stimulators(Scheffers et al. 2010) and endovascular renal sympathetic nerve ablation (RSNA)(Symplicity HTN-2 Investigators et al. 2010). While the Rheos® (CVRx, Inc., Minneapolis, MN) implanted carotid stimulator has failed to pass Phase III clinical trials for resistant hypertension (Bisognano et al. 2011), it has recently obtained FDA approval for use in heart failure(Zile et al. 2018) and is currently under investigation (clinicaltrials.gov: NCT02627196). Nevertheless, both RSNA and implanted barostimulators currently remain in the domain of

investigational procedures pending additional long-term data.

The evidence in support for the multi-systemic utility of autonomic neuromodulation spans interventions for gastroparesis (gastric electrical stimulator(Mason et al. 2005)), lower urinary tract symptoms (pudendal and sacral nerve stimulators(Peters, Feber, and Bennett 2005)), faecal incontinence and sexual dysfunction (sacral nerve stimulation(Matzel et al. 1995; Pauls et al. 2007)), which is testament to the burgeoning enthusiasm for this new and rapidly-expanding field of neurosurgery.

The technique of HRV analysis and its interpretation, though widespread, is not without controversy(von Rosenberg et al. 2017). For these reasons, we cautiously analysed and interpreted our results, and believe that these results represent important proof-of-concept data which warrants additional interrogation in a larger cohort before conclusive generalizations can be made.

Autonomic neuromodulation has simultaneously offered additional therapeutic avenues, and profound scientific insights, into many diseases across various body systems. The ease of use of a well-validated marker of autonomic activity - heart rate variability – facilitated our demonstration of novel human evidence that DRG stimulation has the potential to modulate the activity of the autonomic nervous system. This effect of DRGS was not dependent on its efficacy in relieving pain and suggests that the DRG may represent a new site for autonomic neuromodulation.

9 OPTIMIZING STIMULATION FREQUENCY IN DEEP BRAIN STIMULATION

9.1 Summary

DBS of the PAG/PVG and sensory thalamus are effective treatments for neuropathic pain in carefully selected patients. The efficacy of DBS for pain also depends on stimulation frequency which is patient-specific. This study sought to evaluate the relationship between stimulation frequency and pain relief and whether a patient's baseline LFP characteristics could predict optimal stimulation frequency.

Seventy-six patients with implanted DBS electrodes in the PAG/PVG and/or sensory thalamus for neuropathic pain were included in this study. Correlation between stimulation frequency and pain relief quantified by VAS (n=40) and MPQ scores (n=39) was evaluated. Power spectral densities (PSD) were calculated from PAG/PVG LFP recordings (n=11) and correlated with stimulation frequency.

No correlation was observed between stimulation frequency and reported pain relief. However, normalized baseline LFP power in the PAG/PVG in the 3 – 6 Hz ($r=-0.65$, $p=0.030$), 30 – 60 Hz ($r=0.66$, $p=0.026$) and 60 – 90 Hz ($r=0.79$, $p=0.004$) frequency bands were significantly correlated with optimal stimulation frequency.

Both low and high frequency stimulation can produce therapeutic pain relief in clinical practice. Moreover, normalized LFPs correlate with the optimal stimulation frequency in DBS for chronic pain. These findings suggest that high and low stimulation frequencies may target separate mechanisms and support the utility of neurophysiology in optimizing DBS therapy.

9.2 Introduction

Neuropathic pain is a subtype of chronic pain caused by a lesion or disease of the somatosensory system.(T. S. Jensen et al. 2011) Neuropathic pain syndromes are often difficult to treat and place a significant burden on afflicted patients and society at large.(Breivik, Eisenberg, and O'Brien 2013; Kerstman et al. 2013) The PAG/PVG and sensory thalamus are important structures in pain perception and the pathophysiology of neuropathic pain.(Apkarian, Baliki, and Geha 2009; Romanelli and Esposito 2004) For medically refractory neuropathic pain, DBS targeting these areas has been effective (Boccard, Pereira, and Aziz 2015) in reducing pain intensity as well as improving quality of life and emotional wellbeing,(Gray et al. 2014) although outcomes vary substantially between patients.(Frizon et al. 2020; Levy, Deer, and Henderson 2010) The mechanisms for DBS-induced pain relief are not fully understood (Pereira and Aziz 2014) but may include direct suppression of pathological thalamic activity during stimulation (N. J. Ray et al. 2009) or indirectly during stimulation of the PAG/PVG.(Wu et al. 2014) Other theories include the amplification of pathologically diminished neural oscillations and the augmented release of endogenous opioids during PAG/PVG stimulation.(Pereira, Wang, et al. 2013)

While the efficacy of DBS for various movement disorders has been convincingly demonstrated to depend on stimulation frequency (Birdno and Grill 2008; Ostrem et al. 2014) the same cannot be said for the therapeutic benefits of DBS for the treatment of pain. After DBS implantation, different stimulation frequencies are trialled to identify the most effective parameters for a given patient. In a large cohort study by Boccard et al., lower frequencies (< 50 Hz) tended to be analgesic, whereas higher frequencies were seemingly hyperalgesic,(Boccard et al. 2013) as had previously been reported by Nandi et al. (2003) However, higher (up to 100 Hz) stimulation frequencies have also been successfully used to relieve pain.(Kumar et al. 1997)The identification of an ideal stimulation frequency has not

been studied thoroughly, hence the necessity for iterative optimization trials across a broad range of frequencies without other guidance.

DBS electrodes also allow the recording of LFPs from targeted nuclei. (Zhang et al. 2018) LFPs represent the activity of neuronal ensembles(Buzsáki and Draguhn 2004)) which are responsible for the emergence of various brain functions.(Einevoll et al. 2013) Pain intensity, perception and chronicity are correlated with an increased amplitude in various frequency bands in the PAG and sensory thalamus (Ploner, Sorg, and Gross 2017) and pain relief induced by DBS of the sensory thalamus can be predicted based on LFP recordings(Huang et al. 2018; Huang, Luo, et al. 2016) Importantly, DBS can modulate LFPs in a frequency-dependent manner. (Blumenfeld and Brontë-Stewart 2015; Wu et al. 2014) This informed our hypothesis that baseline LFPs from target nuclei may correlate with the therapeutic stimulation frequency for an individual patient. In addition, recently there has been increasing interest in both the utility of LFPs in the optimisation of stimulation parameters and as a feedback signal for adaptive or closed-loop DBS. (Little et al. 2013; Shirvalkar et al. 2018a; Tsang et al. 2012)

Our objectives were to evaluate the relationship between stimulation frequency and pain relief, as well as to examine the predictive potential of baseline LFP characteristics in determining a patient's ideal stimulation frequency in order to optimize and personalize DBS for chronic pain.

9.3 Materials & Methods

9.3.1 *Subjects*

Sevnenty-six patients who had undergone DBS implantation at the John Radcliffe Hospital, Oxford, targeting the PAG/PVG and/or sensory thalamus (27 in PAG/PVG, 16 in sensory thalamus, 33 in both) for medically refractory chronic neuropathic pain were included in this cohort study. Patients that failed trial stimulation were not included in this study and findings were analysed based on a per-protocol

analysis. Written informed consent was obtained from all patients at the time of recruitment. Ethical approval was obtained from the South-Central Oxford Health Research Authority and all experiments were conducted in accordance with the Declaration of Helsinki.

9.3.2 *Pain assessment*

Patients were asked to rate their pain score on a Visual Analogue Scale (VAS) from 0 to 10, with 0 being no pain and 10 the worst imaginable pain, twice daily (am and pm) over a period of 7 days both pre-operatively and regularly during follow-up. Pain relief was calculated as the percentage reduction in their reported mean VAS score during follow-up compared to their pre-operative baseline score. Total MPQ scores and sub-scores for the various domains (sensory, affective, evaluative and miscellaneous) were also recorded, and the corresponding pain relief (pre- vs. post-operative MPQ) was analysed.

9.3.3 *LFP recording and pre-processing*

LFPs were recorded between day 3 and day 5 post-implantation, by a process which has been described previously.(Huang et al. 2018; Huang, Luo, et al. 2016) Patients were resting, seated, off medications with DBS OFF. Bipolar LFPs were recorded from adjacent pairs of electrodes (contacts 0-1, 1-2, and 2-3) within PAG/PVG in 11 patients. One patient had monopolar recordings for which a bipolar signal was calculated offline. LFPs were amplified (x10,000), filtered between 0.5 Hz and 500 Hz and then digitized at a sampling rate of 2000 Hz during the recordings. The data were displayed on-line and saved on a hard disk using Spike2 (Cambridge Electronic Design, Cambridge, UK). Channels for analysis were chosen based on electrode contacts used for stimulation. Visible artefacts in LFP recordings were excluded. While visually excluding artefacts, 50-s segments were extracted for every patient using Spike2. Using Matlab (MathWorks, Massachusetts, USA), the segments were high-pass filtered at 1 Hz, low-pass filtered at 90 Hz, notch filtered between 47 and 53 Hz, and resampled at 500Hz.

9.3.4 *Correlation and Statistical analysis*

For all patients with pain scores and stimulation frequencies available, the average decrease in pain score was calculated. D'Agostino's K-squared test was applied to assess the distribution of the data. The Spearman's rank correlation coefficient was then calculated for the mean pain relief during follow-up and the reported stimulation frequency. The Mann-Whitney U test was used to compare the difference in the stimulation frequencies between patients with and without substantial pain relief (defined as > 50% decrease in VAS score). This was repeated for the subgroup of patients having only PAG/PVG stimulation and using only sensory thalamus stimulation. For patients with detailed follow-up information available (n=17), the correlation was calculated between percentage of decrease in VAS score at three-month follow-up and the stimulation frequency set at the previous clinic appointment.

9.3.5 *LFP analysis*

The PSD for LFPs was calculated using the Welch-method with a 2-s window and 1.5-s overlap. The power spectra were then normalized to reduce inter-subject variability by dividing each frequency point by the total power in the range of 1-90 Hz. LFP power for every patient with available LFP recordings (PAG/PVG targets) experiencing moderate or better pain relief (defined as > 20% decrease in VAS score)(Farrar et al. 2000) was calculated for the following frequency bands: 3 – 6 Hz, 6 – 9 Hz, 9 – 12 Hz, 12 – 20 Hz, 20 – 30 Hz, 30 – 60 Hz and 60 – 90 Hz. Correlation analysis between normalized power in each frequency band and optimal stimulation frequency (stimulation frequency corresponding with greatest pain relief during follow-up) and pain relief was conducted in GraphPad Prism software version 8.1 (La Jolla California, CA, USA, www.graphpad.com).

9.4 Results

The mean age of the cohort (n=76) was 51 ± 13 (SD) years. Mean follow-up time was 15.3 ± 14.6 (SD) months (range: 3 – 48 months) during which stimulation frequencies and corresponding VAS scores were recorded for 40 patients, and MPQ scores for 39 patients. Of this group, 17 patients had detailed long-term follow-up data and 11 patients with implanted PAG/PVG electrodes (of whom 7 had also sensory thalamus stimulation) had undergone LFP recordings prior to internalization [See Table 6]. For patients with both sensory thalamus and PAG/PVG electrodes, both targets were stimulated at the same frequency.

