

## Protocol for a Pilot Randomized Sham-Controlled Clinical Trial Evaluating the Feasibility, Safety, and Acceptability of Infralow Electroencephalography Neurofeedback Training on Experimental and Clinical Pain Outcomes in People with Chronic Painful Knee Osteoarthritis

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### Abstract

**Introduction:** Persistent pain is a significant contributor to disability in people living with knee osteoarthritis (KOA). Brain imaging, including electrophysiological studies, confirms altered cortical oscillatory and synchrony patterns in cognitive, affective, and somatosensory areas in individuals with KOA pain. Electroencephalography neurofeedback (EEG-NF) training is a form of neuromodulatory intervention that can help to reduce pain via normalizing dysrhythmic cortical oscillatory patterns that are linked to the pain experience. However, there is a dearth of evidence towards the efficacy of NF in individuals with musculoskeletal pain. **Aim:** The proposed research is intended to pilot the NF training protocol and assess the feasibility, safety, and acceptability of NF training in individuals with KOA and estimate the variability of experimental and clinical outcome measures following NF training. **Design:** A parallel, two-armed, double-blind (participant and assessor) pilot randomized sham-controlled clinical trial. **Methods:** Adults aged 44–75 years with a clinical diagnosis of KOA will be recruited and randomized to either active or sham EEG-NF training. Both groups will receive auditory feedback as a reward for achieving a predetermined activity threshold of the target areas of the brain. Outcome measures include feasibility measures (recruitment, randomization, retention, and dropout rates), acceptability, and adverse events; clinical measures (pain, interference, sleep, mood, and physical activity); and experimental pain outcomes (quantitative sensory testing procedures). **Discussion:** Outcomes from this study will inform the feasibility and methodology for a future randomized controlled clinical trial.

**Keywords:** EEG-neurofeedback; chronic pain; brain training; knee pain; osteoarthritis

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### Introduction

Persistent pain is a significant contributor to disability in people living with knee osteoarthritis (KOA); a

highly prevalent, chronic degenerative condition (Abbott, Usiskin, Wilson, Hansen, & Losina, 2017; Bajaj, Bajaj, Graven-Nielsen, & Arendt-Nielsen, 2001). Globally and in New Zealand, hip and knee

osteoarthritis is ranked as the 38th highest in disability-adjusted life years (DALYs) (Cross et al., 2014; Deloitte Access Economics, 2018). It is a significant burden with one in six New Zealanders affected by arthritis; 56% with the knee joint registering a higher incidence (approximately 7,000 in 2013) than the hip or any other peripheral joints.

The pathophysiology of pain due to OA changes are not fully elucidated; however, the primary triggers of nociception have been linked to synovial inflammation and bone marrow edema (Kidd, 2012). Central sensitization of pain is commonly associated with persistent musculoskeletal (MSK) pain including KOA (Woolf, 2011). Studies utilizing quantitative sensory testing observed neuropathic pain-like symptoms (pain hypersensitivity) and dysfunctional conditioned pain modulation (i.e., impaired descending nociceptive modulation) in patients with KOA (Fingleton, Smart, Moloney, Fullen, & Doody, 2015; Foucher, Chmell, & Courtney, 2019). Such symptoms suggested abnormal nociceptive processing (i.e., central sensitization) within the central nervous system (Kidd, 2012; Lee, Nassikas, & Clauw, 2011; Lluch, Torres, Nijs, & Van Oosterwijck, 2014; Martindale, Wilson, Reeve, Chessell, & Headley, 2007; Woolf, 2011). Brain imaging studies demonstrate alterations in the structural and functional organizations within the cortical and subcortical networks in various persistent pain conditions (Cottam, Iwabuchi, Drabek, Reckziegel, & Auer, 2018; Gwilym et al., 2009; Parksl et al., 2011). Such alterations have been proposed as a key factor for the maintenance of persistent pain states (Pinheiro et al., 2016; Pujol et al., 2017).

More recently, electroencephalography (EEG)-based investigations suggest that alterations in the oscillatory and synchrony of the cortical electrical activity patterns are associated with pain processing in patients with KOA (Howard et al., 2012; Ploner, Sorg, & Gross, 2017). In particular, increased amplitudes in the theta and delta frequency bands, and a corresponding decrease in the alpha and beta amplitudes, in patients with hip OA have been demonstrated (Gram et al., 2017; Pujol et al., 2017). Notably, a recent study on pain sensitization in patients with KOA demonstrates the activation of key sensory areas (primary and secondary somatosensory cortex [SSC], the posterior insula, and thalamus) and the cognitive (e.g., prefrontal lobe) and emotional areas (anterior insula [AI], anterior cingulate cortex [ACC]) of the brain (Pujol et al., 2017). Particularly, the SSC, dorsal ACC (dACC), and pregenual ACC (pgACC) are linked to the

effective functioning of the descending nociceptive modulatory system via activation of brainstem centers such as periaqueductal gray (PAG), and rostral ventromedial medulla (RVM) (Brown, El-Deredy, & Jones, 2014; Osaka, Osaka, Morishita, Kondo, & Fukuyama, 2004; Tracey & Mantyh, 2007; Vanneste, Ost, Van Havenbergh, & De Ridder, 2017; Vogt, 2005).

