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Non-invasive brain stimulation interventions for management of chronic central neuropathic pain: a scoping review protocol

Mei Lin Chen[1], Lin Yao[1], Kathryn Mercer[2], Benjamin Thompson[3], Ning Jiang[1]*
[1]Department of Systems Design Engineering, Faculty of Engineering, University of Waterloo, Waterloo, Canada
[2]School of Pharmacy, University of Waterloo, Waterloo, Canada
[3]Optometry and Vision Science, University of Waterloo, Waterloo, Canada
*Corresponding author: Tel: +1 519 888 4567 x 33677; fax: +1 519 888 4567 x 32600. Postal code: N2L 3W8. E-mail: ning.jiang@uwaterloo.ca

Key Words: Brain-computer interface, neuropathic pain, non-invasive brain stimulation, pain management

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ABSTRACT

Introduction

Pain is a common condition that affects people regardless of age, gender, or ethnicity. Chronic central neuropathic pain (CCNP) is a debilitating condition that affects populations such as stoke survivors, amputees, spinal cord injury patients, and multiple sclerosis patients, with prevalence rates between 30~80%. This condition occurs as a direct consequence of to a lesion or disease affecting the somatosensory system. CCNP is notoriously drug resistant, and few effective treatment or management strategies for it exist. The emergence of non-invasive brain stimulation and neuromodulation techniques provide novel avenues for managing chronic central neuropathic pain. To systematically identify the effectiveness of non-invasive brain stimulation techniques for treating and managing chronic central neuropathic pain. To be included in this review, papers must include one or more non-invasive brain stimulation interventions for treating or managing chronic central neuropathic pain.

Methods and analysis

The following database will be searched systematically: PubMed, EMBASE, Cumulative Index to Nursing and Allied Health Literature (CINAHL), IEEE, ACM, and Scopus. Additional literature will be identified by searching the reference lists of identified studies. Studies identified will include reviews, original research, published, and grey literature. Two reviewers will independently screen identified studies for final inclusion. A quantitative analysis on the intervention type, application and efficacy will be synthesized along with a qualitative analysis to describe the effectiveness of each intervention.

Ethics and dissemination

There are no primary data collected, hence there will be no need for formal ethical review. The results of the scoping review will be presented at relevant national and international conferences, published in a peer-reviewed journal and proposed to the stakeholders with plain language to be posted on their websites. This scoping review will provide a solid foundation to guide the development of future primary research on CCNP.

Strengths and limitations of this study

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- This study protocol provides an overview of the current status of the field to inform the development of active stimulation interventions for the management of chronic neuropathic pain
- It identifies gaps in research and the translation of research results into clinical practice
- It is specific to active stimulation interventions, excluding pharmacotherapy interventions

INTRODUCTION

Pain can be beneficial in warning us of harm, however chronic pain impacts the quality of life, resonating through families and employers in society at large [1], [2]. The feeling of pain stems from specialized high-threshold sensory neurons (primary nociceptors) detecting noxious stimuli, followed by the transfer of action potential to the dorsal horn of the spinal cord, and onwards to the thalamus and corticolimbic centres of the brain [3]–[5]. However, pain that occurs after damage to the nervous system (e.g. peripheral nerves, the dorsal root, or the central nervous system) [6] is called neuropathic pain. This type of pain occurs in the absence of potentially harmful stimuli due to reduced nociceptive thresholds that cause normally innocuous stimuli to produce pain [3], [4], [7]. A newly formulated definition of neuropathic pain by International Association for the Study of Pain is: "pain arising as a direct consequence of a lesion or disease affecting the somatosensory system" [4].

The burden of disability associated with neuropathic pain is substantial, including cost, time and quality of life [8]. Health-related quality of life in patients with neuropathic pain is comparable to that experienced by those with conditions such as cancer or chronic heart failure [9]. Chronic pain involves health care costs for Canada that exceed $6 billion per year, and productivity costs at $37 billion per year [10]. Further, an analysis of a large United States insurance database revealed that healthcare costs of patients with neuropathic pain were three times greater than those of age- and sex-matched claimants without neuropathic pain [11].

