Alterations in cortical excitability during acute musculoskeletal pain: Research Proposal for a Combined TMS-EEG Study

Nahian S. Chowdhury, Samantha K. Millard, Alan Chiang, Patrick Skippen, David A Seminowicz , Wei-Ju Chang, Katarzyna Bilska & Siobhan M Schabrun

Musculoskeletal Pain is a common source of disability

Musculoskeletal pain is a common source of disability worldwide [1], yet effective treatments remain elusive. The lack of effective treatment has been attributed to a limited understanding of the mechanisms that mediate musculoskeletal pain. An increased understanding of these mechanisms would assist in developing new interventions for musculoskeletal pain.

Musculoskeletal Pain inhibits corticomotor output

A region implicated in pain is the primary motor cortex (M1), which controls motor output to peripheral muscles. Several studies have shown that corticomotor excitability (CME), measured using transcranial magnetic stimulation (TMS), is reduced during, and after recovery from, acute musculoskeletal pain [4]. This reduction in CME may serve to restrict motor output to peripheral areas, protecting these areas from further injury [5].

But where is the origin of this inhibitory mechanism?

Thus far, CME during acute pain has been assessed using the TMS motor-evoked potential (TMS-MEP) method, where the magnitude of peripheral muscle responses induced by TMS pulses to M1 is used to index CME (see Figure 1). A major limitation of this method is that the MEP is not just indicative of cortical excitability, but cortical, subcortical, spinal and peripheral excitability [7-9]. Thus, previous studies are unable to determine whether changes in excitability are due to cortical, subcortical, spinal and/or peripheral mechanisms.
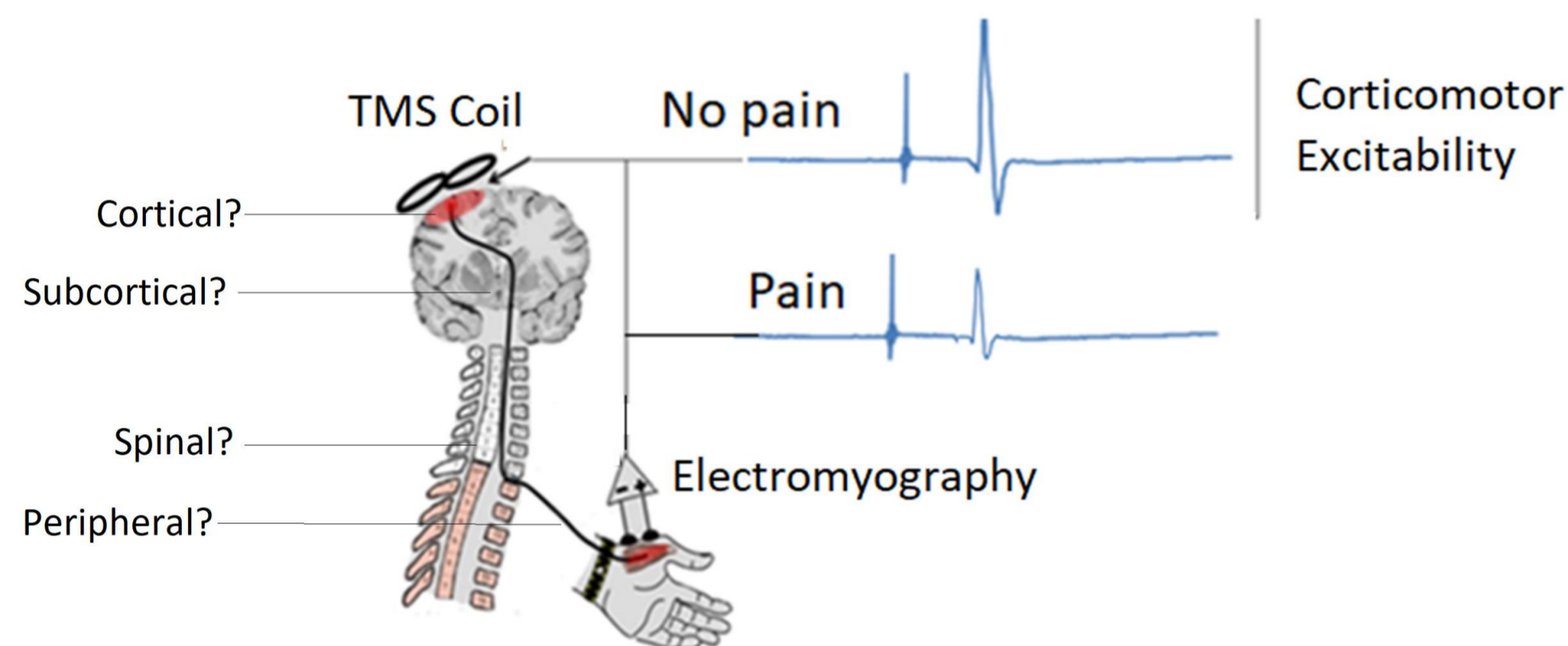