Normalizing abnormal cortical electrical activities have been proposed as a treatment for pain (Brown et al., 2014; Ploner et al., 2017; Tracey & Mantyh, 2007; Vanneste et al., 2017). Neurofeedback (NF) is a form of noninvasive neuromodulatory technique developed for augmenting or reducing brain activity patterns that are linked to disease states (Gaume, Vialatte, Mora-Sánchez, Ramdani, & Vialatte, 2016; Hammond, 2011). NF works under the principle of operant conditioning in which a goal-directed process of modulating one's brain signals through feedback-induced learning (Collura & Thatcher, 2011). EEG-NF is a technique designed to provide feedback on the real-time brain activity to individuals for controlling the activity of critical areas of the brain involved in a disease state. NF treatment protocols can be designed either to upregulate or downregulate the oscillations at the targeted cortical networks. Several studies have investigated the clinical effectiveness of EEG-based NF in various populations include headaches, complex regional pain syndromes (CRPS-1), chemotherapy-induced peripheral neuropathy (CIPN), central neuropathic pain in paraplegia, fibromyalgia, postoperative pain, and cancer pain (Gorini, Marzorati, Casiraghi, Spaggiari, & Pravettoni, 2015; Hassan, Fraser, Conway, Allan, & Vuckovic, 2015; Jensen, Grierson, Tracy-Smith, Bacigalupi, & Othmer, 2007; Prinsloo et al., 2018; Santoro & Cronan, 2014). These studies generally used protocols to upregulate frequencies in the higher ranges (12–15 Hz) and inhibit theta (4–7 Hz) and high beta (22–30 Hz) for reducing pain severity (Santoro & Cronan, 2014). Moreover, recent studies highlight the infraslow fluctuations (ISF) which are below 0.1 Hz across brain areas and are linked with pain experience (Ploner et al., 2017). Preclinical research highlights that the infraslow fluctuations (ISF) have the ability to influence higher oscillations at alpha and gamma frequency bands associated with persistent pain conditions (Mantini, Perrucci, Del Gratta, Romani, & Corbetta, 2007; Monto, Palva, Voipio, & Palva, 2008). Infraslow fluctuation neurofeedback (ISF-NF) is a recent development in EEG-NF training, focusing on modulating slow-wave activity (0.0–0.1 Hz). Some potential therapeutic effects of ISF-NF have been established on food craving, targeting the

posterior cingulate cortex (PCC) of the brain (Leong et al., 2018).

Pain modulation involves the dynamic interaction of a complex neuronal network of multiple functional areas of the brain. This enhances a balance between the sensory discriminative, motivational affective, and descending hubs of pain neurophysiological network (Vanneste et al., 2017). Various neurofeedback protocols have been established to target individual areas of the brain instead of targeting multiple areas of the brain. We hypothesize that using a novel ISF-NF protocol that can simultaneously downregulate the electrical activities of SSC, dACC and upregulate the pgACC could reduce both experimental and clinical pain measures in people with persistent KOA pain. To date, no ISF-NF clinical trial has been performed for any MSK pain conditions. Since the proposed ISF-NF training protocol is novel, a pilot testing of the protocol including assessing the feasibility, safety, and acceptability of ISF-NF training in individuals with KOA is warranted. Therefore, the objectives of the study are:

1. To pilot a novel ISF-NF training protocol targeting three key cortical areas associated with pain modulation in individuals with KOA.
2. To assess the feasibility, safety, and acceptability of ISF-NF training in individuals with KOA.
3. To estimate the variability of experimental and clinical outcome measures following ISF-NF training to inform the sample size of the fully powered randomized controlled trial (RCT).

## Methods

### Study Design

This is a pilot RCT involving randomization, double-blinding (participant and assessor), two-arm, parallel, sham-controlled trial. A research administrator, not involved in any treatment or assessment procedures, will randomize eligible volunteers using an open-access randomization software program, to receive either ISF-NF or sham ISF-NF. Methodological descriptions of this study followed the CONSORT 2010 checklist for reporting feasibility trial (Eldridge et al., 2016). A well-structured description of the study intervention is summarized in Table 1 based on the TIDieR (Template for Intervention Description and Replication) guide (Hoffmann et al., 2014). Ethical approval has been obtained from the Health & Disability Ethics Committee (HDEC), New Zealand (19CEN182) and the Ngāi Tahu Research Consultation Committee was consulted. The trial has been registered with Australian New Zealand Clinical Trials Registry (ACTRN12620000273987).

**Table 1**

*Description of ISF-NF intervention, as per the template for intervention description and replication.*

Item Number	Item	Description
1	<b>BRIEF NAME</b> Provide the name or a phrase that describes the intervention.	Neurofeedback training for Osteoarthritic Knee Pain
2	<b>WHY</b> Describe any rationale, theory, or goal of the elements essential to the intervention.	Patients with persistent KOA pain have demonstrated altered cortical neuronal higher frequency oscillations in pain neuromatrix that are associated with dysfunctional pain modulation. ISF below 0.1 Hz across brain areas are capable of shaping the higher oscillations at alpha (8–12 Hz) and gamma (> 30 Hz) and expected to normalize neuronal oscillations. Therefore, ISF-NF is believed to be an effective intervention to achieve normalization of altered cortical oscillations with persistent MSK pain, thereby improving clinical/experimental pain outcomes.