***Table 6**. Patient demographics and clinical characteristics*

	VAS scores and stimulation parameters available	**MPQ scores and stimulation parameters available**	**Detailed Information available**	**LFP recordings available**
N	40	39	17	11
Age, mean (SD) years	51.0 (12.6)	52.8 (12.6)	48.2 (11.9)	48.1 (11.3)
Female, N (%)	12 (30.0)	11 (28.2)	2 (11.7)	1 (9.1)
Target, N (%)				
- **Both**	19 (47.5)	17 (43.6)	9 (52.9)	6 (54.5)
- **Only PAG/PVG**	18 (45.0)	14 (35.9)	8 (47.1)	5 (45.4)
- **Only sensory thalamus**	3 (7.5)	10 (25.6)	0	0
Diagnosis, N (%)				
- **Anaesthesia dolorosa**	4 (10.0)	6 (15.4)	2 (11.7)	1 (9.1)
- **Amputation**	7 (17.5)	7 (17.9)	5 (29.4)	5 (45.4)
- **Brachial plexus**	3 (7.5)	5 (12.8)	2 (11.7)	1 (9.1)
- **Cerbrovascular accident**	15 (37.5)	14 (35.9)	5 (29.4)	3 (27.3)

- **Back and spinal cord** - **Surgical, trauma and visceral**	4 (10.0) 7 (17.5)	4 (10.3) 5 (12.8)	0 3 (17.6)	0 1 (9.1)

9.4.1 *Stimulation frequency and pain relief*

Average stimulation frequency across all patients was found to be 25 Hz (range 5-80 Hz) with a mean pain relief of 32.66 ± 24.18%. There was no statistically significant correlation observed between stimulation frequency and average decrease in VAS score (r=0.19, p=0.49 [n=40]). Fourteen patients had stimulation frequency data and corresponding VAS scores available at three-month follow-up, which also demonstrated no significant correlations (r=0.09, p=0.75 [n=14]) [See Figure 35A – B]. There was also no significant difference in stimulation frequency for patients exhibiting substantial pain relief (n=12 ; at three-month follow-up, n=5) compared to those experiencing moderate-to-poor pain relief (n=29; at three-month follow-up, n=9) based on mean reported VAS score, or at three-month follow-up [See Figure 35C – D]. For patients exhibiting > 50% reduction in pain, median stimulation frequency was 27.5 Hz (IQR 20 – 40 Hz) compared to 20 Hz (12.5 – 35 Hz) in those experiencing < 50% pain relief (p=0.29). At three-month follow-up, patients with substantial pain relief (n=5) had a median stimulation frequency of 30 Hz (IQR 20 – 60 Hz) while those with moderate-to-poor pain relief (n=9) had a median stimulation frequency of 20 Hz (IQR 20 – 50 Hz, p=0.68).

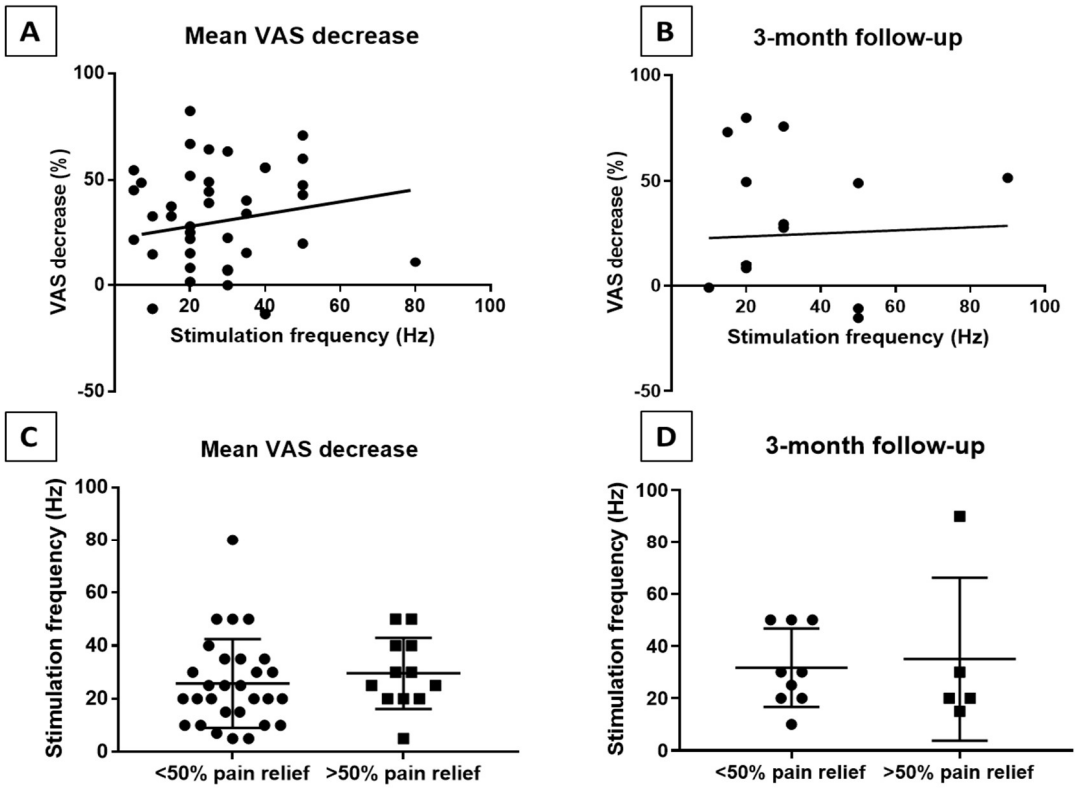

Figure 35. *Scatterplot of stimulation frequency and percentage reduction in VAS score for (A) all patients (n=40), and (B) those with reported three-month follow-up pain scores (n=14). (C) Difference in stimulation frequency for all patients experiencing substantial (> 50%) vs. moderate-to-poor (< 50%) pain relief and (D) at three-month follow-up.*

There was no significant correlation between pain relief and stimulation frequency when patients were analysed by target [See Table 7]. For PAG/PVG stimulation only, mean reduction in VAS was found to be 37.78±27.33% (n=18; r=0.07, p=0.78) while for lone sensory thalamus stimulation the average pain relief was found to be 41.45±25.56% (n=3; r=0.87, p=0.67) [See Table 7].

Table 7. *Correlation between percentage reduction in mean VAS/MPQ scores and stimulation frequency based on anatomical DBS target*

Target	**Only PAG/PVG stimulation**			**Only sensory thalamus stimulation**		
Score	**N**	**Mean decrease (%)**	**Spearman r (p-value)**	**N**	**Mean decrease (%)**	**Spearman r (p-value)**
Mean VAS	18	37.78	0.07 (0.78)	3	41.45	0.87 (0.67)
Total MPQ	13	29.34	-0.13 (0.68)	10	44.00	0.13 (0.70)
MPQ – sensory	13	24.57	-0.40 (0.19)	10	29.03	0.12 (0.75)
MPQ – affective	12	21.21	0.24 (0.45)	9	35.42	0.31 (0.40)
MPQ – evaluative	11	45.00	0.21 (0.53)	9	30.00	-0.45 (0.23)
MPQ – miscellaneous	13	37.50	-0.12 (0.71)	10	80.00	-0.06 (0.87)

9.4.2 *LFP analysis*

Mean (±SD) pain relief for the 11 patients included in LFP analysis was 48.6% (±21.3). There was a higher overall power in the theta frequency (3 – 6 Hz) band observed in those patients that benefitted from low frequency stimulation (n=7). In contrast, there was a higher overall power in the gamma

frequency range (30 – 60, 60 – 90 Hz) observed in those patients that benefitted from high frequency stimulation (n=4) [See Figure 36].

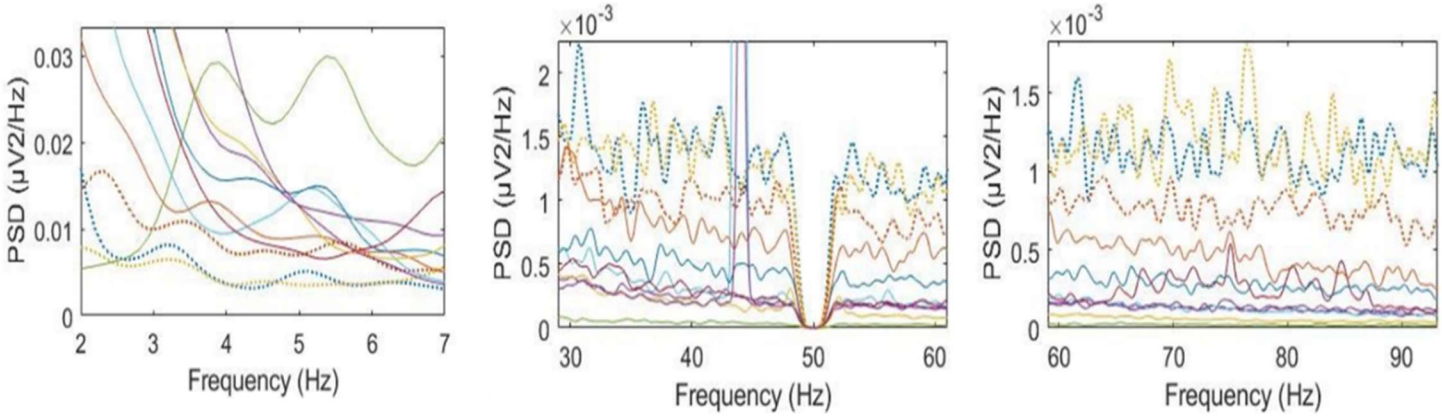

Figure 36. *Power Spectral Density (PSD) plot of PAG/PVG recordings with dotted lines representing patients with an optimal stimulation frequency ≥50 Hz, and solid lines representing patients with an optimal stimulation frequency < 50 Hz in the 3-6 Hz, 30-60 Hz and 60-90 Hz frequency bands.*

There was a significant negative correlation observed in the 3 – 6 Hz frequency band (r=-0.65, p=0.030), while a significant positive correlation was seen in the 30 – 60 Hz (r=0.66, p=0.026) and 60 – 90 Hz (r=0.79, p=0.004) frequency bands [See Figure 37]. Correlation in the 20 – 30Hz frequency band trended towards significance (r=0.59, p=0.056). A power peak was identifiable for two patients at 43 – 45 Hz (likely artefact), however, due to the relatively low stimulation frequencies this peak did not contribute to the correlation's strength or significance. There was no significant correlation found in the 6 – 9, 9 – 12 or 12 – 20 Hz frequency bands. Neither a significant correlation was found between pain relief and power in any of the frequency bands.

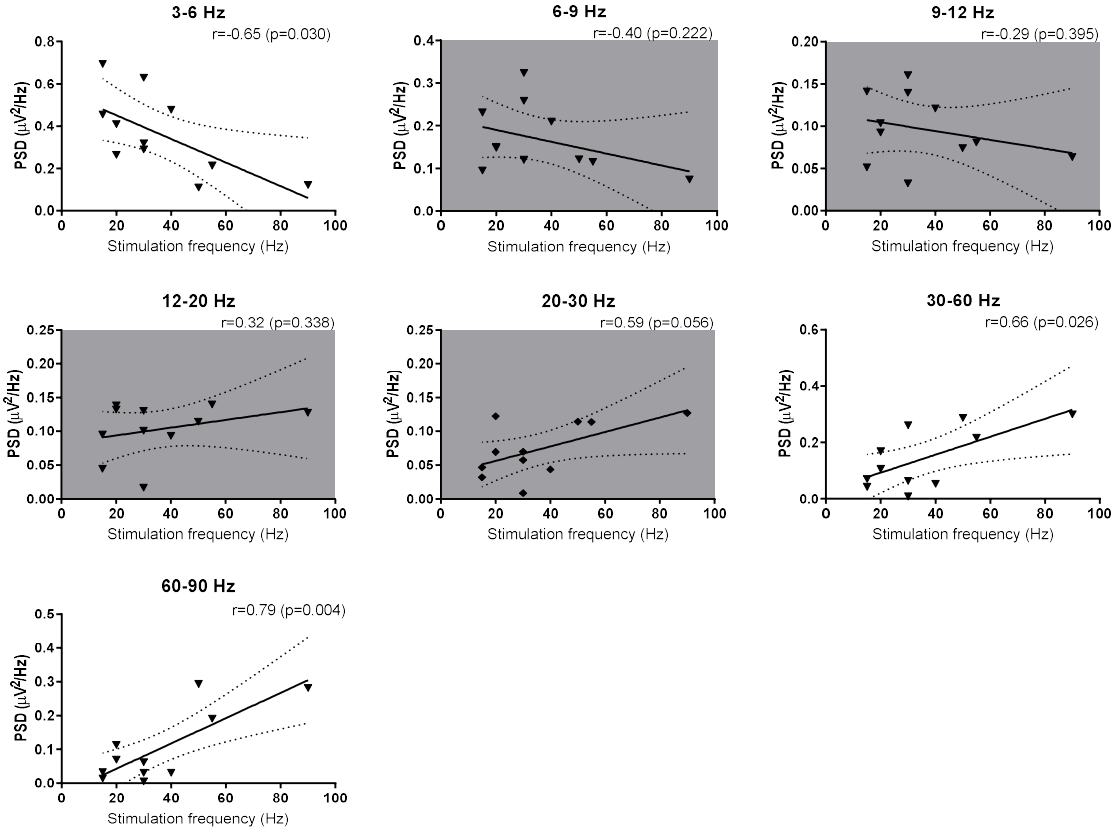

Figure 37. *Scatterplots of total normalized power in each frequency band for PAG/PVG recordings correlated with optimal stimulation frequency (dotted line represents the 95%-CI)*

9.5 Discussion

In this study, we investigated and systematically analysed the effect of DBS frequency on pain relief. We observed that, although the majority of patients used lower stimulation frequencies (< 50 Hz), higher frequencies were just as effective in relieving pain in some patients. Importantly, we observed that the baseline patient-specific LFP features (high baseline theta and gamma power) correlated with the clinically-identified effective stimulation frequency, thus providing a plausible explanation of the observed variability in effective stimulation frequencies. This underscores the potential value of neurophysiology in optimizing stimulation parameters and personalizing DBS for chronic pain. With a

larger patient cohort, the potential exists to establish a model for calculation of the patient-specific effective stimulation frequency based on LFP oscillatory activity, as observed in this study.