There is currently no treatment to prevent the development of neuropathic pain following injury to the somatosensory system, nor to adequately, predictable, and specifically control it when it is established. Pharmacotherapy for neuropathic pain has been generally disappointing [12]–[15]; neuropathic pain patients do not respond well to non-steroidal anti-inflammatory drugs, and resistance or insensitivity to opiates is common [2], [16], [17]. Pharmacological treatments include tricyclic or serotonin and norepinephrine uptake inhibitors, antidepressants, and anticonvulsants, which all have limited efficacy and undesirable side-effects [2], [12]. Ancillary treatments such as physical and psychological therapies are often used to help patients cope with pain, although they are less effective for severe pain [13].

Alternatively, a number of non-invasive brain stimulation techniques are increasingly proposed either as substitute for or in addition to current medical therapies [13]. Non-invasive brain stimulation techniques include: transcranial direct-current stimulation (tDCS) [18], transcranial magnetic stimulation (TMS), and repetitive transcranial magnetic stimulation (rTMS) [13], [19], [20]. These techniques vary greatly in their mechanisms and rationale, but they are all adjustable and reversible [13]. There also exists equivocal evidence among these methods of intervention. For example, some reports indicated that rTMS is able to produce long lasting pain relief [19] while some found contradictory evidence stating that its effects are uncertain [21].

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This shows the need for a systematic overview of the existing evidence to support further research. There are currently no reviews that synthesize the evidence for non-invasive brain stimulation techniques for chronic central neuropathic pain. This scoping review will fill this gap in research by summarizing the extent, efficacy, and clinical application of current non-invasive brain stimulation interventions for chronic central neuropathic pain, distilling the existing research to support the future development of primary research [22], [23].

AIM

This article describes a protocol for a scoping review which will locate, summarize, and report literature that informs the current and proposed non-invasive brain stimulation interventions for chronic central neuropathic pain, as well as identify areas to direct future research.

The scoping review will:

1. Review the extent, range, and nature of peer reviewed literature that has examined or evaluated the non-invasive brain stimulation techniques for chronic central neuropathic pain in technology and medical databases;
2. Review the extent and nature of a sampling of non-peer reviewed non-invasive brain stimulation interventions for chronic central neuropathic pain from key organizational websites, professional regulatory bodies, and special interest organizations and disease specific groups.

METHODS AND ANALYSIS

Our scoping team of reviewers will be multi-disciplinary, comprising clinician-researchers, engineering researchers and health researchers. Consistent with the broad scope of interest of the research team, the scoping review methodology laid out by Arksey and O'Malley [23] and further clarified by Levac *et al* [22] will be used. The approach will review the existing literature, and provide transparency, reproducibility and utility within this protocol [24].

Identifying Research Question

The research question was framed by assimilating themes from the preliminary searches and opinions were sought from experts in the field of pain rehabilitation and neurotechnology. Using a concept, target population and outcomes of interest approach, we formulated a broad research question: "What are the nature, adherence, extent, efficacy, exposure, quality of delivery and clinical application of non-invasive brain stimulation techniques currently used and proposed in managing chronic central neuropathic pain?".

Eligibility criteria

The following inclusion criteria were used to guide the search and will be used when reviewing articles:

- Published in the English language
- Human subjects
- Years of Publication: none specified
- All age groups
- Articles that include at least 1 non-invasive brain stimulation intervention

Exclusion criteria

- Commentaries

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- Editorials
- Narrative reviews
- Books and book chapters
- Lectures and addresses
- Animal studies

Types of Study

Meta-analysis, systematic reviews, randomized control trials, cohort studies, case control studies, case series/case reports, cross sectional trials, and editorials.

Databases

Published studies will be identified from the following electronic database: PubMed, EMBASE, Cumulative Index to Nursing and Allied Health Literature (CINAHL), IEEE, ACM, and Scopus. Additional literature will be identified by hand searching the reference list of identified eligible studies and as well through identified grey literature sources.

Search Strategy

The in-depth search strategy has been developed in each of the six databases to capture the broad literature on the topic. In order to maximize the sensitivity of the search, the following steps will be taken: consult with experts in the field; search in clinical trials registers, conference proceedings, selected grey literature such as PhD theses; perform forward and backward citation tracking; contact the websites of key organizations; and hand-search journal references.

Study Selection

Study screening will be reported and guided according to Levac *et al.*'s framework and the reporting will follow the Preferred Reporting Items for Systematics Reviews and Meta-analyses' (PRISMA) checklist, and will be performed in four major stages [25]. First, search results will be merged and duplicates will be removed via reference management software (EndNote V.X5). Second, a data extraction form based on the eligibility criteria described above will be developed by the research team. Third, a pilot test of this data extraction form will be performed: two reviewers will independently screen the first 25 titles, abstracts and grey literature of retried publications according to the eligibility criteria by using the data extraction form. Fourth, all eligible studies and those classified as unclear (needing more information) will be reviewed in full-text by each reviewer independently to determine if all inclusion criteria are met and if the article is to be included in the study. Inter-rater agreement will again be calculated on a random sample of 25 articles. Disagreement on study eligibility will be discussed and resolved with a third reviewer.