Item Number	Item	Description
3	<p><b>WHAT</b></p> <p><b>Materials:</b> Describe any physical or informational materials used in the intervention, including those provided to participants or used in intervention delivery or training of intervention providers. Provide information on where the materials can be accessed (e.g., online appendix, URL).</p>	<p>An ISF-NF training program will be administered with a 21-channel DC-coupled amplifier produced by BrainMaster Technologies, Inc. An EEG cap with sensors (Ag/AgCl) will be fixed to the individual's scalp, with reference electrodes placed at the mastoids.</p>
4	<p><b>Procedures:</b> Describe each of the procedures, activities, and/or processes used in the intervention, including any enabling or support activities.</p>	<p>Participants will be asked to sit on a chair in an upright position with back supported and relaxed for 10 min. Both ISF-NF and sham ISF-NF will be implemented with a 21-channel DC-coupled amplifier produced by BrainMaster Technologies, Inc. The Comby EEG lead cap with sensors (Ag/AgCl) will be fixed to the individual's scalp, with reference electrodes placed at the mastoids. The impedance of the active electrodes will be monitored through the amplifier and will be kept less than 5 k<math>\Omega</math>. Before the commencement of the training, participants will be instructed to close their eyes, relax, and listen to the sound being played. The participants will also be emphasized to minimize eyeball movement, head and neck movements, swallowing, and clenching of teeth to avoid motion artifact in EEG. A distinct tone will be played when the participant's brain activity meets infraslow magnitude at the SSC, dACC, and pgACC. Conditions for the sham ISF-NF group will be exactly the same as ISF-NF group except the participants will receive feedback according to someone else's prerecorded session.</p>
5	<p><b>WHO PROVIDED</b></p> <p>For each category of intervention provider (e.g., psychologist, nursing assistant), describe their expertise, background, and any specific training given.</p>	<p>A postgraduate student with a physiotherapy background; adequately trained to provide NF intervention.</p>
6	<p><b>HOW</b></p> <p>Describe the modes of delivery (e.g., face to face or by some other mechanism, such as internet or telephone) of the intervention and whether it was provided individually or in a group.</p>	<p>Each participant will receive face to face ISF-NF training.</p>
7	<p><b>WHERE</b></p> <p>Describe the type(s) of location(s) where the intervention occurred, including any necessary infrastructure or relevant features.</p>	<p>The intervention will be delivered in the School of Physiotherapy, University of Otago.</p>

Item Number	Item	Description
8	<b>WHEN and HOW MUCH</b> Describe the number of times the intervention was delivered and over what period of time including the number of sessions, their schedule, and their duration, intensity, or dose.	All participants either in ISF-NF or sham ISF-NF will be required to attend nine sessions (30-min each; three sessions per week; 3 consecutive weeks) of training. Assessment of clinical and EEG outcomes will be carried out at two separate sessions of 90-min duration; baseline (S1) and immediately following the final treatment session (S11).
9	<b>TAILORING</b> If the intervention was planned to be personalized, titrated, or adapted, then describe what, why, when, and how.	Intervention is personalized. All the participants will receive auditory feedback based on their real-time cortical activity recorded during the NF training. If required, manual NF threshold adjustments will be done based on the real-time electrical activity of each participant, for each session.
10	<b>MODIFICATIONS</b> If the intervention was modified during the course of the study, describe the changes (what, why, when, and how).	Not applicable. This is a protocol.
11	<b>HOW WELL</b> <b>Planned:</b> If intervention adherence or fidelity was assessed, describe how and by whom, and if any strategies were used to maintain or improve fidelity, describe them.	Intervention adherence will be maintained across each participant for every session; for both the groups. All the participants will undergo nine sessions of NF training for 30 min. The NF program is default set for 30 min of training.
12	<b>Actual:</b> If intervention adherence or fidelity was assessed, describe the extent to which the intervention was delivered as planned.	Not applicable. This is a protocol.