For example: Fstim=a*Power3-6Hz+b*Power30-60Hz+c*Power60-90Hz+d

Based on our findings, employing neurophysiology to inform clinical decision-making is likely the next step in optimizing DBS parameters for chronic pain. In the context of movement disorders, the potential for using LFPs to modify DBS therapy has been investigated more extensively.(Little 2013, Tsang 2012) In DBS studies, theta (4 – 8 Hz) and gamma (30 – 75 Hz) oscillations have been shown to be associated with pain and pain relief (A. L. Green et al. 2009; Huang et al. 2018) and our results suggest that LFP power in these frequency bands might also be related to the most clinically effective stimulation frequency.

Pathological thalamic theta (4 – 9 Hz) activity has been proposed as one of the putative mechanisms responsible for the production and propagation of neuropathic pain in humans (Llinás et al. 1999; Sarnthein et al. 2006) and has substantive support from animal studies.(Gerke et al. 2003; Hains, Saab, and Waxman 2006) Its suppression, either directly via thalamic DBS or indirectly via PAG/PVG stimulation, may be contributory to the perception of pain relief.(N. J. Ray et al. 2009; Wu et al. 2014) As the field of functional neurosurgery has grown, hypotheses regarding the mechanisms which underlie the disparate effects of HFS and LFS DBS have generated significant interest in the literature.(Chiken and Nambu 2016; McIntyre et al. 2004) A prominent theory, based primarily on research in movement disorders, has posited that low frequency stimulation augments neuronal activity, while high frequency stimulation is largely inhibitory, similar to the ablative effect of lesional procedures.(Benazzouz and Hallett 2000; Montgomery and Baker 2000) Although elements of these observations are true, it seems there is a more nuanced mechanisms at play, specifically regarding the interruptive effect of a given stimulation frequency relative to the native synchrony of neuronal

oscillations, whether they be pathologic or physiologic.(Birdno and Grill 2008) In our patients, we have demonstrated that optimal stimulation frequencies were low when theta power spectral activity was elevated and may suggest that suppressive action on pathological theta activity by low frequency stimulation as a mechanism of generating pain relief.

High power spectral activity in the gamma (30 – 60 Hz) frequency band of the dorsal PAG/PVG is also related to pain and has been shown to increase with the administration of naloxone suggestive that stimulation of this target may act via opioidergic mechanisms.(Pereira, Wang, et al. 2013) We similarly observed that high power in the gamma frequency bands was associated with clinical efficacy at high stimulation frequencies. These findings may indicate that high stimulation frequencies might achieve pain relief via a separate mechanism than low frequency stimulation dependent on activity in the high (gamma) frequency range.

A limitation of this study is that despite a large initial patient cohort, there was a large attrition in data due to clinical practicalities. As such, limited information was available about the adjustments made to stimulation frequency and how these parameters changed over time. Therefore, VAS scores for each patient were averaged to derive an estimate of the overall effectiveness of the DBS and used this variable for correlation analysis with recorded stimulation frequencies. This approach was supported by the results of the smaller subset of patients for whom more specific data was available. Based on these results taken together, there does not seem to be sufficient basis for a prescriptive frequency in all chronic pain patients treated with DBS of the PAG/PVG or sensory thalamus.

The LFP analysis was also limited by the small sample size and availability of patients. Nevertheless, this study remains one of the largest neurophysiologic studies of PAG/PVG LFPs in humans. The heterogeneity in patient diagnosis (cause and location of pain) and variability in precise anatomical location of each electrode make a larger sample size desirable and validation of these results with

additional patients should be sought. To account for this, analyses of the absolute power were conducted, which did not reveal a correlation in any frequency band, which was to be expected due to the variations in overall power across subjects. However, when normalizing the power with the integral power between 6 and 30 Hz, the correlation between 3 and 6 Hz remained significant ($r = -0.6264$, $p=0.043$) indicating that the significant correlation between stimulation frequency and LFP characteristics robustly occurred in the normalized 3 – 6 Hz power.

This study has demonstrated that while low frequency stimulation is more commonly employed, high stimulation frequencies can also be effective in the treatment of chronic pain. Additionally, baseline LFP characteristics correlate with the clinically observed “ideal” stimulation frequency for individual patients treated with PAG/PVG DBS.

It is therefore advisable that in clinical practice, where possible, baseline LFP characteristics can be a used to identify the optimal frequency of stimulation for a given patient and, eventually, may be useful in an adaptive or closed-loop DBS system. In lieu of this, both low and high stimulation frequencies should be utilized during programming trials in order to maximize benefit for patients treated with DBS for chronic neuropathic pain. Our findings support the personalization of DBS therapy based on deep brain neurophysiology, and also alludes to the possibility of different, frequency-dependent mechanisms contributing to the neuromodulation of chronic pain.

10 DISCUSSION

This thesis has achieved some of the aims set forth and has generated novel insights into the mechanisms of pain and pain relief. Our studies have shown that acute DRGS can effectively reduce the sensory dimensions of chronic pain (VAS & sensory-discriminative dimension MPQ), improve task performance (n-back) during high working memory conditions but it does not reliably modulate the affective dimension of pain (affective dimension MPQ & FERT). This thesis has also demonstrated autonomic effects of DRGS based on metrics of cardiac autonomic activity and changes in cortical activity which are likely indicative that it engages supraspinal mechanisms to achieve pain reduction in DRGS. Our results reaffirm the efficacy of DRGS and DBS in the treatment of chronic pain, with mean reductions in pain intensity of 37% and 33% respectively. However, our clinical trial further demonstrates that active anodal tDCS can increase the efficacy of DRGS-mediated pain relief to 57% after a single-session, though long-term effects of this relief are yet to be investigated.

The dissociation of the affective and sensory dimensions of pain have been explored with variable success in the literature. Hypnotic suggestion techniques which have demonstrated some efficacy in selectively modulating the affective dimension of pain,(Dahlgren et al. 1995; Rainville et al. 1999) have relied on the subjective reports of pain “unpleasantness”. In order to improve reliability, we preferred to employ a well-validated metric of the affective dimension, which could be easily administered in a restricted experimental timeframe. The McGill Pain Questionnaire (Melzack et al. 2001) is the most widely used, but others such as the Brief Pain Inventory (Atkinson et al. 2012) have also been used to disambiguate effects on the affective dimension of pain. However, these metrics are more suitable for long-term evaluations (days/weeks) which made the short form McGill Pain Questionnaire (SF-MPQ) most appropriate for the experimental designs employed in this thesis.

Unfortunately, the SF-MPQ results presented in this thesis were mixed. Our initial MEG cohort did not demonstrate a significant reduction in the affective dimension of pain (mean 23%, p=0.17), while our PAINS study cohort did reveal a significant DRGS-mediated reduction in the affective dimension (mean 61%, p=0.02). The sacrifice of sensitivity for efficiency in employing the SF-MPQ,(Melzack 1987) is likely contributory to these mixed results, which was a concern during the experimental design phase. This led to the use of a supplemental behavioural assessment tool to evaluate patient affect – the facial expression recognition task. While the results of the FERT study were intriguing and confirm existing literature regarding positive and negative emotional biases present in chronic pain, we were unable to conclusively demonstrate a modulation of these affective responses during DRGS. Future considerations to characterize the affective dimension of pain could involve the use of facial expressions of pain,(Yamada and Decety 2009) which have been used to characterize pain empathy, a surrogate indicator for the affective dimension of pain. Similar neural correlates of pain empathy have been investigated by using images of extremities in painful scenarios,(Corradi-Dell'acqua, Hofstetter, and Vuilleumier 2011) and may show some promise, however remain indirect measures of the emotional component of an individual's subjectively experienced pain.

Our interrogation of the cognitive dimension of chronic pain produced both expected and unexpected results. While the use of the n-back task was not nearly as controversial as the FERT, due to its reproducible attentional effects in chronic pain,(D. J. Moore, Keogh, and Eccleston 2012; Sprenger et al. 2012) our studies did not demonstrate an analgesic effect of cognitive load on the perception of chronic pain. This "attentional analgesia" has been likened to a placebo effect, and may involve the engagement of the default mode network (prefrontal cortex, posterior cingulate cortex, precuneus) and attenuated activity of the salience network (somatosensory cortex, midcingulate cortex, insula) which is responsible for detecting and responding to biologically relevant stimuli.(Kucyi, Salomons, and Davis 2013) It is

possible that, during our experiments, the time between task performance and the recording of pain scores may have introduced a recall bias for attention-related analgesia, or may reflect a genuine return of salience network activation after task completion. Improvements to this design may incorporate a prompt to record pain scores during performance of the working memory task in order to overcome this delay in evaluation of the attentional effect on pain relief. The possibility also exists that participants did not find the task sufficiently difficult or lacked the motivation to exert optimal mental effort in performing the task. Buhle and Wager, 2010 employed a 3-back task, with a monetary incentive, and have demonstrated significant effects on pain alleviation which may be another reasonable improvement on the experimental design employed in this thesis. Additionally, cortical gamma activity was indeed a useful neural signature to interrogate pain and cognition. However, our results suggest that their effects on cortical gamma activity are not interrelated. It is encouraging that our results support the existing literature which has demonstrated the utility of gamma oscillations as a physiologic marker of pain and cognition. However, it is possible that the interrogation of different features of gamma activity (ERPs/ERFs, coherence) may reveal a relationship between these two phenomena, even though we were unable to demonstrate it.

Our experiments also provide novel evidence for DRGS-mediated autonomic modulation, which is seemingly independent of its effect on pain relief. However, the lack of a relationship between these two outcomes raises new questions. It remains to be elucidated whether autonomic effects of DRGS can contribute to pain relief, and whether our observations are primarily an acute phenomenon or would have significant neuroplastic effects in the long term. Reduction of sympathetic outflow during DRGS has also been demonstrated by microneurography recordings of muscle sympathetic nerve activity, which is potentially dependent on the location of stimulation.(Sverrisdottir et al. 2020) Definitive statements about the contribution of stimulation level (cervical vs. thoracic vs. lumbar) or laterality (left-sided vs.

right-sided) of stimulation cannot be made due to the limited sample size, however would be of interest if this type of neuromodulation is to be applied for the treatment of primary dysautonomias. Nevertheless, the demonstration of such a mechanism provides important preliminary data to support the further investigation of DRGS in the treatment of other autonomic disorders.