Data extraction

A customised data extraction form will be constructed to extract all relevant data from each study. Two reviewers will use the form to extract data from the first 15 eligible articles. Then they will meet to compare consistency of data extraction and coding. Clarification and update of extraction form will be an iterative process until all authors reach consensus on the final version. The data extraction form will be piloted on a few of the eligible studies to evaluate its reliability in capturing the study data of interest. Data extraction will be undertaken independently by two reviewers according to the extraction form.

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Descriptive summary tables will be produced to recapitulate the evidence base. The following data will be extracted:

- Author(s) and date;
- Geographical location;
- Research design;
- Aim;
- Research question;
- Methods;
- Settings;
- Participants (total number, mean age, gender if available);
- Primary cause of pain;
- Pain characteristics;
- Intervention studied/proposed;
- Intervention rationale/mechanism;
- Intervention extent;
- Intervention number, length, and frequency of implementation;
- Attitude towards intervention;
- Patient response, participation, and enthusiasm in intervention;
- Simultaneous interventions (if applicable);
- Neuropathic pain comorbidities;
- Key findings;
- Research gaps identified.

Other variables may be added when revising and updating the data extraction form after analysis of the first 15 eligible articles.

Data Synthesis

An initial map will be developed to explore the interventions available for chronic central neuropathic pain. The findings will be quantitatively and qualitatively synthesized for all identified interventions. The quantitative synthesis will comprise of numerical counts such as number of interventions by setting, and by its application. A qualitative description approach will be used to describe the characteristics of each intervention (i.e., definition of intervention, mechanism, efficacy, side-effects, frequency of use, feasibility). This overall synthesis of stimulation interventions will allow a thorough description of the current state and trends of using non-invasive brain stimulation to manage chronic central neuropathic pain, and identify gaps and support the future development of primary research.

ETHICS AND DISSEMINATION

There are no primary data collected, hence there will be no need for formal ethical review. The results of the scoping review will be presented at relevant national and international conferences, published in a peer-reviewed journal and proposed to the stakeholders with plain language to be posted on their websites.

CONCLUSION

This scoping review will map the key concepts and insights of the current field of active stimulation interventions for treating and managing chronic central neuropathic pain. It will also

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provide a comprehensive evaluation of current methodologies and identify gaps for future research, and share the key research findings with relevant stakeholders.

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AUTHOR CONTRIBUTIONS

Designed the scoping review protocol: MLC KM. Performed literature search: MLC LY KM BT NJ. Contributed analysis tools: LY BT NJ. Wrote the paper: MLC. Proofread manuscript: MLC LY KM BT NJ.

We have read and understood BMJ policy on declaration of interests and declare that we have no competing interests.

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Non-invasive brain stimulation interventions for management of chronic central neuropathic pain: a scoping review protocol

Mei Lin Chen[1], Lin Yao[1], Kathryn Mercer[2], Benjamin Thompson[3], Ning Jiang[1]*
[1]Department of Systems Design Engineering, Faculty of Engineering, University of Waterloo, Waterloo, Canada
[2]School of Pharmacy, University of Waterloo, Waterloo, Canada
[3]Optometry and Vision Science, University of Waterloo, Waterloo, Canada
mlchen@uwaterloo.ca, lin.yao@uwaterloo.ca, kmercer@uwaterloo.ca, ben.thompson@uwaterloo.ca, ning.jiang@uwaterloo.ca
*Corresponding author: Tel: +1 519 888 4567 x 33677; fax: +1 519 888 4567 x 32600. Postal code: N2L 3W8.

ABSTRACT

Introduction

Pain can affect people regardless of age, gender, or ethnicity. Chronic central neuropathic pain (CCNP) is a debilitating condition that affects populations such as stoke survivors, amputees, spinal cord injury patients, and multiple sclerosis patients, with prevalence rates between 30~80%. This condition can be caused by a lesion or disease affecting the somatosensory system. CCNP is notoriously drug resistant, and few effective CCNP treatment or management strategies exist. The emergence of non-invasive brain stimulation and neuromodulation techniques provide novel avenues for managing chronic central neuropathic pain. This scoping review aims to systematically identify the methods and effectiveness of non-invasive brain stimulation techniques for treating and managing chronic central neuropathic pain.