### Sampling and Recruitment Strategy

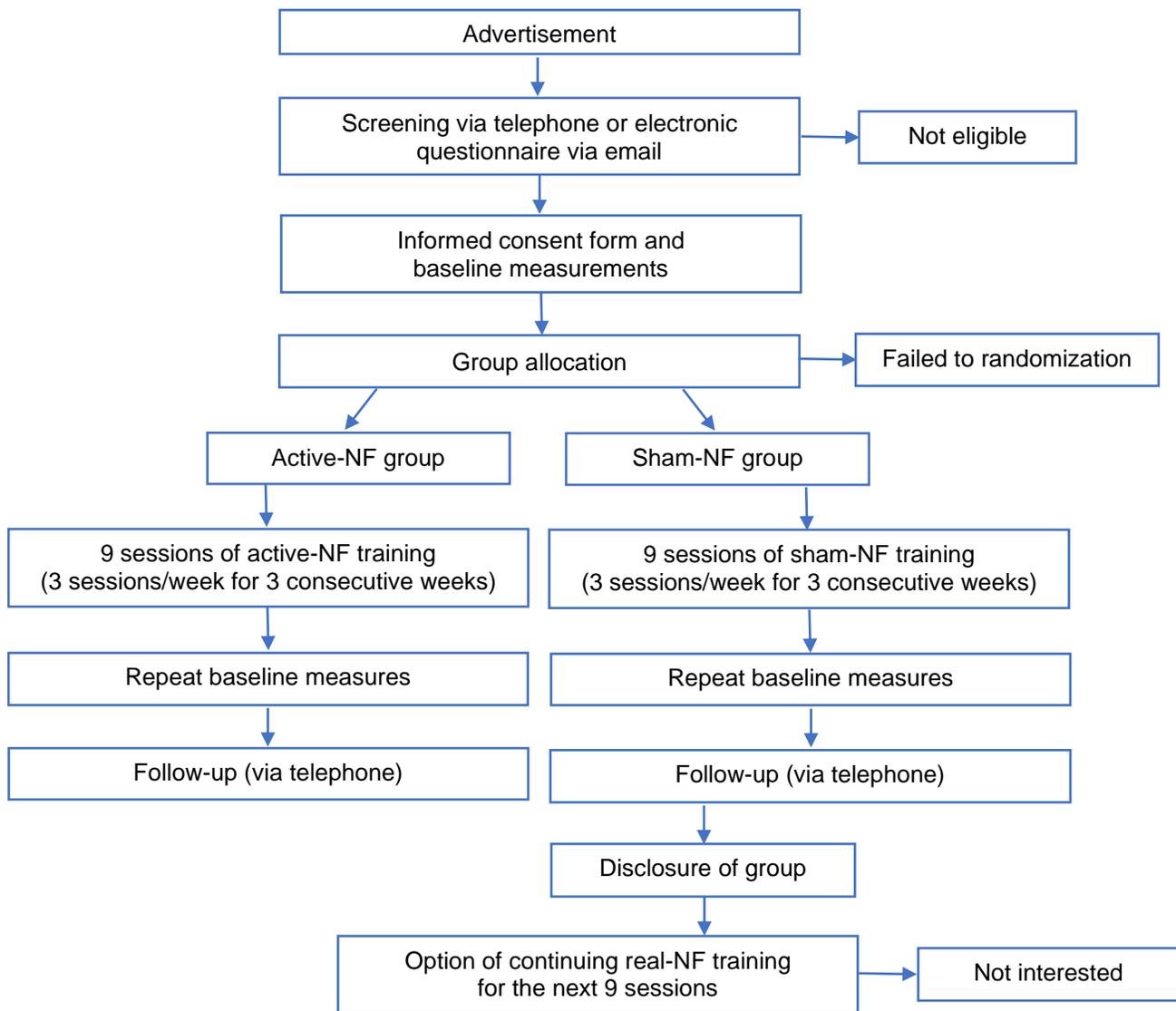
Convenience sampling technique will be used to recruit participants from the Dunedin community. Periodic advertising in newspapers and social networking sites, including emails to the staff of the University of Otago, will be carried out. Patients attending primary care medical or physiotherapy practices will be invited to participate in the study. Interested volunteers will contact the primary researcher via telephone or e-mail for screening and participation. Figure 1 represents a detailed study flow chart.

### Sample Size Estimation

Since this is a pilot/feasibility study, sample size was not determined.

### Participants

Adults aged 44–75 years, with a clinical diagnosis of KOA; with pain (at least  $\geq 4$  on an 11-point numerical rating scale) for a minimum duration of 3 months will be eligible to participate in the study (Bartley et al., 2016; Fingleton et al., 2015; Goggins, Baker, & Felson, 2005).



**Figure 1.** Diagram of participant flow for the study

The participants will be excluded if they have one of the following situations or conditions: (1) underwent surgery or other invasive procedures in the last 6 months and any surgical procedures scheduled within 8 weeks after screening; (2) undertaken any steroid injections to the knee joint in the past 3 months or on oral steroids in the previous month; (3) current intake of centrally acting medications (e.g., antidepressants, anticonvulsants, neuropathic pain drugs) or intention of taking new medications in the next 8 weeks; (4) neurological conditions or diseases (brain, spinal cord or peripheral nerve injuries, radiculopathy, and neuropathies); (5) soft tissue injuries of the knee (e.g., meniscus, muscle, tendon, or ligament injury) in the

last 3 months; (6) cognitive impairments (dementia, posttraumatic stress disorders, Alzheimer's disease); (7) difficulty or inability to read or understand English, or provide informed consent; (8) hearing problems (hearing loss, tinnitus) and ear infections; (9) pregnancy or 6 months postlabor.

#### Confirmative Screening

A paper-based Mini-Mental State Examination (MMSE) will be carried out for screening volunteers with cognitive impairments. The maximum MMSE is scored out of 30 points, and volunteers scoring a total score of 24 or below will be excluded from the study (Mani, Adhia, Leong, Vanneste, & De Ridder, 2019;

Pottie et al., 2016). Written consent will be obtained from the eligible participants. Eligible participants will be required to attend nine sessions (30 min; three sessions/week) of NF treatment (Leong et al., 2018) at the School of Physiotherapy and two 90-min sessions for undergoing baseline (S1) and postintervention assessments (S11). Participants will require to refrain from alcohol and caffeinated drinks for 24 hours prior and from food and drinks for at least one hour respectively, prior to any assessment sessions (Jobert et al., 2012).

### Baseline Assessment

Participants will complete questionnaires including demographics and general health-related information. Assessment of resting-state EEG and the clinical and experimental pain outcomes will be conducted by an independent researcher, blinded to group allocation. Resting-state EEG will be recorded using Mitsar EEG system with WinEEG software. The recording will be done for 10 min with participants' eyes closed, and the participants will be instructed to avoid any facial movements, head and neck movements, and swallowing to minimize potential artifact in the EEG recordings. At the baseline assessment, the following constructs will be measured using validated questionnaires.

**Neuropathic Pain Component.** The painDETECT questionnaire (PD-Q) will be used to identify the presence of a neuropathic pain component in their knee. The chosen tool was found to have the face and content validity for use in older individuals with KOA. The questionnaire consists of 12 items that measure pain quality rated on a 5-point Likert scale (1 = *never* to 5 = *very strongly*), pain radiation from the primary area of pain (*yes* or *no*), and pain course pattern (scored from -1 to 2). The total score ranges from -1 to 38 points with a score of  $\geq 19$  indicative of a likely neuropathic pain ( $\leq 12$ : nociceptive pain and 13–18: possible neuropathic pain component [or mixed type]; Freynhagen, Tölle, Gockel, & Baron, 2016; Mani et al., 2019).

