Investigating spinal cord stimulation using electroencephalography in chronic pain patients with a spinal cord stimulator implant

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List of Abbreviations

ACH	Auckland City Hospital
ADHB	Auckland District Health Board
DMP	Data management plan
DSMC	Data safety monitoring committee
DSMP	Data safety monitoring plan
EEG	Electroencephalography/electroencephalogram
EMG	Electromyography/electromyogram
SCS	Spinal cord stimulation/stimulator
TARPS	The Auckland Regional Pain Service

Study Summary

Title	Investigating spinal cord stimulation using electroencephalography in chronic pain patients with a spinal cord stimulator implant
Short title	Investigating SCS using EEG
Lay title	Investigating brain waves during spinal cord stimulation
IRB Protocol Number	HDEC 19/NTA/169
Study Design /Methodology	Intervention study, basic research
Study Duration	Six months
Study Centre	Auckland District Health Board
Objectives	To investigate the electrophysiological response and noise induced by SCS.
Number of Subjects	20
Eligibility Criteria and main objective	Volunteers 18+ years of age, recruited from those undergoing SCS therapy at TARPS.
Study Interventions and Measures	Participants will have their EEG recorded while SCS is administered. SCS parameters will be manipulated with feedback from the participant. EMG electrodes will be placed on the back near the site of the SCS electrodes and pulse generator. Key outcomes will be related to participant characteristics, device characteristics, and the EEG signal.
Statistical Methodology	Description of participant characteristics, device characteristics, and EEG recordings.

Background and Study Rationale

Spinal cord stimulation (SCS) is used as a modality of treatment in selected patients at The Auckland Regional Pain Service (TARPS). Previous studies have shown that SCS is an effective treatment for many patients with chronic pain and refractory angina pectoris (Moore & McCrory, 2016). The SCS consists of a battery and pulse generator unit (typically implanted subcutaneously in the lower back) connected to electrodes implanted in the epidural space.

When operational, the device delivers rhythmic stimulation to the spinal cord. The precise mechanism of action is unknown, with a number of proposals (Moore & McCrory, 2016). Basic research on SCS has the potential to improve our knowledge of the human nervous system, and may identify opportunities for improving this treatment or finding novel applications for it. For instance, recent publications have indicated that SCS may be used to recover function in patients paralysed by spinal cord injury (Angeli et al., 2018; Moritz, 2018; Wagner et al., 2018), underscoring the importance of a greater understanding of SCS mechanisms.

Some studies have looked at patients' electroencephalogram (EEG) both before and after SCS therapy (e.g. De Ridder & Vanneste, 2016). However, EEG studies during SCS are rare (e.g. Poláček, Kozák, Vrba, Vrána, & Stančák, 2007), and the studies that do exist have tended to focus on the response evoked by somatosensory stimulation during SCS, rather than the response evoked by SCS *per se*.

The most commonly cited study investigating the evoked response to SCS is almost 50 years old (Nashold, Somjen, & Friedman, 1972). The technology used was entirely analogue, and our conception of the EEG response to SCS could be vastly improved simply on the basis of subsequent advances in digital signal processing. For instance, Nashold et al (1972) were not able to even average recordings. Nevertheless, they did demonstrate some

results that probably remain reliable. Chiefly, their EEG traces indicate that SCS did not produce a significant non-biological EEG artefact (although they did not reproduce the trace from before stimulus administration). In addition, they demonstrated the evoked potential to have a central distribution, tending to peak around the vertex, although some participants demonstrated more frontal or occipital peaks. Another potentially interesting finding was that the participant always perceived SCS paraesthesia detectable by EEG, but the converse did not always hold. This may be relevant to the analgesic mechanism of SCS: for conventional SCS it is necessary for patients to perceive the SCS in order for analgesia to be produced. On the other hand, newly available waveforms are analgesic in the absence of detectable paraesthesia. Many recently implanted devices can be switched from tonic (conventional) to burst (no paraesthesia) stimulation, depending on patients' preferences. It would therefore be worth retesting this hypothesis using current technology as a first step towards an in depth exploration of the EEG characteristics of SCS.

Whether Nashold and colleagues' (1972) observations hold on more modern EEG equipment using modern processing techniques (e.g. time-frequency analysis, steady-state evoked potentials) is an open question. Likewise, the EEG evoked response to more recently developed high-frequency burst SCS regimens is unknown.

The present study aims to investigate the electrophysiological response and noise induced by the SCS. Our participants will be chronic pain patients with existing SCS implants. We hypothesise that an electrophysiological response to SCS will be detectable in EEG as an increase in power compared to baseline at the frequency of stimulation. We further hypothesise that SCS stimulation will only produce an evoked response on EEG when perceptible by the patient. We will test this hypothesis for both tonic and burst stimulation. We will also undertake an exploratory descriptive analysis of the response.