Mouraux and Iannetti, 2018 discuss the methodology, limitations, utility, and possibly the futility of searching for an objective neurophysiologic biomarker of pain. The authors describe the challenges encountered while experimentally probing for an objective metric of the subjective pain experience including (i) the questionable external validity of healthy control participants to model clinical pain, (ii) the importance of carefully controlled experimental conditions, (iii) the significance of comparing verbally reported pain with a potential biomarker and (iv) the utility of a biomarker to stratify and personalize therapy in chronic pain. This thesis has demonstrated the usefulness of each of these recommendations, examining the supraspinal signature of dorsal root ganglion stimulation (DRGS) in a cohort of neuropathic pain patients. We believe the findings of this thesis satisfy the aforementioned concerns for exploration of pain biomarkers by investigating (i) a diverse cohort of neuropathic pain patients, including a unique pain-free control group (ii) using a randomized crossover design to limit between-subject variability. Our findings demonstrated (iii) a well-established neurophysiologic marker which correlated with the severity of verbally reported pain and pain relief, (iv) which ultimately served as the basis for patient stratification and personalized therapy.

The dorsal root ganglion, as a component of the peripheral nervous system, was once thought of as a passive actor in the genesis of neuropathic pain. However, this has changed, and investigations of the DRG have demonstrated alterations in neuronal hyperexcitability and transcriptomic changes in patients suffering from neuropathic pain.(R. Y. North et al. 2019) Our MEG findings in a heterogenous cohort of pain patients undergoing neuromodulation of this key structure are consistent with a central pain

mechanism known as thalamocortical dysrhythmia (TCD), in which a shift towards enhanced low frequency activity (theta) is observed in neurogenic pain syndromes, and a compensatory shift towards high frequency activity (beta) during pain relief.[See Figure 38] This mechanism is widely reported to be pain-sensitive.(Jeanmonod, 2001; Schulman *et al.*, 2005; Alshelh *et al.*, 2016; Groh *et al.*, 2018) It is not, however, pain-specific – its presence in other neurologic disorders, such as tinnitus,(De Ridder et al. 2011) migraine(Hodkinson et al. 2016) and neuropsychiatric disorders,(Schulman et al. 2011) weakens its applicability as a "biomarker of pain". However case-controlled studies included in a recent systematic review (Pinheiro, de Queirós, et al. 2016) that reported PSD estimates from EEG studies of pain have reported similar results to those presented in our series. Studies examining thalamic local field potentials (LFPs) have also demonstrated abnormal burst activity in the alpha frequency range in chronic pain

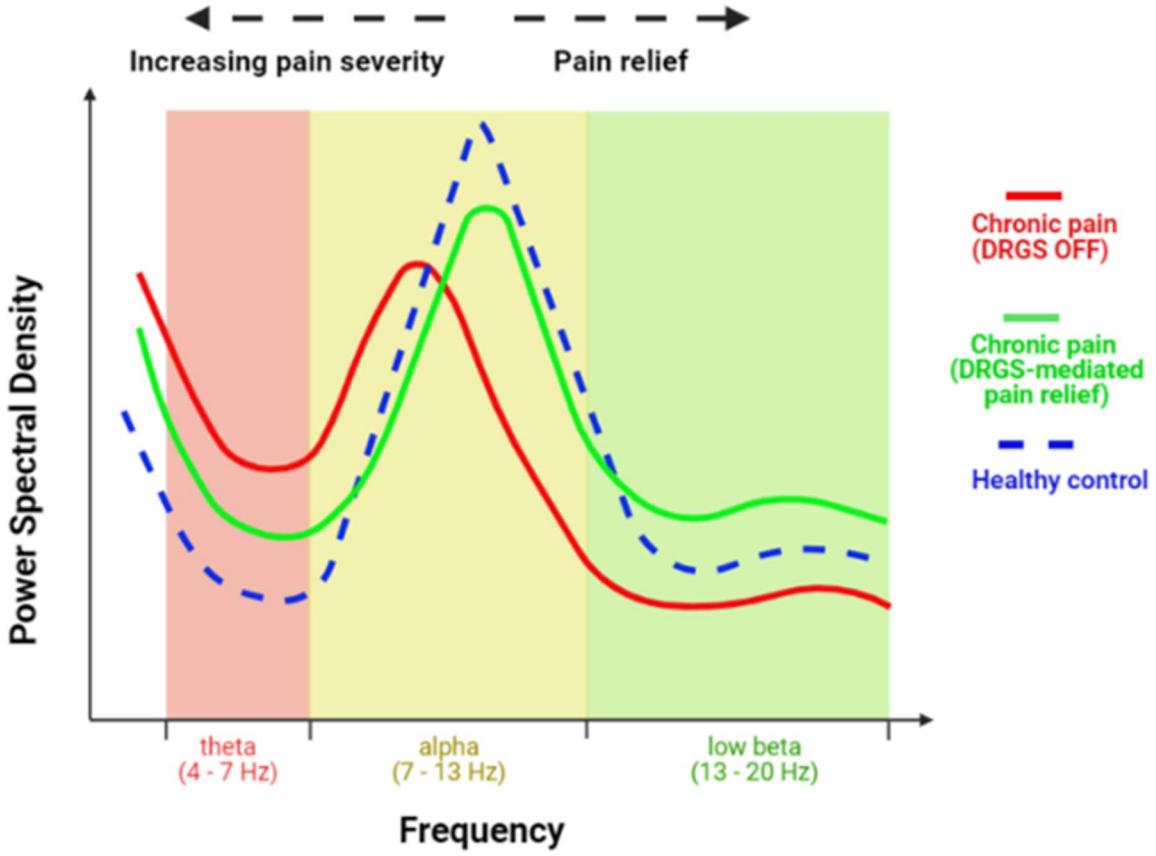

Figure 38 *Diagrammatic illustration of shifts in power spectral densities in ongoing chronic pain, DRGS-mediated pain relief contrasted with healthy controls based on the TCD hypothesis of neuropathic pain.*

patients.(A L Green et al. 2009) These studies explored the neurophysiologic signatures of pain in a variety of pain disorders and the reproducibility of such an effect lends support to its utility in demystifying the subjective experience of pain. However, it must also be recognized that the abundance of neurophysiologic techniques like MEG and EEG, as well as the variability in experimental paradigms across the chronic pain literature, has resulted in an unfortunate degree of heterogeneity in the interpretation of these potential "biomarkers of pain." For example, while the TCD model outlined above may have some supportive evidence, contradictory evidence also exists which suggests that beta activity may also be an indicator of ongoing pain.(González-Roldán et al. 2016; Lim et al. 2016) The abundance of findings, including both increases and decreases in power spectral density, across many frequencies of interest (Pinheiro, de Queirós, et al. 2016; Ploner, Sorg, and Gross 2017) speak to the need for a consensus in investigating and reporting on the "signatures" of chronic pain if objective metrics are to be identified for clinical application. Therefore, while these findings might add to a particular hypothesis of chronic pain neurophysiology, they also inadvertently contribute to an expanding body of work that is at times conflicting and largely inconclusive.

It is also possible, that investigating pain neurophysiology in a vacuum disregards the dynamic neuroanatomic connectivity that likely typifies the pain connectome. Pre-clinical studies have demonstrated cortical changes in BOLD signal during DRGS (Pawela, Kramer, and Hogan 2017), suggestive of an underlying supraspinal mechanism of DRGS in modulating the descending anti-nociceptive system. In our MEG cohort, regions involved in both the default mode network (cingulate cortex) and the salience network (insular and somatosensory cortex) have demonstrated decreased activity contralateral to the location of pain in response to DRG stimulation. However, individual source localization results revealed significant heterogeneity between participants,[See Appendix C] particularly dependent on the location of their pain. This led to the proposal of employing non-invasive brain stimulation, specifically tDCS, to

probe causality of the observed cortical activity in each individual's pain network. The paired invasive/non-invasive stimulation (PAINS) study was initially designed determine whether this cortical activity was an epiphenomenon – neural activity which signifies a change in patient perception without contributing to pain relief itself – or was indeed a true reflection of a supraspinal mechanism of DRGS. Regrettably, this type of study would have required the use of cathodal tDCS to inhibit regions of identifiable supraspinal pain relief in order to definitively demonstrate causality. It was believed that this experimental design would be ethically dubious and generate undue suffering to voluntary participants suffering from chronic pain. Therefore, this design was supplanted by the application of anodal tDCS as a potential augmenter of pain relief and its exploration as a potential adjunct in the treatment of DRGS-implanted chronic pain patients. Unfortunately, these ethical and experimental adaptations limit our ability to conclusively state whether or not the aforementioned physiologic changes in chronic pain represent supraspinal changes of DRGS. These limitations notwithstanding, tools like MEG and EEG remain powerful neuroscientific tools in the effort to arrive at a more comprehensive understanding of the physiology involved in pain processing.

Arguably the most important conclusions from this thesis were the demonstration of the safety, and superior efficacy, of combined invasive (DRGS) and non-invasive (tDCS) neurostimulation in chronic pain. The additive therapeutic benefit we observed was complemented by our predicted metric of pain relief – augmented cortical beta activity – and serves as a useful foundation for the further investigation of the synergistic effects. These observations are likely due to the differential site of action of tDCS (CNS) and DRGS (PNS). DRGS may preferentially target the contributions of peripheral sensitization to ongoing pain, while tDCS mitigates the effect of central sensitization,(Meeker et al. 2019) resulting in non-overlapping efficacy on these mechanisms of chronic pain.

Validation of these findings should include a similar trial design utilising transcranial alternating current stimulation (tACS). The mechanism of tACS involves the administration of an alternating current, usually in a sinusoidal waveform, at a chosen frequency to synchronize and amplify the native cortical oscillations. In contrast, tDCS can only alter cortical excitability and does not provide the added flexibility to target specific oscillatory frequencies. This type of intervention would be preferable to demonstrate the utility of biomarker-based therapy, by augmenting regions of high cortical beta activity and support our findings of therapeutic synergism between invasive and non-invasive neuromodulation targeting elements of the central and peripheral nervous system simultaneously.

These clinical and neurophysiologic findings should ideally be replicated in a randomized crossover study design over months to years in a larger sample size to demonstrate long-term safety and efficacy of dual neurostimulation. However, this would require either (i) at-home administration of tDCS treatments (and the investment in patient education to ensure correct use) or (ii) frequent patient visits for tDCS sessions which will inevitably be dependent on patient motivation and sufficient funding.

We also have shown that while DBS efficacy does not appear to be dependent solely on the frequency of stimulation, baseline neurophysiology of these chronic pain patients can be useful in predicting therapeutic response at a given stimulation frequency. While our results did not support the hypothesis of superior efficacy of low frequency stimulation in producing pain relief, they do suggest the potential for applications of closed-loop DBS paradigms which can record, and stimulate accordingly in real-time, depending on dynamic changes in LFPs.(Shirvalkar et al. 2018b) Closed loop DBS, however, remains a developing field with its applications still confined to research. Therefore, we believe these results will be more useful in the short-term by informing and personalizing DBS parameters for appropriately selecting chronic pain patients based on their dominant LFP oscillations recorded at rest. Ideally, these results should be replicated in a larger prospective cohort, with initial stimulation settings randomized to

a control frequency (eg. 30 Hz) or to LFP-predicted frequency with follow-up pain scores at monthly intervals. This type of study design would overcome the challenges of missing data encountered during our retrospective investigation of patient records, validate our findings and provide the basis for new protocols in DBS parameter selection for chronic pain patients.

10.1 Conclusion

The findings of this thesis provide supportive evidence for the usefulness of neuroimaging/neurophysiologic methods in identifying biomarkers of pain. However, the methodological approaches employed across the literature require greater standardization, more robust experimental designs and further validation in larger patient populations. Nevertheless, as pain remains one of the most distressing and costly (Gutierrez et al. 2014) public health concerns in the twenty-first century, we believe that the search for objective measures of pain will, and must, continue.