**Sleep.** Sleep disturbance and quality will be measured using the Pittsburgh Sleep Quality Index (PSQI), a valid and reliable index for evaluating sleep quality in patients with arthritis. The PSQI consists of seven components: subjective sleep quality (one item), sleep latency (two items), sleep duration (one item), habitual sleep efficiency (three items), sleep disturbances (nine items), use of sleeping medications (one item), and daytime dysfunction (two items). The response options vary with different items. The overall score range is 0 to 21 points, with

higher scores indicating better sleep quality (Omachi, 2011).

**Coping Strategies.** A brief version (14 items) of the Coping Strategies Questionnaire (CSQ) will be used to score various pain coping strategies used by the participant. A 14-item scale is scored on a 0 to 6 scale, representing the frequency of seven pain coping strategies (adaptive strategies: Diverting Attention, Reinterpreting Pain Sensations, Ignoring Sensations, Coping Self-Statements, Increased Behavioral Activities; maladaptive strategies: Catastrophizing, Praying and Hoping). CSQ is considered to be a valid and reliable tool to use in KOA (Alschuler, Molton, Jensen, & Riddle, 2013).

**Fears and Beliefs.** The fear and beliefs concerning knee OA will be recorded on an 11-item Knee Osteoarthritis Fears and Beliefs Questionnaire (KOFBeQ) using a 10-point Likert scale (0 = *totally agree* to 9 = *totally disagree*). Higher scores indicate substantial fears and beliefs. KOFBeQ has demonstrated good test–retest reliability with an ICC of 0.81 (Benhamou et al., 2013).

**Brief Resilience Scale (BRS).** BRS is a six-item reliable and valid measure of one's ability to bounce back from stress. The BRS is scored by reverse coding items 2, 4, and 6 and finding the mean of the six items. The following instructions are used to administer the scale: "Please indicate the extent to which you agree with each of the following statements by using the following scale: 1 = *strongly disagree*, 2 = *disagree*, 3 = *neutral*, 4 = *agree*, 5 = *strongly agree*" (Windle, Bennett, & Noyes, 2011).

**Self-efficacy.** A two-item Pain Self-Efficacy (PSE) scale will be used to rate the confidence of the participant on a 7-point scale, with 0 = *not at all confident* and 6 = *completely confident* (Nicholas, 2007).

**Pain Catastrophizing Scale (PCS).** The PCS will be used to measure the extent of catastrophic thoughts about the pain. The tool consists of 13 items rated on a 5-point Likert scale that measures three dimensions of catastrophizing; rumination, magnification, and helplessness. The total score ranges from 0 to 52, where higher scores indicate greater levels of catastrophic thoughts about pain (Severeijns, Vlaeyen, van den Hout, & Weber, 2001).

**Depression, Stress, and Anxiety.** A 21-item Depression, Anxiety, and Stress Scale (DASS-21) will be used to measure three psychological constructs:

depression, anxiety, and stress over the past week. The items will be rated on a 4-point Likert scale, with a higher score indicating higher levels of depression, anxiety, and stress (Wood, Nicholas, Blyth, Asghari, & Gibson, 2010).

**Central Sensitization.** Symptoms of central sensitization will be evaluated by using Central Sensitization Inventory (CSI) questionnaire. The CSI consists of two parts—part A assesses 25 health-related symptoms common to central sensitivity syndromes, with a total score ranging from 0 to 100, and part B (is not scored) asks about previous diagnoses of one or more specific disorders, including central sensitivity syndromes (Mani et al., 2019).

**Level of Motivation.** The level of motivation with the training will be measured using an adapted version of the Questionnaire for Current Motivation-Brain Commuter Interference (QCM-BCI) recorded on a 7-point Likert scale. Participants will rate items that assess four different components of motivation: (1) *mastery confidence*, which indicates how much confidence a participant had that the training would be successful, (2) *fear of incompetence*, which indicates how much a participant feared to fail in the training, (3) *interest*, which indicates how interested the participant was in the training, and (4) *challenge*, which indicates how challenging the participant considered the training. The tool holds acceptable psychometric characteristics and widely used in BCI-incorporated research.

The following constructs will be measured at every training session.

**Mood.** The mood of the participant will be measured before every NF session using a single item of Brief Mood Introspection Scale (BMIS). The overall mood of the participant will be rated on a 21-point numeric scale, with 0 being in the center. Marking of 0–10 towards right-hand side rates *very pleasant* and 0–10 towards left-hand side rates *very unpleasant*. Cronbach's alpha reliabilities of BMIS range from 0.76 to 0.83, which was deemed to be quite satisfactory. The scale was also found to have good factor validity (Kokkonen & Pulkkinen, 2001; Mayer & Gaschke, 1988).

**Visual Analogue Scale (VAS) Motivation.** Participants will be asked to indicate their motivation on a 10 cm long horizontal line (0 = *extremely unmotivated* and 10 = *extremely motivated*) prior to every NF session (Kleih & Kubler, 2013; Kleih et al., 2011).

**Level of Engagement.** The level of engagement with the NF training session will be recorded from each participant on a 10-point Likert scale after every NF session, where 1 = *least engaged* and 10 = *highly engaged*.