Our longer-term goal is to increase understanding of the mechanisms of SCS, and of

the human central nervous system in general. From a clinical perspective, understanding of the EEG correlates of SCS could lead to improvements in tuning of SCS parameters and also, ultimately, to novel SCS waveform patterns.

Objectives

Primary objective

To investigate the EEG electrophysiological response evoked by SCS.

Hypotheses

Our primary hypothesis is that an electrophysiological response to SCS will be detectable in EEG as an increase in power compared to baseline at the frequency of stimulation. We further hypothesise that SCS stimulation will only produce an evoked response on EEG when perceptible by the patient. We will test this hypothesis for both tonic and burst stimulation.

Study Design and Methods

General Study Design

This study is a basic science project focused on investigating the properties of the EEG signal during SCS.

Participants

Participants will be up to 20 chronic pain patients with existing SCS implants (i.e. no devices will be implanted as part of this study). Participants will be offered a $30 petrol voucher as reimbursement for any costs of participation.

Inclusion criteria

1. Age 18+ years old
2. Operational SCS implant
3. No surgery at implant site in at least three months
4. Willing to participate

Materials

The School of Medicine has several EEG recording devices which could be used for this study. EMG recording capabilities may be added.

Recruitment and Consent

Patients will be recruited from patients presenting to The Auckland Regional Pain Service (TARPS) for routine review of established spinal cord stimulation at Greenlane Clinical Centre. The attending clinician will screen patients, and ask permission to provide their details to a researcher or clinician. The researcher or clinician will then extend an invitation to participate using provided contact details. We will focus on patients who have devices with St Jude Medical Eon programmers, as these are relatively common and offer a straightforward method for the participant to disable stimulation. We will not recruit patients who have their stimulator active continuously, as the experiment will involve periods of deactivation.

A researcher will approach all such patients by telephone and provide information on the study in oral and written form. The patient will be offered time to consider whether he or she wishes to participate.

Patients who meet the inclusion/exclusion criteria and provide written informed consent will then be enrolled. We will record numbers of eligible patients, patients approached, and patients consented.

Procedure

Participants will be asked to attend an experiment session at TARPS. We will aim to conduct recordings directly after the patient's routine follow-up appointment. A review of the participant's clinical notes will provide data pertaining to demographic, device specifications, and pain characteristics. An interview at the session will gather basic information about the nature of their pain, and their therapeutic regimen/s (see Data Management Plan and Case Report Forms).

In order to record EEG, the participant will be seated in a quiet room, and an EEG cap applied. EMG electrodes will be adhered to the participant's back over the SCS electrodes and pulse generator.

With the input of the patient and a registered nurse experienced in the programming procedure (ED), we will add six experimental programs to the patient's controller, with pulse frequencies of 15Hz, 25Hz, and 35Hz. Pulse width will be 300μs. At each frequency, stimulation amplitude will be increased in steps from zero until the patient just perceives paraesthesia, and then go several steps above that. This will give us three perceptible stimulation patterns. At each frequency we will program a non-perceptible stimulation pattern a few steps below the threshold of perceptibility, for six total experimental programs. We will program each stimulation pattern to activate for 4 seconds every 10 seconds. When the stimulation program is activated, it fires immediately. The response to the first stimulation is unlikely to be analysed (there will be no baseline beforehand), but will be for the participant to confirm that he/she wants to continue.

Before each block, one of the six stimulation programs will be selected randomly by computer. This program will then be activated using the controller by the participant, and interrupted after four activations (i.e. one block), either by the experimenter or participant. The participant will have access to a deactivation button at all times, and will be encouraged

to use it if they want to cease stimulation for any reason.

After each block of four trials, we will ask the participant to record his/her comfort level on a visual analogue scale, give him/her an opportunity to elect to discontinue, and adjust the stimulation program in the case of continuation. We aim to collect data from 72 trials in 18 blocks, but will stop if at any point the participant requests so. We expect that the experiment, including programming, EEG cap application, and measurements, will take around 90 minutes.

Statistical Plan

Key outcomes

Device-related outcomes

1. Device specifications (Make/Model/Version/Electrode/Controller type)
    a. Make
    b. Implantable Pulse Generator model/version
    c. Controller model/version
    d. Lead model/version
    e. Number of leads
2. Range of possible values for parameters.