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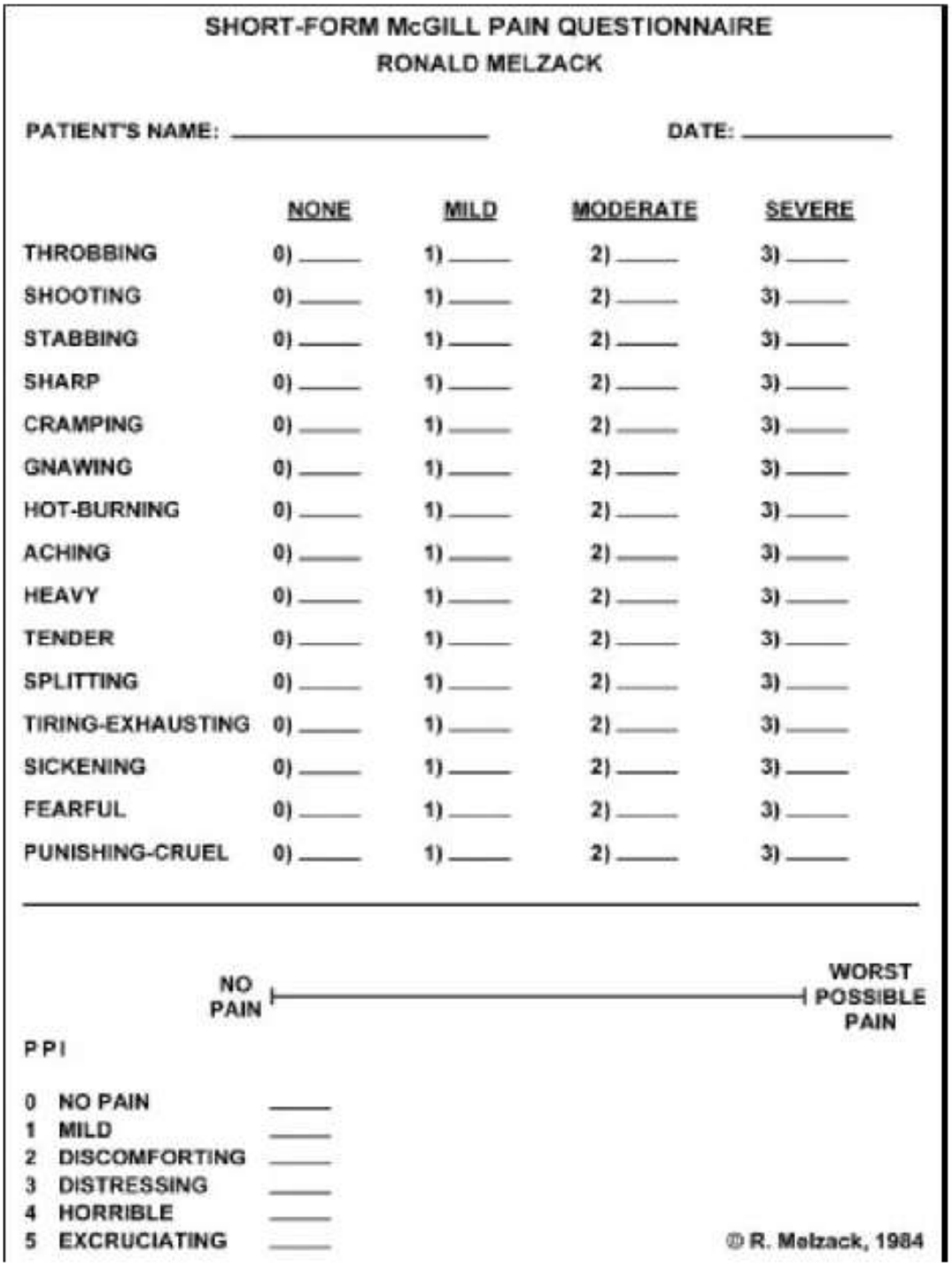
Appendix A – Short from McGill Pain Questionnaire and Visual Analogue Scale



SHORT-FORM McGILL PAIN QUESTIONNAIRE

RONALD MELZACK

PATIENT'S NAME: _____ DATE: _____

	NONE	MILD	MODERATE	SEVERE
THROBBING	0)	1)	2)	3)
SHOOTING	0)	1)	2)	3)
STABBING	0)	1)	2)	3)
SHARP	0)	1)	2)	3)
CRAMPING	0)	1)	2)	3)
GNAWING	0)	1)	2)	3)
HOT-BURNING	0)	1)	2)	3)
ACHING	0)	1)	2)	3)
HEAVY	0)	1)	2)	3)
TENDER	0)	1)	2)	3)
SPLITTING	0)	1)	2)	3)
TIRING-EXHAUSTING	0)	1)	2)	3)
SICKENING	0)	1)	2)	3)
FEARFUL	0)	1)	2)	3)
PUNISHING-CRUEL	0)	1)	2)	3)

NO PAIN ——— WORST POSSIBLE PAIN

PPI

0 NO PAIN _____
1 MILD _____
2 DISCOMFORTING _____
3 DISTRESSING _____
4 HORRIBLE _____
5 EXCRUCIATING _____

© R. Melzack, 1984

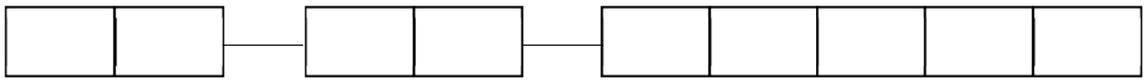
Appendix B – Participant Consent Form

Mr. Alex Green

John Radcliffe Hospital

01865 741166

Study Code: *Site ID Code:* *Participant identification number:*



CONSENT FORM

<Study Title>: Cerebral Signature for pain perception and modulation

Name of Researcher: Dr Tariq Parker, MBBS, Msc *If you agree, please initial box*

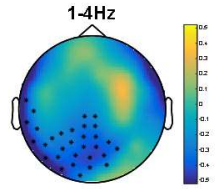
1. I confirm that I have read the information sheet dated _____ (version 7) for this study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily.	
2. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my medical care or legal rights being affected.	
3. I understand that relevant sections of my medical notes (if relevant) and data collected during the study may be looked at by individuals from University of Oxford, from regulatory authorities and from the NHS Trusts, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records.	
4. I understand that the information collected about me may be used in an anonymous form to support other research in the future. It will not be possible for me to be identified by it.	

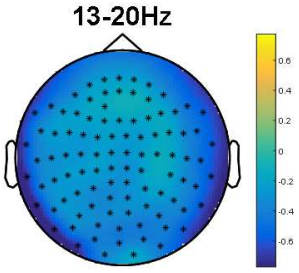
5. I understand that this is a research scan that is not useful for medical diagnosis, and that scans are not routinely looked at by a doctor. If a concern is raised about a possible abnormality on my scan, I will only be informed if a doctor thinks it is medically important such that the finding has clear implications for my current or future health.		
6. I agree to take part in this study.		
7. I agree to be contacted about ethically approved research studies for which I may be suitable. I understand that agreeing to be contacted does not oblige me to participate in any further studies.	Yes	No

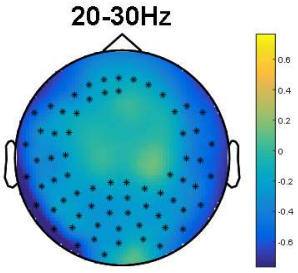
Name of Participant	Date	Signature
Name of Person taking Consent	*Date*	*Signatu*

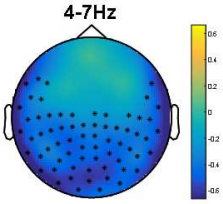
**1 copy for participant; 1 copy for researcher site file; 1 (original) to be kept in medical notes* (if participant is a patient).

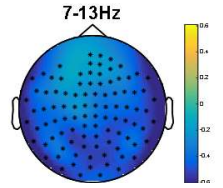
Appendix C – Individual patient MEG sensor space localization