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Strengths and limitations of this study

- This study protocol provides an overview of the current status of the field to inform the development of a scoping review of non-invasive brain stimulation interventions for the management of chronic central neuropathic pain
- The scoping review will identify gaps in research and in the translation of research results into clinical practice
- The scoping review is specific to active stimulation interventions, excluding pharmacotherapy interventions

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- A limitation is that this a scoping review that aims to explore the field for existing and novel methods rather than a systematic review that seeks to answer a specific question

Key Words: Brain-computer interface, neuropathic pain, non-invasive brain stimulation, pain management
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INTRODUCTION

Pain is a critical mechanism for harm prevention. However, the experience of chronic pain can dramatically reduce one's quality of life, affecting the individual, their families and society at large [1], [2]. The feeling of pain is understood to stem from specialized high-threshold sensory neurons (primary nociceptors) for detecting noxious stimuli. These neurons connect to the dorsal horn of the spinal cord, then to the thalamus and the corticolimbic centres of the brain [3]–[5]. The pain that results due to damage to the nervous system (e.g. the peripheral nerves, the dorsal root, or the central nervous system) is termed neuropathic pain [6]. Neuropathic pain can occur in the absence of potentially harmful stimuli due to reduced nociceptive thresholds that cause normally innocuous stimuli or the body's natural activities to produce pain [3], [4], [7]. The International Association for the Study of Pain define neuropathic pain as: "pain arising as a direct consequence of a lesion or disease affecting the somatosensory system" [4].

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Alternatively, a number of invasive and non-invasive stimulation techniques are increasingly being proposed either as substitute for or in combination with current medical therapies [13]. Peripheral stimulation techniques include: transcutaneous electrical nerve stimulation (TENS) and nerve root stimulation (NRS). TENS involves surface electrodes placed over the painful area or its associated nerve, delivers stimulation at high frequency and low intensity to activate the Aβ afferents and evoke paresthesia in the pain area, providing short term (20-30 min) pain relief in accordance with the gate-control theory [13]. NRS involves implantation of an electrode in the root exit from the spine. These peripheral stimulation techniques provide only temporary pain relief which lasts for the duration of the stimulation [13]. Other invasive stimulation techniques

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include: spinal cord stimulation (SCS), deep brain stimulation (DBS), and motor cortex stimulation (MCS). These procedures involve the implantation of a stimulating device into their respective target areas: SCS targets the posterior thoracic space of the thoracic or cervical spine; DBS targets the sensory thalamus or periventricular gray matter; and MCS targets the motor cortex. The effectiveness of these invasive techniques varies significantly across patients [18] and their mechanisms of action are unclear [19]. Further, the techniques are only applicable to patients who can safely undergo surgery [13].

Examples of non-invasive brain stimulation techniques include: transcranial direct-current stimulation (tDCS) [20], [18], and repetitive transcranial magnetic stimulation (rTMS) [13], [21], [22]. Both stimulation techniques are adjustable and reversible [13]. tDCS has shown promising results in inducing cortical-plasticity with clinical benefits [23]. It passes a weak (commonly≤ 2mA) monophasic electric current to the cerebral cortex through the scalp, modifying neuron membrane excitability, leading to neuroplasticity [23]. A single tDCS session can induce transient cortical effects, but daily sessions may induce longer-lasting effects [23]. For rTMS, the stimulation is applied using a magnetic stimulation coil placed against the head. A rapidly changing magnetic field is induced in the coil that generates an electrical current in the cortical area below the coil. rTMS has been found to affect neuropathic pain processing [13], [24]. The clinical effects are modest and short-lasting from a single session, [13] but repeated sessions may cause greater and longer-lasting effects. There exists equivocal evidence and differing perspectives on the effects of rTMS – for instance, one study suggests that rTMS can produce long-lasting pain relief [21], while anther states that its effects are uncertain and may be mediated by other factors such as mood [25]. Given that non-invasive brain stimulation may relieve neuropathic pain, and the effect size is modest, there is significant heterogeneity between studies that should be further investigated [26].