### Randomization and Allocation Concealment

On the day of eligibility confirmation, a research administrator will randomize eligible volunteers using an open-access randomization software program, to receive either ISF-NF or sham ISF-NF. In order to ascertain an equal number of participants in both groups and decrease allocation bias, the concealed allocation will be done using block randomization. The administrator will prepare opaque sealed randomization envelopes containing the information for the participant regarding the allocation group and details. The envelope will be given to the participant by the assessor after the completion of the baseline assessment. Both the participants and the outcome assessor will be blinded to the group allocation.

### Interventions

During each session, participants will be asked to sit on a chair with back supported and relaxed for 10 min, which allows the trainer to prepare the participant for NF training. Both ISF-NF and sham ISF-NF will be administered using a 21-channel DC-coupled amplifier produced by BrainMaster Technologies, Inc. The Comby EEG lead cap with sensors (Ag/AgCl) will be fixed to the individual's scalp, with reference electrodes placed at the mastoids (Leong et al., 2018; Figure 2).

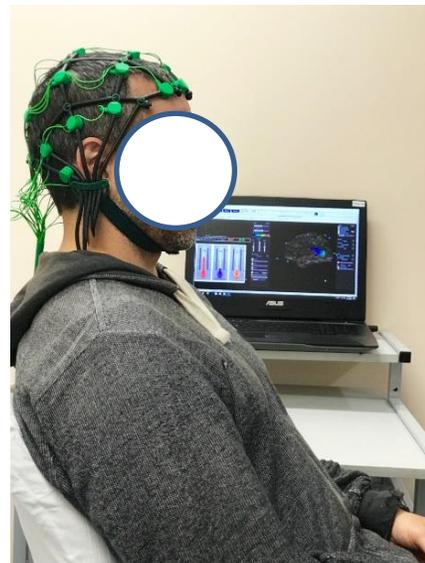


Figure 2 Intervention setup

The impedance of the active electrodes will be monitored and kept below 5 k $\Omega$ . The participants will also be emphasized to minimize eyeball movement, head and neck movements, swallowing, and clenching of teeth to minimize motion artifact in EEG.

### ISNF-NF Groups

Participants will be instructed to close their eyes, relax, and listen to the sound being played. A distinct tone will be played when the participant's brain activity meets ISF (0.0–0.1 Hz) magnitude (threshold) at the following cortical areas of the brain defined as regions of interest (ROI): SSC, dACC, and pgACC. The brain regions are chosen based on brain imaging studies on KOA and previous NF studies (Gram et al., 2017; Gwilym et al., 2009; Howard et al., 2012; Ploner et al., 2017; Pujol et al., 2017; Vogt, 2005). For the purpose of this study, the authors developed an ISF-NF program to down-train SSC and dACC activity, simultaneously with the up-training of pgACC. Efforts will be made to keep the reward threshold in real-time between 60% and 80%. In other words, for 60% to 80% of the time, a sound will be played (reward) when the participant's brain activity meets the infraslow magnitude (threshold). The chosen 60% to 80% reinforcement schedule for this study was decided based on the insights from our previous study (Leong et al., 2018) and the author's clinical experience. Reaching a predetermined threshold brain activity (activities) is a response and the reinforcement to reach the threshold is the auditory stimulus. The auditory stimulus will be delivered within 30 milliseconds when the activity threshold is met (upregulation of pgACC and downregulation of SSC and dACC). However, further improvement in the response would be dependent on how the participant responds to the reinforcement.

Standardized low-resolution brain electromagnetic tomography (sLORETA) source localization permits the section of any region of the brain for feedback on the current density (Vanneste, Joos, Ost, & De Ridder, 2018). A center voxel for each ROI is given in Table 2; where dACC and pgACC are designer ROIs and SSC ROI is made up of Brodmann areas 1, 2, 3, and 5, as defined by the Montreal Neurological Institute (MNI) coordinate database (Fuchs, Kastner, Wagner, Hawes, & Ebersole, 2002; Jurcak, Tsuzuki, & Dan, 2007).

**Table 2**

*Centre voxel coordinates for the somatosensory cortex (SSC), pregenual anterior cingulate cortex (pgACC), and dorsal anterior cingulate cortex (dACC).*

		X	Y	Z
SSC				
	Right	53	-22	49
	Left	-53	-22	49
pgACC				
	Right	4	41	36
	Left	-4	41	36
dACC				
	Right	4	6	38
	Left	-4	6	38

### Sham ISF-NF Group

Conditions for the sham ISF-NF group will be the same as ISF-NF group except the participants will receive feedback according to someone else's prerecorded session. To ensure this, we have trained healthy participants with an active NF program for nine sessions, and we captured the feedback sound using Audacity software, which is a free and open-source digital audio editor and recording application (Maheshkumar, Dilara, Maruthy, & Sundareswaren, 2016). Participants in the sham ISF-NF will be prepared as same as ISF-NF group, and they will receive these prerecorded feedback sounds. This process has been incorporated in order to record the real-time EEG of the participants undergoing NF training in the sham group. The Audacity software uses the computer's sound card as an audio to digital (A/D) converter and eliminates the additional requirement of an external microprocessor (Maheshkumar et al., 2016). The software has many offline editing options which could be used to draw the precise percent success of the participant during the training and average time of the feedback received by the participant during each training. The prerecorded signals will be selected randomly by the chit method form a set of nine files.