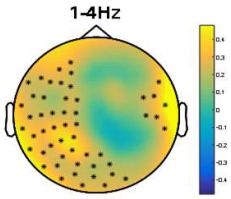




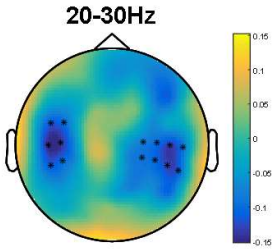




Patient 3 Rest On v Off



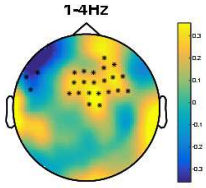
NS 13 – 20 Hz

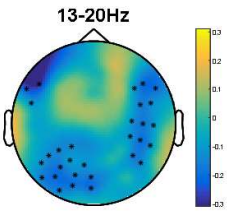


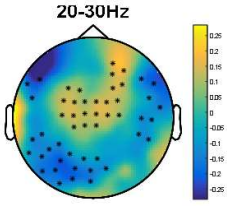
NS 4 – 7 Hz

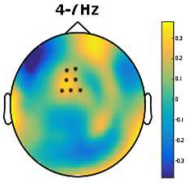
Patient 3 OFF 2back v 0back

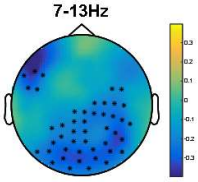
NS 7 – 13 Hz



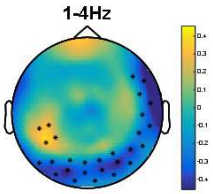


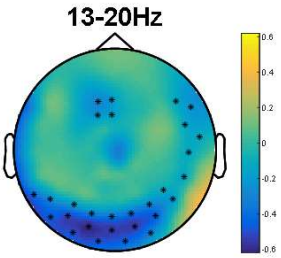


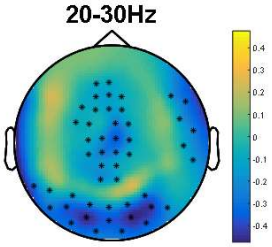


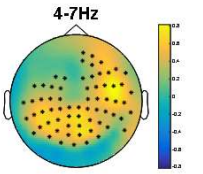


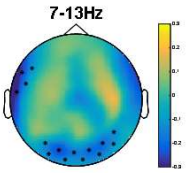
Patient 3 Task On v OFF



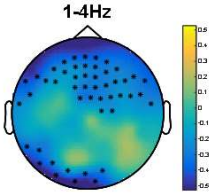


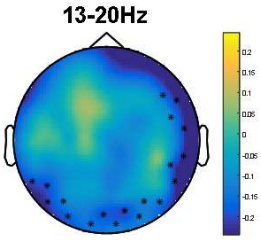


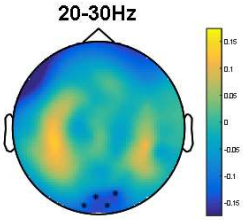


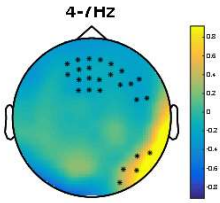


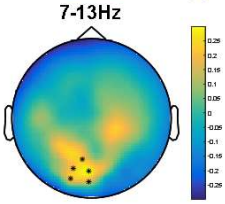
Patient 5 Rest On v Off



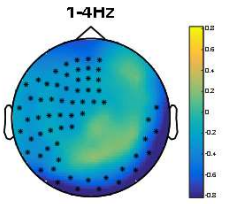


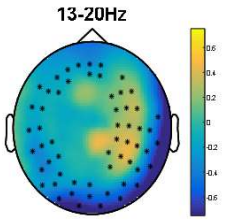


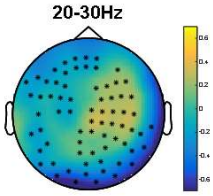


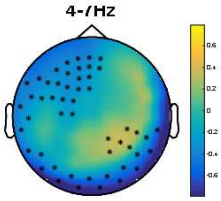


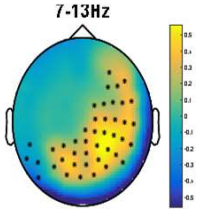
Patient 5 OFF 2back v 0back



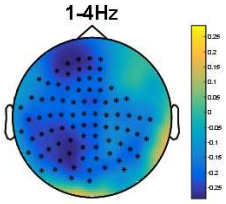


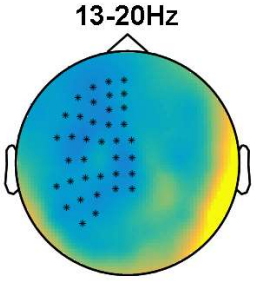


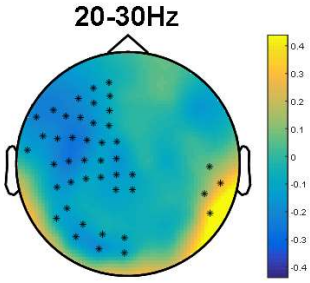


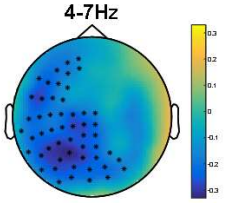


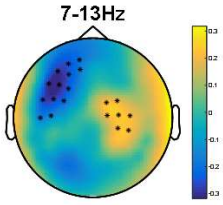
Patient 5 Task On v OFF



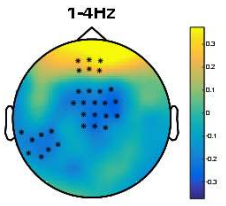


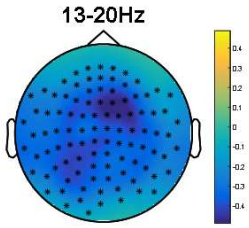


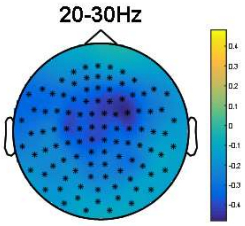


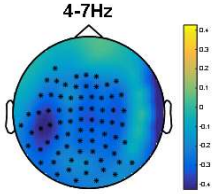


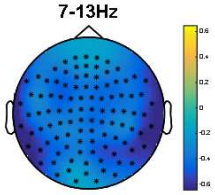
Patient 6 Rest On v Off





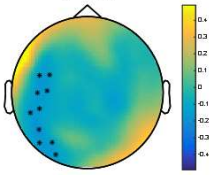


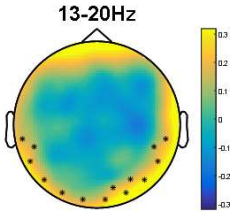


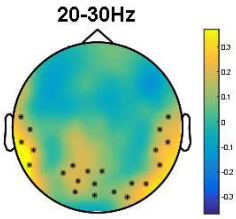


Patient 6 OFF 2back v 0back

NS 1 – 4 Hz

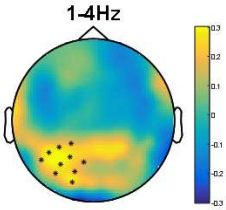


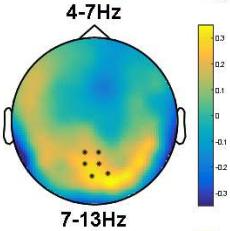


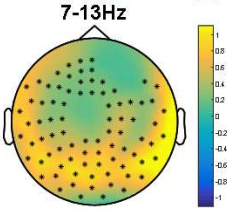


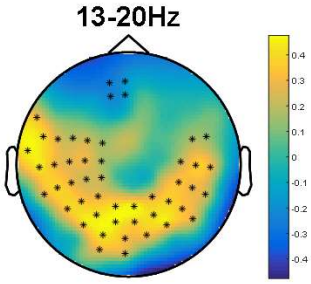
Patient 6 Task On v OFF

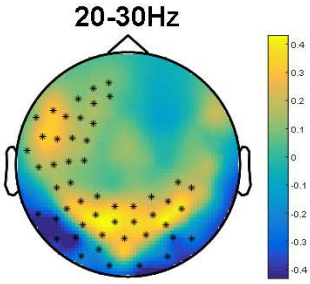
NS 7 – 13 Hz



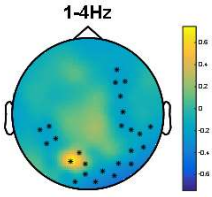


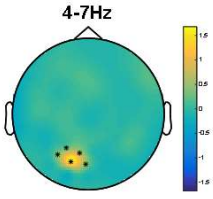


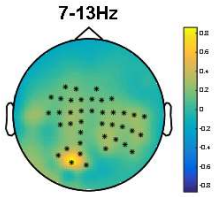


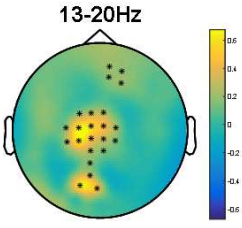


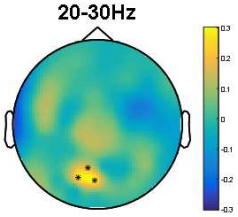
Patient 7 Rest On v Off



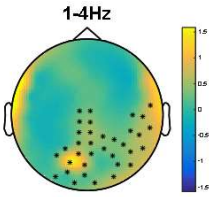


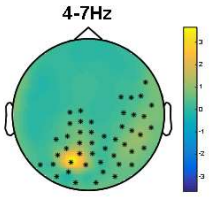


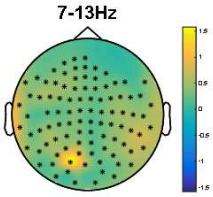


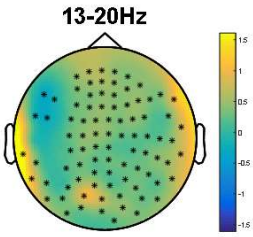


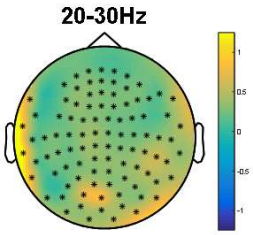
Patient 7 OFF 2back v 0back



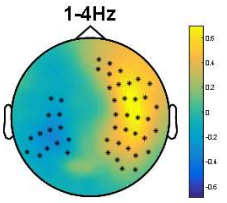


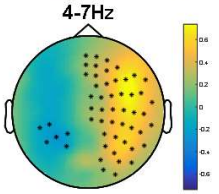


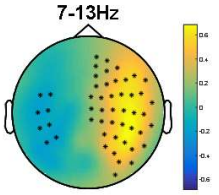


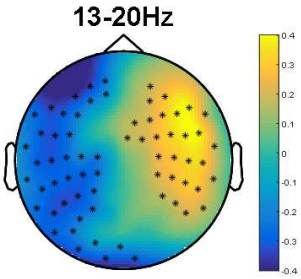


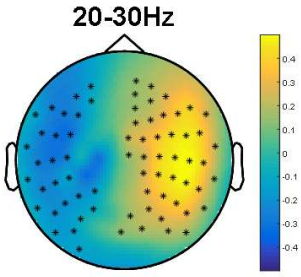
Patient 7 Task On v OFF



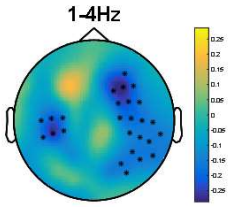


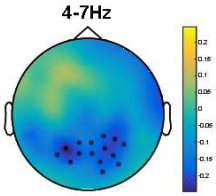


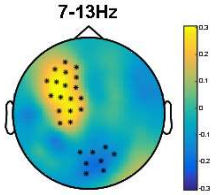


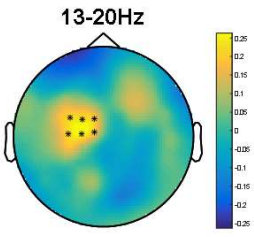


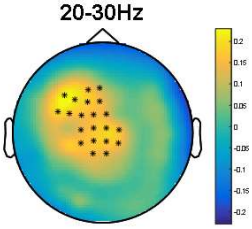
Patient 8 Rest On v Off



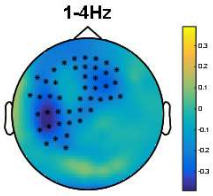


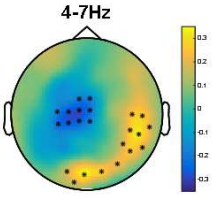


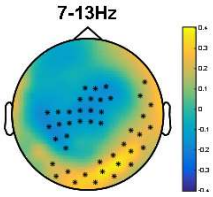


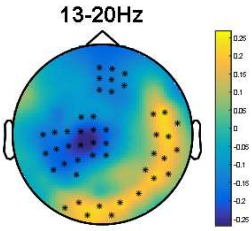


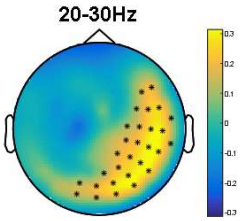
Patient 8 OFF 2back v 0back



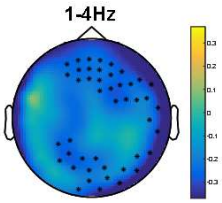


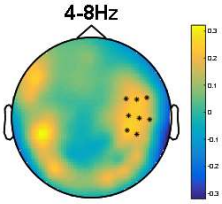


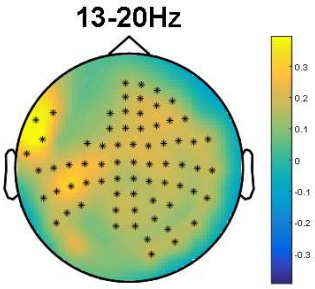




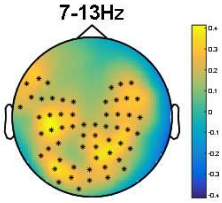
Patient 8 Task On v OFF



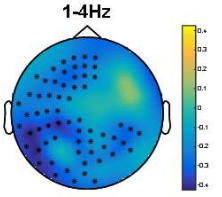


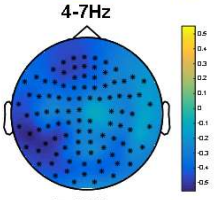


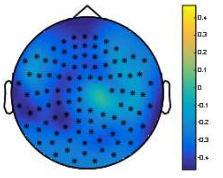
NS 20 – 30 Hz

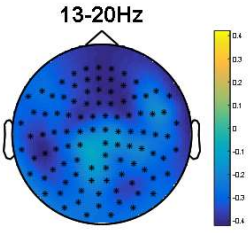


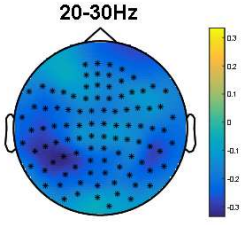
Patient 9 Rest On v Off



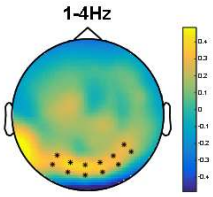


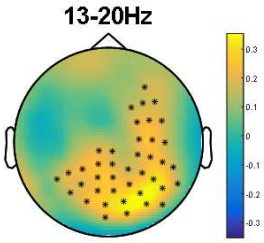


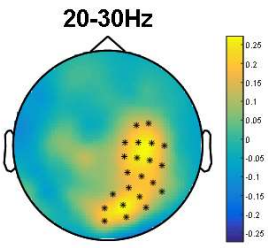


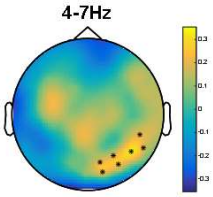


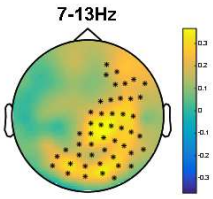