Figure 1. The TMS-MEP Methodology. This method has shown that corticomotor output is reduced during pain. However this method is unable to deduce the source of the inhibitory mechanism.

TMS-EEG can directly measure cortical excitability

One way to address this limitation is to use combined TMS-electroencephalography (EEG) to measure TMS-evoked potentials (TEPs). The method allows for the assessment of cortical excitability directly from the cortex without subcortical, spinal and peripheral influences [7-9]. See Figure 2. Accordingly, this project aims to investigate cortical excitability changes (as indexed by TEPs) during acute musculoskeletal pain.
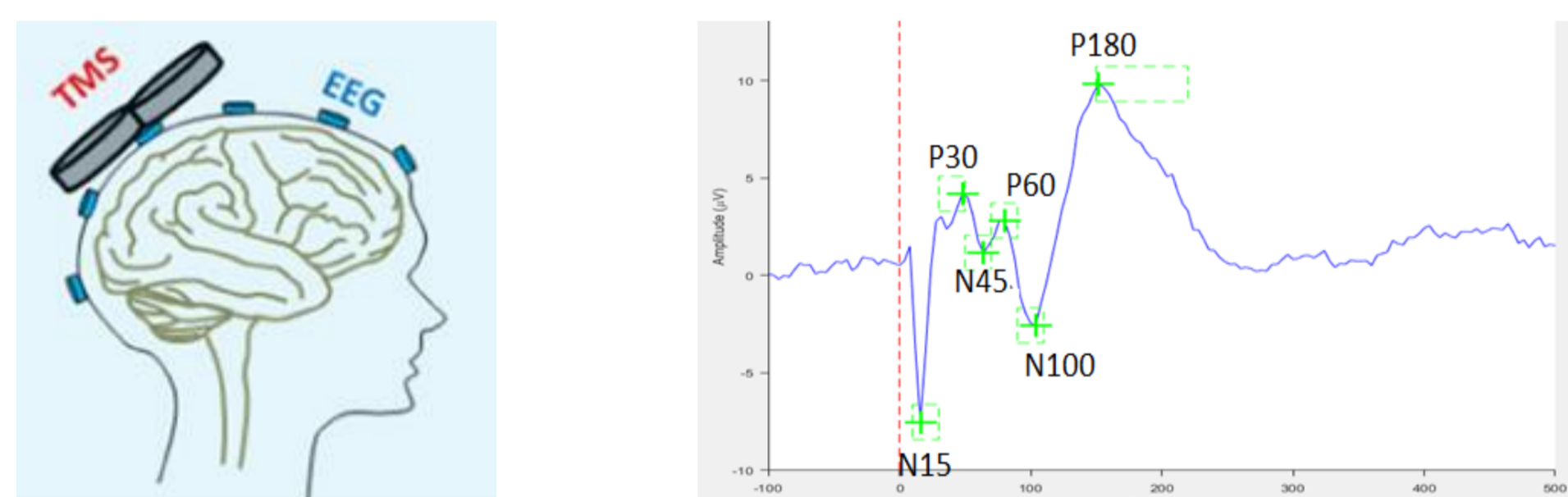

Figure 2. The TMS-EEG Methodology, and an example of a TMS-Evoked Potential produced in our lab