## Outcome Measures

### Primary Outcomes

The primary outcomes are feasibility measures and adverse events (Bowen et al., 2009; Tickle-Degnen, 2013). Feasibility outcomes from this trial include (1) recruitment rate (number of participants attending screening assessment), (2) randomization rate (a ratio of the number of participants willing to be randomized into the trial from amongst those eligible will be expressed), (3) retention rate (number of sessions attended by the participant), and (4) dropout rate (number of dropouts in each group). An adverse effect is described as any harmful sign, or symptom resulting from the trial, which could reasonably be related to the procedure. Although EEG-NF is a safe technique, participants will be asked about any adverse effects experienced from the previous session at each visit. All the participants will be instructed to complete a Discontinuation-Emergent Sign and Symptom (DESS) inventory. The DESS is a checklist of 43 symptoms, consisting of emotional, behavioral, cognitive, and physical conditions that can be considered possible side effects from NF training. The participant will report the worsening of side effects compared to the status prior to the first session. They will report “1” if the side effect worsened or a “0” if there is no change in the symptom (Rogel et al., 2015). All the participants will be asked, “Which condition do you think you received?” at the end of the third training session every week (Leong et al., 2018). Acceptability of the NF training as an intervention will be measured in the follow-up assessment (Sekhon, Cartwright, & Francis, 2017).

### Secondary Clinical Outcome Measures

The following pain, function, psychological, social, and behavioral constructs will be collected using validated questionnaires by a researcher blinded to the groups. The multidimensional constructs were chosen based on the biopsychosocial model of pain literature.

**Pain Intensity and Interference.** Brief Pain Inventory (BPI) is a valid and reliable questionnaire developed to measure the severity of pain and the impact (interference) of pain on daily functions. BPI includes three pain severity items (pain worst, pain average, and pain now) and the seven interference items (how pain interferes with activity, mood, relations with others, walking ability, work, enjoyment of life, and sleep) rated on an 11-point (0 to 10) numeric scale (Keller et al., 2004; Mendoza, Mayne, Rublee, & Cleland, 2006).

**Pain Unpleasantness.** (Affective component) will be measured using an 11-point VAS-unpleasantness scale, with 0 = *not at all pleasant* and 10 = *most unpleasant imaginable* (Price, Bush, Long, & Harkins, 1994; Starr et al., 2011).

**Pain Bothersomeness.** Participants will be asked about the bothersomeness of their knee pain with a categorical question:

“In the last one week, how bothersome has your knee pain been?”

“In the last 24 hours, how bothersome has your knee pain been?”

Here will be five possible responses: *not at all, slightly, moderately, very much, and extremely*. The bothersome domain is modified and incorporated from outcome measures in low back pain (Dunn & Croft, 2005; Price, McGrath, Rafii, & Buckingham, 1983).

**Physical Function, Physical Activity, and Participation.** Knee injury and Osteoarthritis Outcome Score (KOOS) is a 42-item self-reported questionnaire that has five reported dimensions: pain (9 items), other symptoms (7 items), function in daily living (17 items), function in sport and recreation (5 items), and knee-related quality of life (4 items). The scoring system of the KOOS utilizes a 5-point Likert scale, with anchors of zero (*no problems*) to 4 (*extreme problems*). Scores are transformed to a 0 to 100 scale, with zero representing extreme knee problems and 100 representing no knee problems. This transformed score is calculated using the following formula:  $100 - [(actual\ raw\ score \times 100) / possible\ raw\ score\ range]$ . KOOS holds clinically acceptable psychometric properties (Peer & Lane, 2013). Physical activity levels, sedentary behaviour, and social participation will be captured using validated questionnaires.

**Physical Performance Measure.** Based on the Osteoarthritis Research Society International (OARSI) recommendations a 30-s chair stand test will be performed for every participant. The maximum number of chair stand repetitions possible in a 30-s period will be noted (Dobson et al., 2013).

### Experimental Pain Outcomes Measures

The following quantitative sensory testing (QST), and activity-related pain protocols including tactile acuity and body schema assessments will be performed. All

these experimental pain and sensory outcomes will be measured in S1 and S11.

**Pressure Pain Threshold (PPT).** A computerized algometer (AlgoMed; Medoc Ramat Yishai, Israel) will be used for measuring PPT at the most symptomatic region over the symptomatic knee and over the dorsal distal forearm. Two familiarization trials will be performed at the mid-forearm before the formal trials. The 1-cm<sup>2</sup> algometer probe will be pressed over the marked test sites perpendicularly to the skin at a rate of 30 kPa/s. The participants will be instructed to press the algometer trigger button in the patient control unit when the pressure sensation changed to first sensation of pain. PPT will be measured thrice at each location and the mean of three measurements will be used for the analysis. Familiarization trial will be carried out on the forearm of the participant (Rolke et al., 2006).

**Mechanical Temporal Summation (MTS).** MTS will be assessed using a nylon monofilament (Semmens monofilament 6.65, 300 g) at the patella of the index knee and the back of the ipsilateral hand, in randomized order. Participants will be instructed to provide a verbal 0–100 (NRS) rating of pain following a single contact of the monofilament on the test site. Subsequently, participants will be instructed to provide another 0–100 rating of their highest pain intensity experience following a series of 10 contacts with an interstimulus interval (ISI) of 1 s (one contact per second). This procedure will be repeated thrice at each anatomical location. For each trial, MTS will be calculated as the difference between the NRS rating after the first contact and the highest pain rating after the 10th contact. An average of the three trials will be taken for pain rating, with a positive score indicating an increase in MTS (Goodin et al., 2014; Mani et al., 2019).