Participant-related outcomes

1. Pain characteristics:
    a. Clinical indication for SCS
    b. Pain location
    c. Pain severity
    d. Pain frequency
2. Implant characteristics:

   a. Integrity of electrodes (i.e. impedance)
   b. Anatomical location of the SC electrodes.
   c. Implantation date
3. Stimulation parameters programmed for therapy
4. Comfort after each block (visual analogue scale)
5. Number of trials completed

Signal-related outcomes

1. High-level description of the EEG trace after SCS:
   a. Presence or absence of evoked response (primary outcome variable)
   b. Stimulus artefact
   c. Electrophysiological response
2. EEG power at tonic SCS frequency
3. Spatial arrangement of SCS response
4. Description of SCS artefact recorded at epidermal electrodes placed over the SCS electrode and pulse generator site

Analysis

To test our signal-related hypotheses, we plan to use the filter-Hilbert time-frequency decomposition on EEG and epidermal electrode data. Spectral power values at the SCS frequency converted to Z-values using a pre-stimulation baseline. Thus, a Z-value over 1.96 at the relevant frequency will indicate significant (i.e. two-tailed 95%) facilitation in the relevant frequency band.

We do not yet know what the stimulus artefact (i.e. non-biological) component of the EEG signal will be (or if it exists, for that matter), but we will investigate techniques for isolating and ameliorating it. It is difficult to say what this artefact-correction procedure will look like *a priori*, and our analysis methods may change in response to the outcomes of this

process. This uncertainty about the electrophysiological signature of SCS also renders it unfeasible to perform statistical power calculations for this study.

Ethical Considerations

This study involves an implantable active device (albeit one that the patient already has implanted), and the delivery of stimulation that would not necessarily be part their treatment regimen. We have therefore established an Independent Data Safety Monitoring Committee, as outlined in our Data Safety Monitoring Plan (DSMP)

Patient Comfort

The patients that we enrol will have their SCS in place as part of chronic pain treatment. We will work with the patient when programming SCS parameters for the purposes of experimentation, and use settings around those just perceptible by the participant. We will not enrol patients who have their SCS constantly active as part of their treatment. Participants will have access to the programmer button that ceases stimulation at all times. We will monitor patient comfort after each block, and we emphasise the participant's right to discontinue the session at any point.

The EEG cap is immersed in an electrolytic solution before application, this solution will wet the participant's head. We will provide towels with which the participant can dry his/her head.

Data Security

We have composed a Data Management Plan (DMP) and DSMP, which can be queried for more information.

Māori responsiveness

This project has been presented to Taia te Hauora, the Māori Research Advisory

Committee for the Department of Anaesthesiology and Centre for Medical and Health Sciences Education. There was some consideration around touching patients' heads, which is also potentially sensitive in other cultures. It was recommended that assent to touch the patient's head be obtained from all participants before contact is made.

We acknowledge our role as kaitiaki of data, and that Māori should be given the option to retain rangatiratanga over their data. To this end we are piloting a data sharing protocol that offers participants the chance to have ongoing involvement in how and where their data are reused. This is described in our DMP.

References

Angeli, C. A., Boakye, M., Morton, R. A., Vogt, J., Benton, K., Chen, Y., … Harkema, S. J. (2018). Recovery of Over-Ground Walking after Chronic Motor Complete Spinal Cord Injury. *New England Journal of Medicine*, NEJMoa1803588. https://doi.org/10.1056/NEJMoa1803588

De Ridder, D., & Vanneste, S. (2016). Burst and tonic spinal cord stimulation: Different and common brain mechanisms. *Neuromodulation*, *19*(1), 47–59. https://doi.org/10.1111/ner.12368

Moore, D. M., & McCrory, C. (2016). Spinal cord stimulation. *BJA Education*, *16*(8), 258–263. https://doi.org/10.1093/bjaed/mkv072

Moritz, C. (2018). A giant step for spinal cord injury research. *Nature Neuroscience*. https://doi.org/10.1038/s41593-018-0264-4

Nashold, B., Somjen, G., & Friedman, H. (1972). Paresthesias and EEG potentials evoked by stimulation of the dorsal funiculi in man. *Experimental Neurology*, *36*(2), 273–287.

Poláček, H., Kozák, J., Vrba, I., Vrána, J., & Stančák, A. (2007). Effects of spinal cord stimulation on the cortical somatosensory evoked potentials in failed back surgery syndrome patients. *Clinical Neurophysiology*, *118*(6), 1291–1302. https://doi.org/10.1016/j.clinph.2007.02.029

Wagner, F. B., Mignardot, J.-B., Le Goff-Mignardot, C. G., Demesmaeker, R., Komi, S., Capogrosso, M., … Courtine, G. (2018). Targeted neurotechnology restores walking in humans with spinal cord injury. *Nature*, *563*(7729), 65–71. https://doi.org/10.1038/s41586-018-0649-2