Methods

In this study, healthy men and women aged between 18 and 65 years will be recruited. Participants will receive an intramuscular injection of hypertonic saline to the right first interosseous (FDI) muscle of the right index finger to induce ~15 minutes of moderate muscle pain [4]. For TMS, single biphasic stimuli will be delivered to the left hemisphere. Electromyographic (EMG) activity will be recorded from the right FDI muscle. 100 MEPs will be obtained before, during, and immediately after recovery from pain. The interval between TMS pulses will be 2 seconds, thus, each block of TMS will run for 3-4 minutes. While MEPs are recorded in response to TMS, concurrent EEG activity will be recorded to obtain 100 TEPs, which has been shown to be a reliable number of trials [10]. Scalp EEG will be collected using a 64-channel EEG system. In order to obtain EEG activity *in the absence of TMS-induced brain activation*, an additional block of TMS will be included at each time point, where a sham condition is used. This sham condition will involve the use of a sham coil that produces the same clicking sound as the active coil but the magnetic field is too weak to stimulate cortical neurons. The sham condition will also involve concurrent cutaneous stimulation of the scalp to simulate the somatosensory component of the active TMS condition. Cortical excitability at each time point will be computed by subtracting the TEPs obtained on the sham TMS block from the active TMS block.
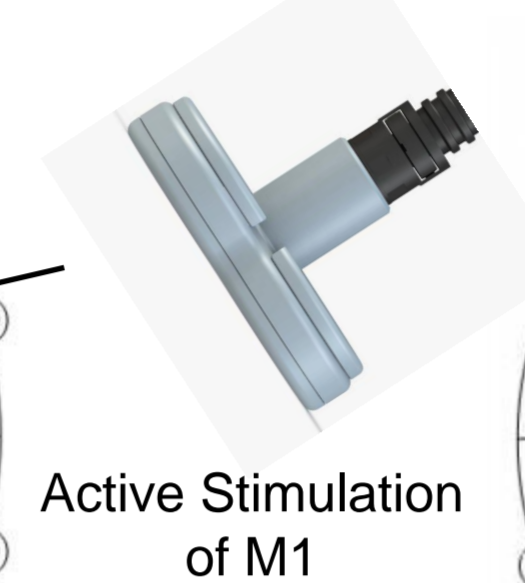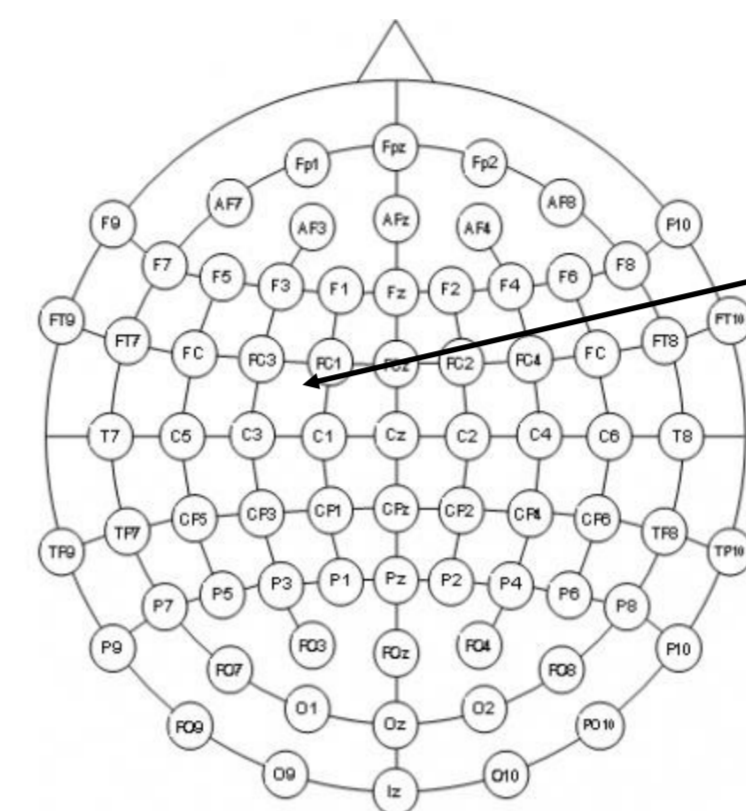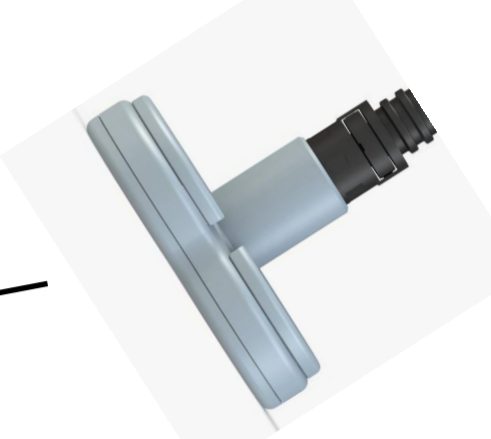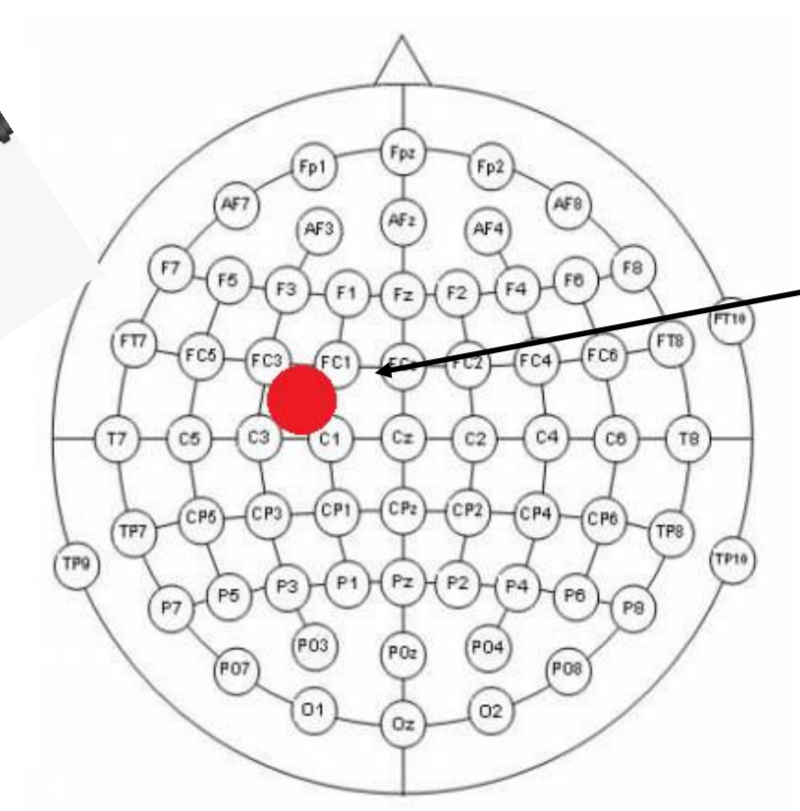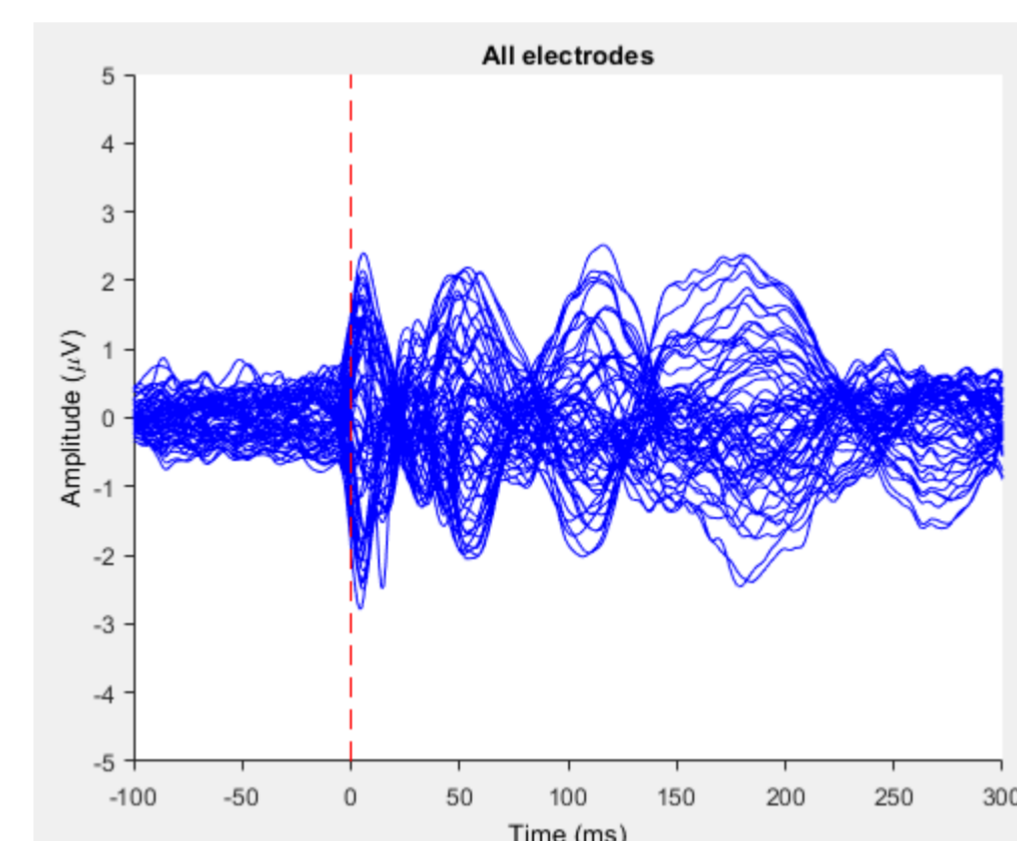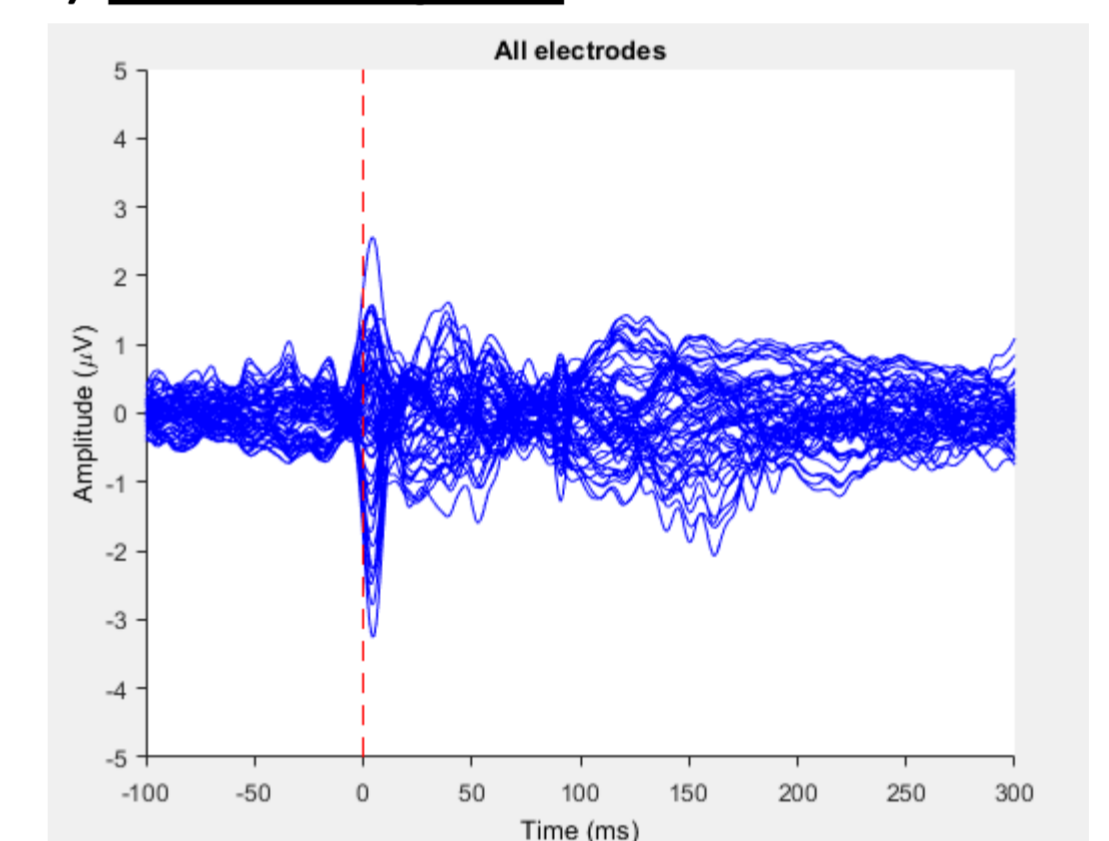
Figure 3. A) Design of the proposed experiment. B) Details of the active and sham conditions. C) Pilot data showing the response to the active stimulation and the sham stimulation without pain.