Patient 9 OFF 2back v 0back



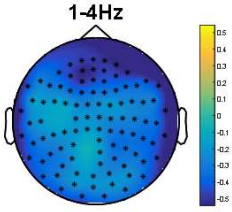


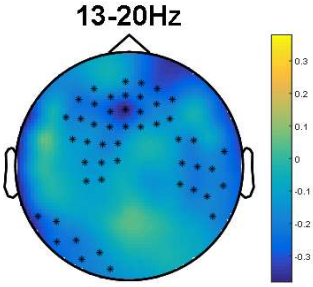


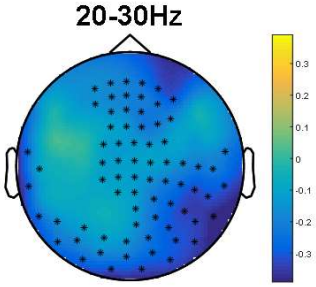


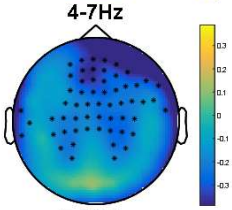


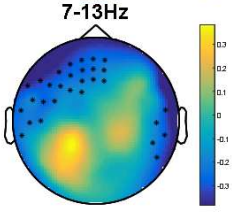
Patient 9 Task On v OFF



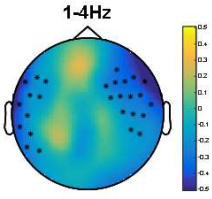


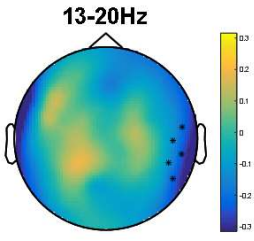


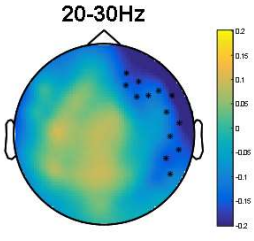


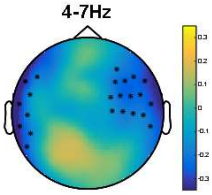


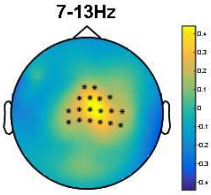
Patient 10 Rest On v Off



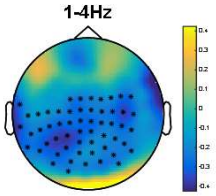


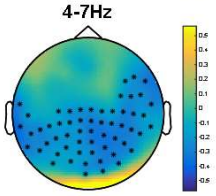


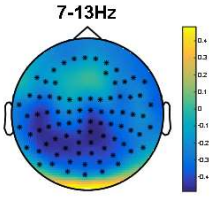


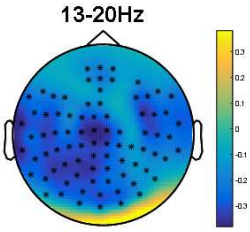


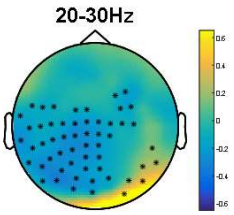
Patient 10 OFF 2back v 0back



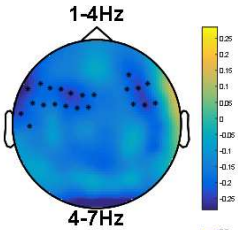


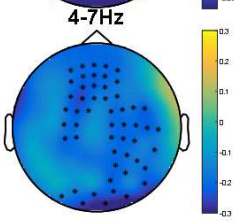


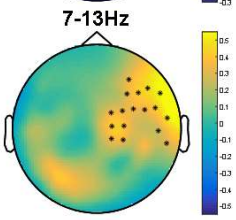




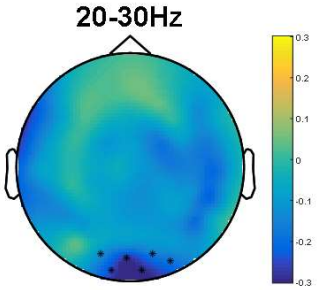
Patient 10 Task On v OFF



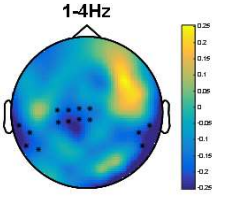


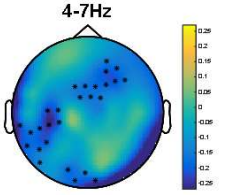


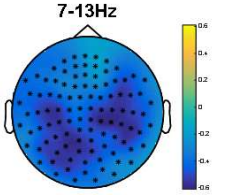
NS 13 – 20 Hz

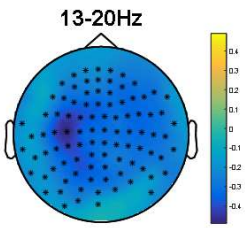


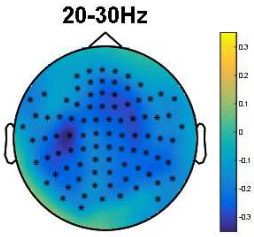
Patient 11 Rest On v Off



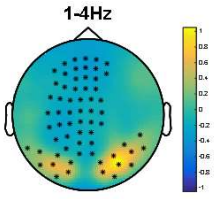


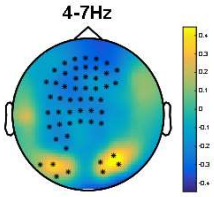


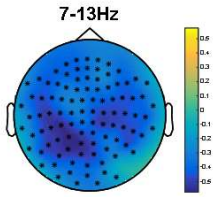


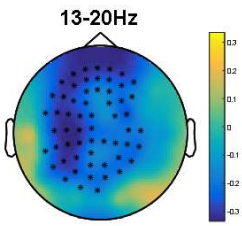


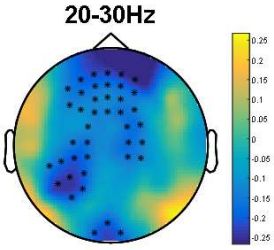
Patient 11 OFF 2back v 0back







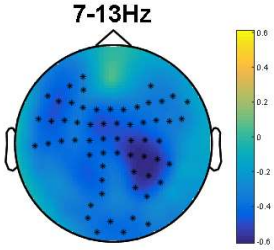


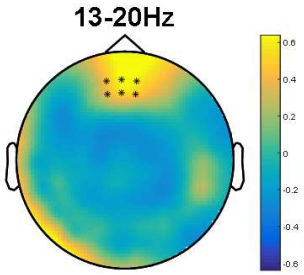


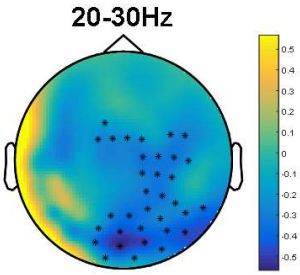
Patient 11 Task On v OFF

NS 1 – 4 Hz

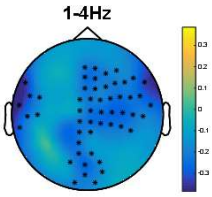
NS 4 – 7 Hz

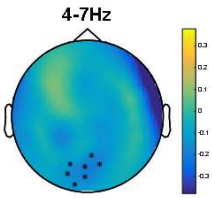


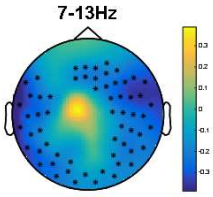


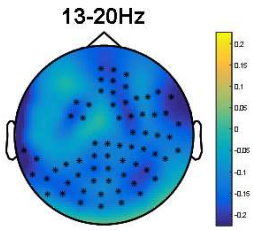


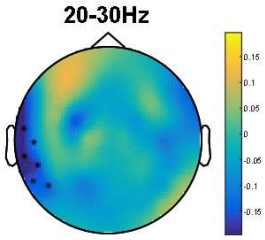
Patient 12 Rest On v Off





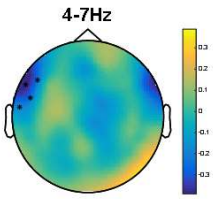


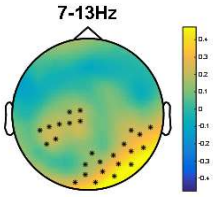


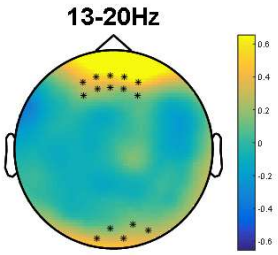


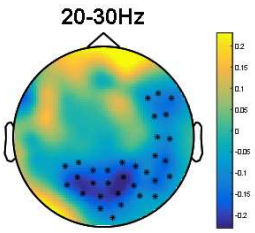
Patient 12 OFF 2back v 0back

NS 1 – 4 Hz

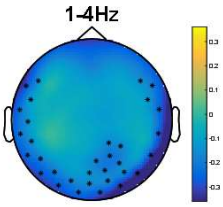


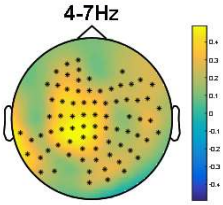


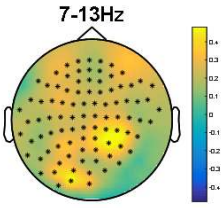


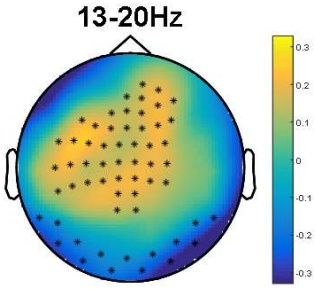


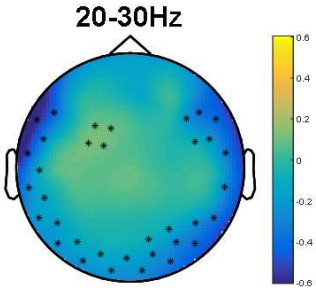
Patient 12 Task On v OFF





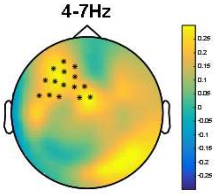


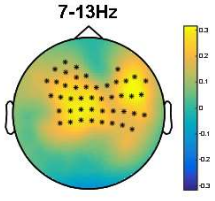




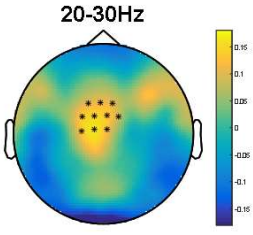
Patient 13 Rest On v Off

NS 1 – 4 Hz

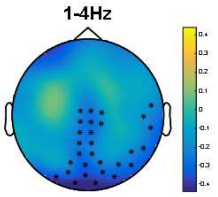


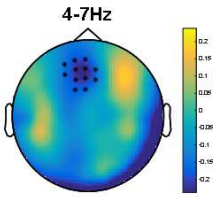


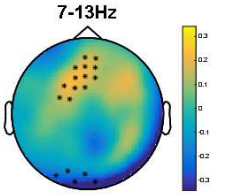
NS 13 – 20 Hz

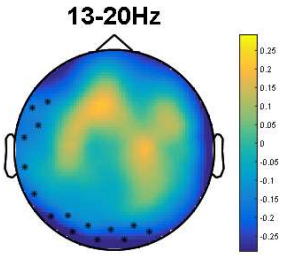


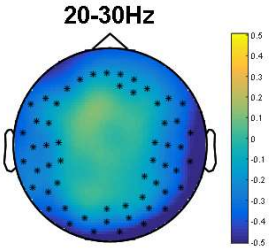
Patient 13 OFF 2back v 0back



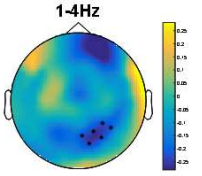


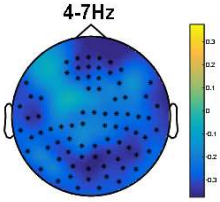


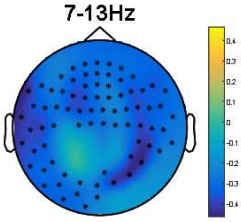


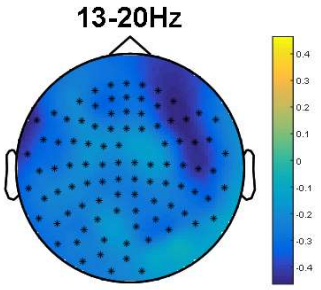


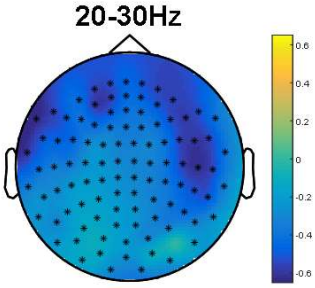
Patient 13 Task On v OFF



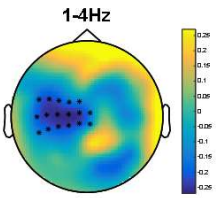


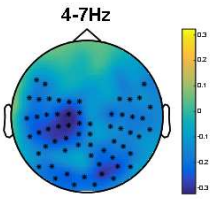


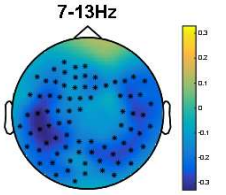


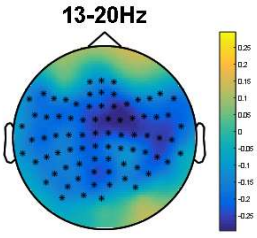


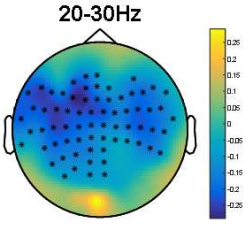
Patient 14 Rest On v Off





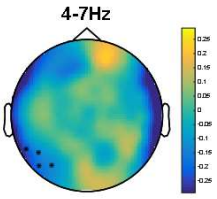


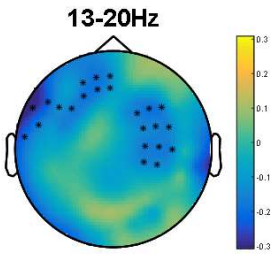


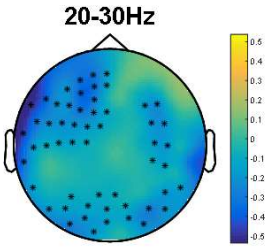


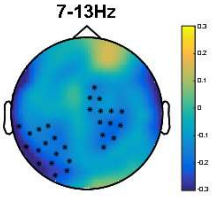
Patient 14 OFF 2back v 0back

NS 1 – 4 Hz

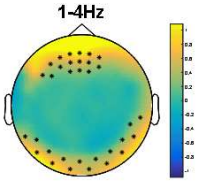


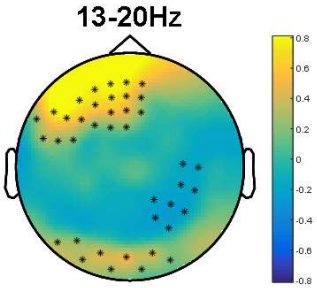


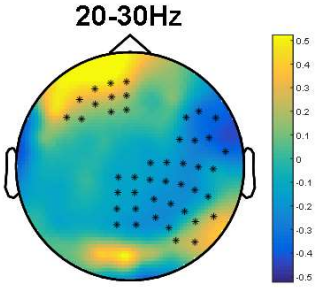


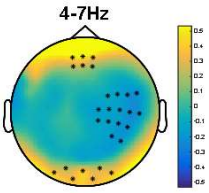


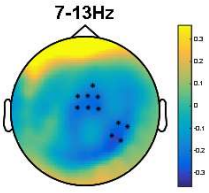
Patient 14 Task On v OFF



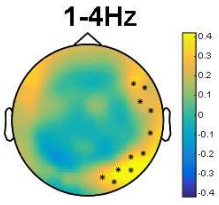


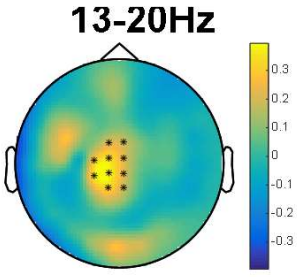


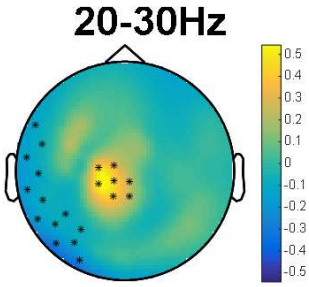




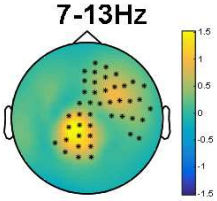