**Conditioned Pain Modulation (CPM).** Studies have demonstrated disruption of descending pain inhibition in individuals with persistent OA pain. Conditioned pain modulation (CPM) is a method of examining pain inhibitory mechanisms, by applying a noxious stimulus at a remote site, that causes inhibition of pain at the affected knee. Recent recommendations on the practice of CPM testing will be followed after 15 to 20 minutes of MTS procedure. Suprathreshold (pain40) PPT will be measured at the painful knee using a 1 cm<sup>2</sup> probe, applied at a rate of 30 kPa/s until the participant reported a change from the pressure to a pain intensity of 40 out of 100 on the NRS. The pressure threshold at which the subject reported pain will be recorded and the average PPT from three trials

will be calculated, with a 30-s time interval between trials. CPM will be established using a cold pressor test on the contralateral hand of the painful knee. The participant will be instructed to immerse their hand up to the wrist crease in a circulated cold water bath, maintained at the temperature at  $-6 \pm 1^\circ\text{C}$ , for a maximum period of 2 minutes. The participant will report their pain intensity on NRS during immersion (every 15 s) and immediately after removing the hand from the cold bath. Total immersion time will be recorded. Three PPT (P40) trials will be measured at 30, 60, and 90 seconds after immersing the hand. A percentage score will be established for each time point of CPM measurement with a positive score indicating an increase in PPTs (pain4) after the conditioning stimulus and thus presence of CPM effect (Lewis, Luke, Rice Rome, & McNair, 2012; Mani et al., 2019; Nir & Yarnitsky, 2015; Yarnitsky et al., 2015). Participants with cardiovascular conditions, cold-sensitive conditions, and peripheral vascular diseases (PVD), involving the extremities will refrain from CPM testing.

**Cold Hyperalgesia.** Sensitivity to cold will be tested by massaging the knee area with an ice cube, for 30 s. Following, the participants will be asked to rate their pain on a 100 mm pain VAS, with 0 mm indicative of no pain at all and 100 mm indicative of the worst pain imaginable (Tilley & Bisset, 2017).

**Vibration Detection Threshold (VDT).** Ability to detect vibration will be tested using a tuning fork (64 Hz, 8/8 scale) placed on the medial tibial condyle with suprathreshold vibration intensity and kept there until the participant could no longer feel the vibration. On a 0 to 8 scale measuring the intensity of vibration, with high intensity indicating high sensitivity. The VDT will be determined as the arithmetic mean of three consecutive measurements (Jakorinne, Haanpää, & Arokoski, 2018; Panosyan, Mountain, Reilly, Shy, & Herrmann, 2016).

**Tactile Acuity.** Repeated light touches of a blunt tip plastic caliper tool, increasing and decreasing the distance (in mm) of two points to determine the two-point discrimination threshold (TPD). TPD is defined as the shortest distance between caliper points at which the participant could clearly detect two points instead of one. TPD will be measured 2 cm medial of the medial border of the patella (using the tibiofemoral joint line as a reference point; Stanton et al., 2013).

**Body Part Recognition Task.** An iPad/tablet application (Recognise) will be used to record the performance accuracy on determining the left and

right judgment of the image (a body part) appears on the screen. Participants will be required to perform the task as quickly and as accurately as possible. Accuracy of the judgment will be computed in percentage and will be generated by the software, with three trials (Stanton et al., 2013).

**Sensitivity to Physical Activity (SPA).** Literature has highlighted the importance of activity-related pain among individuals suffering from KOA. Commonly, the SPA is associated with weight-bearing activities like walking and stair climbing. A 6-min walk test (6MWT) will be performed to evaluate the level of knee discomfort on a 0 (no discomfort) to 100 (extreme discomfort) numeric scale. This is believed to capture a wider range of unpleasant activity related to sensation, not limited to pain sensation. Participants will be instructed to cover as many laps as they can walk in 6 min. Participants will be asked to rate their discomfort seven times in relation to each walking task, once immediately before the task and once after each minute of walking. An index of SPA will be calculated by subtracting participants' first ratings from their peak ratings for each trial (S1 and S11). SPA scores will then be averaged across both trials (Wideman et al., 2014).

### Follow-up

All the participants will be contacted by phone call or email (mode preferred by the participant) after 2 weeks of the final assessment and pain intensity (BPI), pain bothersomeness, pain unpleasantness (VAS) and status with the adverse events (if any on DESS) will be recorded.

### Data Analysis

Feasibility, acceptability, and adverse events over the NF will be summarized descriptively. Means and standard deviations (or medians) of the clinical (pain and function) and experimental outcome measures (PPT, MTS, CPM) for each group will be derived.

Standardized low-resolution brain electromagnetic tomography (sLORETA) software will be used to perform a voxel-by-voxel analysis (comprising 6239 voxels) for the different frequency bands of the current density distribution to identify potential differences in brain electrical activity. Nonparametric statistical analyses of functional sLORETA images (statistical nonparametric mapping: SnPM) will be performed for each contrast using sLORETA's built-in voxel-wise randomization tests (5,000 permutations) and employing a log-F-ratio statistic for independent groups with a threshold  $p < .05$  to

compute the cortical three-dimensional distribution of current density (Leong et al., 2018; Tanaka et al., 2019). Current density, power to power nesting, whole brain analysis, and functional connectivity will be established based on the data availability.

### Discussion

This study will pilot test the novel ISF-NF training protocol and assess the feasibility of conducting a randomized sham-controlled clinical trial using the novel ISF-NF training protocol targeting multiple areas of the brain in people with chronic KOA pain. To our knowledge, for the first time, this study will use the ISF frequency range for influencing higher frequency cortical oscillations in the brain areas associated with pain modulation. The results of this pilot RCT will provide feasibility and safety data including the level of acceptability of NF intervention by study participants. Such data will be used to design a definitive randomized controlled clinical trial.

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