There is a need for a systematic overview of the existing evidence to support further research. Previous reviews have been done to gather the research evidence on isolated topics and NIBS techniques for specific conditions. However, a broad scoping review with a clear search strategy is needed to scope the wide-ranging evidence for non-invasive brain stimulation techniques for chronic central neuropathic pain. This scoping review will fill this gap by summarizing the breadth, depth, and clinical applications of current non-invasive brain stimulation interventions for chronic central neuropathic pain, distilling the existing research to support the future development of primary research [27], [28].

AIM

This article describes a protocol for a scoping review which will locate, summarize, and report literature that informs the current and proposed non-invasive brain stimulation interventions for chronic central neuropathic pain, as well as identify areas to direct future research.

The scoping review will:

1. Review the breadth and depth of peer reviewed literature that has examined or evaluated the application of non-invasive brain stimulation techniques to chronic central neuropathic pain in technology and medical databases;
2. Review the extent and nature of a sampling of non-peer reviewed non-invasive brain stimulation interventions for chronic central neuropathic pain from key organizational

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websites, professional regulatory bodies, and special interest organizations and disease specific groups.

METHODS AND ANALYSIS

Our scoping team of reviewers will be multi-disciplinary, comprising of clinician-researchers, engineering researchers and health researchers. The scoping review methodology laid out by Arksey and O'Malley [28] and further clarified by Levac *et al* [27] will be used. The approach will review the existing literature, and provide transparency, reproducibility and utility within this protocol [29].

Identifying the Research Question

The research question was framed by assimilating themes from preliminary searches and opinions were sought from experts in the field of pain rehabilitation and neurotechnology. Using a concept, target population and outcomes of interest approach, we formulated a broad research question: "What are the nature, adherence, extent, efficacy, exposure, quality of delivery and clinical application of non-invasive brain stimulation techniques currently used and proposed in managing chronic central neuropathic pain?".

Eligibility criteria

The following inclusion criteria were used to guide the search and will be used when reviewing articles:

- Published in the English language
- Human subjects (healthy participants and pain patients)
- Years of Publication: none specified
- All age groups
- Articles that include at least 1 non-invasive brain stimulation intervention

Exclusion criteria

- Commentaries
- Editorials
- Narrative reviews
- Books and book chapters
- Lectures and addresses
- Animal studies

Types of Study

Meta-analysis, systematic reviews, randomized control trials, cohort studies, case control studies, case series/case reports, and cross sectional trials.

Databases

Published studies will be identified from the following electronic database: PubMed, EMBASE, Cumulative Index to Nursing and Allied Health Literature (CINAHL), IEEE, ACM, and Scopus. Additional literature will be identified by hand searching the reference list of identified eligible studies and as well through identified grey literature sources.

Search Strategy

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The in-depth search strategy has been developed in each of the six databases to capture the broad literature on the topic. In order to maximize the sensitivity of the search, the following steps will be taken: consult with experts in the field; search in clinical trials registers, conference proceedings, selected grey literature such as PhD theses; perform forward and backward citation tracking; contact the websites of key organizations; and hand-search journal references.

Please see a sample search strategy in PubMed as follows:
("neuralgia"[MeSH Terms] OR "neuralgia"[All Fields] OR ("neuropathic"[All Fields] AND "pain"[All Fields]) OR "neuropathic pain"[All Fields]) AND ("therapy"[Subheading] OR "therapy"[All Fields] OR "treatment"[All Fields] OR "therapeutics"[MeSH Terms] OR "therapeutics"[All Fields]) OR ("Brain Stimul"[Journal] OR ("brain"[All Fields] AND "stimulation"[All Fields]) OR "brain stimulation"[All Fields]) OR (non[All Fields] AND invasive[All Fields]) AND (Clinical Trial[ptyp] AND "humans"[MeSH Terms] AND English[lang]).

Study Selection

Study screening will be reported and guided according to Levac *et al.*'s framework and the reporting will follow the Preferred Reporting Items for Systematics Reviews and Meta-analyses' (PRISMA) checklist, and will be performed in four major stages [30]. First, search results will be merged and duplicates will be removed via reference management software (EndNote V.X5). Second, a data extraction form based on the eligibility criteria described above will be developed by the research team. Third, a pilot test of this data extraction form will be performed: two reviewers will independently screen the first 25 titles, abstracts and grey literature of retrieved publications according to the eligibility criteria by using the data extraction form. Fourth, all eligible studies and those classified as unclear (needing more information) will be reviewed in full-text by each reviewer independently to determine if all inclusion criteria are met and if the article is to be included in the study. Inter-rater agreement will again be calculated on a random sample of 25 articles. Disagreement on study eligibility will be discussed and resolved with a third reviewer.