Patient 15 Rest On v Off



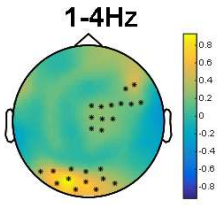


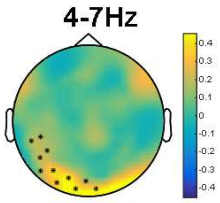


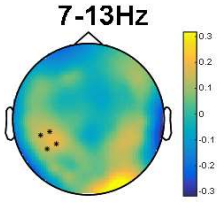
NS 4 – 7 Hz

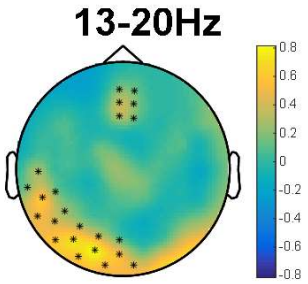


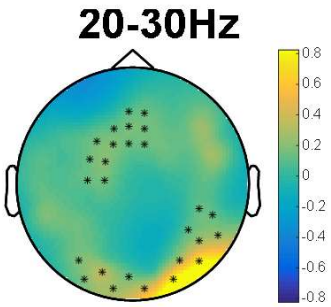
Patient 15 OFF 2back v 0back



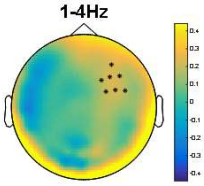


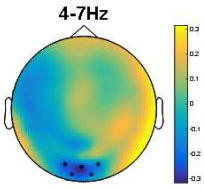


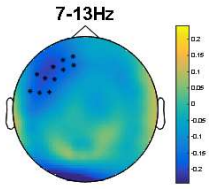


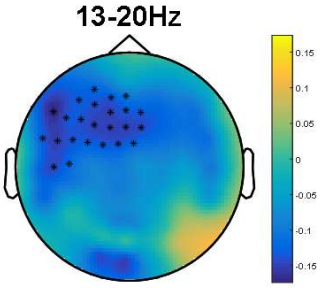


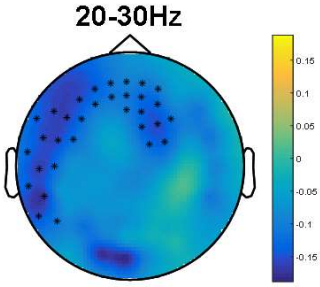
Patient 15 Task On v OFF







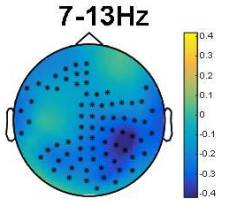


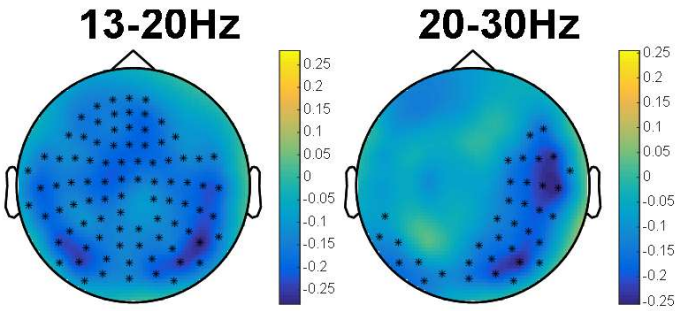


Patient 16 Rest On v Off

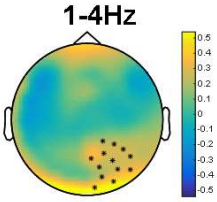
NS 1 – 4 Hz

NS 4 – 7 Hz

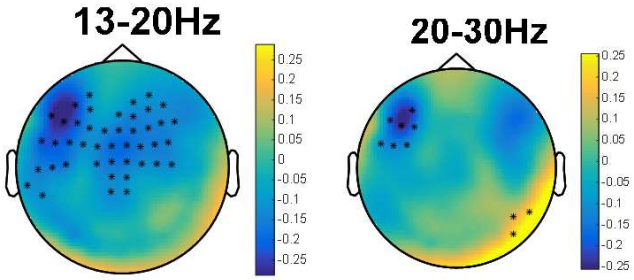


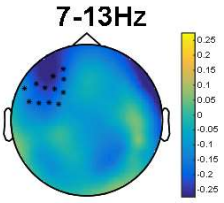


Patient 16 OFF 2back v 0back



NS 4 – 7 Hz





Patient 16 Task On v OFF

Appendix D – PAINS Trial Blinding/Adverse effects questionnaire

Questionnaire of sensations related to transcranial electrical stimulation (TES)

(To be filled in by the participants and by the investigator)

Investigator:
Participant name/code:_____ **Date**: / /
Experiment/Treatment: _____
No stimulations experienced before ☐ Experienced ☐ # of **stimulations sessions before:**
…….
Type of electrical stimulation used here_____ **Intensity** ____mA (if known)
Electrodes dimension: anode (if known) ___*___ cathode (if known) ___*___ (shape _____)
other_____
Participant:
Did you experience any discomfort during the electrical stimulation? Please indicate the degree of intensity of your discomfort according to the following scale:
- **None = I did not feel the sensation addressed**
- **Mild = I mildly felt the sensation addressed**
- **Moderate = I felt the sensation addressed**
- **Strong = I felt the sensation addressed to a considerable degree**

In the first stimulation block I felt:

	None	*Mild*	*Moderate*	*Strong*
Itching	☐	☐	☐	☐
Pain	☐	☐	☐	☐
Burning	☐	☐	☐	☐
Warmth/Heat	☐	☐	☐	☐
Metallic/Iron taste	☐	☐	☐	☐
Fatigue/Decreased alertness	☐	☐	☐	☐
Other	☐	☐	☐	☐

In case of perceived sensation, when did it begin*? (this part can be multiplied and completed for each sensation, e.g. one for pain, one for itching etc and could/should be modified according to the type of experiments)*
☐ At the beginning; ☐ At approximately in the middle; ☐ Towards the end of the stimulation
Duration (multiple options allowed)
☐ Only initially ☐ It stopped in the middle of the block ☐ It stopped at the end of the block
How much did these sensations affect your general state?
☐ Not at all ☐ Slightly ☐ Considerably ☐ Much ☐ Very much
Location of sensations:
☐ Diffuse ☐ localized ☐ close to the electrode, (which one?)_____; ☐ Other_____
If you would like to provide more details, please briefly describe the experimented sensations in relation to the "Other" or "Fatigue" or ….. response:

In the second stimulation block I felt:

	None	*Mild*	*Moderate*	*Strong*
Itching	□	□	□	□
Pain	□	□	□	□
Burning	□	□	□	□
Warmth/Heat	□	□	□	□
Metallic/Iron taste	□	□	□	□
Fatigue/Decreased alertness	□	□	□	□
Other	□	□	□	□

To be administered at the end of the entire experiment
Do you believe that you received a real or placebo stimulation?
In the first stimulation block: □ real □ placebo □ I don't know
In the second stimulation block: □ real □ placebo □ I don't know
Investigator*:*
Please report any adverse event/problem (typically skin irritation and redness – separately for the electrodes -, headache, scalp pain, dizziness, or others, please specify) that occurred and rate the event/problem on a scale from 0 to 3 as previously described.
_____
_
_____
_
_____
_
_____
Additional comments:
_____
_
_____
_
_____
A structured questionnaire on intensity and frequency of AEs increases safety, when transcranial electrical stimulation is used. It is a recommended procedure for publication of TES experiments/trials.