Hypotheses

Applying TMS to M1 produces several reproducible EEG components that are of specific interest to this project: the P30 and the N100 [7]. The P30 is thought to be involved in the same mechanisms as the MEP [11]. Therefor, we hypothesise the P30 amplitude will reduce during and after pain. The N100 is believed to be a marker of inhibitory neurotransmission [12] and has been implicated in suppression of motor responses [13]. As the N100 may be involved in reducing motor output, we hypothesise its amplitude will increase during and after pain.

Significance

This study will be the first to use combined TMS-EEG to index cortical excitability during pain. Using a novel methodology that has not yet been applied to pain research, this study will enrich our understanding of the neural mechanisms underlying musculoskeletal pain. The information gained has the potential to aid the discovery of novel biomarkers in pain research.

References

1. Vos, T., et al., Years lived with disability (YLDs) for 1160 sequelae of 289 diseases and injuries 1990–2010: a systematic analysis for the Global Burden of Disease Study 2010. The Lancet, 2012. 380(9859): p. 2163-2196.
2. Melzack, R., Pain and the neuromatrix in the brain. 2001. 65(12): p. 1378-1382.
3. Treede, R.-D., et al., The cortical representation of pain. 1999. 79(2-3): p. 105-111.
4. Schabrun, S.M. and P.W. Hodges, Muscle pain differentially modulates short interval intracortical inhibition and intracortical facilitation in primary motor cortex. J Pain, 2012. 13(2): p. 187-94.
5. Burns, E., L.S. Chipchase, and S.M. Schabrun, Primary sensory and motor cortex function in response to acute muscle pain: A systematic review and meta-analysis. Eur J Pain, 2016. 20(8): p. 1203-13.
6. Seminowicz, D.A., et al., Slow peak alpha frequency and corticomotor depression linked to high pain susceptibility in transition to sustained pain. 2018.
7. Farzan, F., et al., Characterizing and Modulating Brain Circuitry through Transcranial Magnetic Stimulation Combined with Electroencephalography. Front Neural Circuits, 2016. 10: p. 73.
8. Rogasch, N.C., et al., Analysing concurrent transcranial magnetic stimulation and electroencephalographic data: A review and introduction to the open-source TESA software. Neuroimage, 2017. 147: p. 934-951.
9. Miniussi, C. and G. Thut, Combining TMS and EEG offers new prospects in cognitive neuroscience. Brain Topogr, 2010. 22(4): p. 249-56.
10. Kerwin, L.J., et al., Test-retest reliability of transcranial magnetic stimulation EEG evoked potentials. Brain Stimulation, 2018. 11(3): p. 536-544.
11. Darmani, G. and U. Ziemann, Pharmacophysiology of TMS-evoked EEG potentials: A mini-review. Brain Stimul, 2019. 12(3): p. 829-831.
12. Premoli, I., et al., TMS-EEG signatures of GABAergic neurotransmission in the human cortex. J Neurosci, 2014. 34(16): p. 5603-12.
13. D'Agati, E., et al., Motor cortical inhibition in ADHD: modulation of the transcranial magnetic stimulation-evoked N100 in a response control task. J Neural Transm (Vienna), 2014. 121(3): p. 315-25.