Data extraction

A customised data extraction form will be constructed to extract all relevant data from each study. Two reviewers will use the form to extract data from the first 15 eligible articles. Then they will meet to compare consistency of data extraction and coding. Clarification and updating of the extraction form will be an iterative process until all authors reach consensus on the final version. The data extraction form will be piloted on the first 5 eligible studies to evaluate its reliability in capturing the study data of interest. Data extraction will be undertaken independently by two reviewers.

Descriptive summary tables will be produced to recapitulate the evidence base. The following data will be extracted:

- Author(s) and date;
- Geographical location;
- Research design;
- Aim;
- Research question;
- Methods;

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- Settings;
- Participants (total number, mean age, gender if available);
- Primary cause of pain;
- Pain characteristics;
- Intervention studied/proposed;
- Intervention rationale/mechanism;
- Intervention frequency, site, duration of stimulation and the delay between times of stimulation and the clinical effects;
- Attitude towards intervention (positive, negative feelings towards intervention – from the healthcare provider; positive or negative feelings towards treatment – from the participant/patient, etc);
- NIBS characteristic (intensity, number of pulses, montage, current pattern/waveform, duration);
- Length of follow up;
- Duration of effect;
- Patient response, participation, and enthusiasm in intervention;
- Simultaneous interventions (if applicable);
- Neuropathic pain comorbidities;
- Key findings;
- Research gaps identified;
- Potential biases in study.

Other variables may be added when revising and updating the data extraction form after analysis of the first 15 eligible articles.

Data Synthesis

An initial map will be developed to explore the interventions available for chronic central neuropathic pain. The findings will be quantitatively and qualitatively synthesized for all identified interventions. The quantitative synthesis will comprise of numerical counts such as number of interventions by setting, and by application. A qualitative description approach will be used to describe the characteristics of each intervention (i.e., definition of intervention, mechanism, efficacy, side-effects, frequency of use, feasibility).

ETHICS AND DISSEMINATION

There are no protected/private health information collected, hence there will be no need for formal ethical review. The results of the scoping review will be presented at relevant national and international conferences, published in a peer-reviewed journal and proposed to the stakeholders with plain language to be posted on their websites.

CONCLUSION

This scoping review will map key concepts and empirical results relating to the use of non-invasive brain stimulation to treat and manage chronic central neuropathic pain. It will also provide a comprehensive evaluation of current methodologies and identify gaps for future research, and share the key research findings with relevant stakeholders.

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AUTHOR CONTRIBUTIONS

Designed the scoping review protocol: MLC KM. Performed literature search: MLC LY KM BT NJ. Contributed analysis tools: LY BT NJ. Wrote the paper: MLC. Proofread manuscript: MLC LY KM BT NJ.

We have read and understood BMJ policy on declaration of interests and declare that we have no competing interests.

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PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item
ADMINISTRATIVE INFORMATION		
Title: **(page 1)**		
Identification	1a	Identify the report as a protocol of a systematic review
Update	1b	If the protocol is for an update of a previous systematic review, identify as such
Registration **(none)**	2	If registered, provide the name of the registry (such as PROSPERO) and registration number
Authors: **(page 1)**		
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author
Contributions **(page 9)**	3b	Describe contributions of protocol authors and identify the guarantor of the review
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments
Support: **(none)**		
Sources	5a	Indicate sources of financial or other support for the review
Sponsor	5b	Provide name for the review funder and/or sponsor
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol
INTRODUCTION		
Rationale **(page 2-3)**	6	Describe the rationale for the review in the context of what is already known
Objectives **(page 3)**	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)
METHODS		
Eligibility criteria **(page 4)**	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage
Search strategy **(page 5)**	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated
Study records: **(page 5)**		
Data management **(page 5)**	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review

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Selection process **(page 5)**	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)
Data collection process **(page 5-6)**	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators
Data items **(page 6)**	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications
Outcomes and prioritization **(page 5-6)**	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale
Risk of bias in individual studies **(page 6)**	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis
Data synthesis **(page 6)**	15a	Describe criteria under which study data will be quantitatively synthesised
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned
Meta-bias(es) **(page 6)**	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)
Confidence in cumulative evidence **(n/a for scoping review)**	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

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Non-invasive brain stimulation interventions for management of chronic central neuropathic pain: a scoping review protocol

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Non-invasive brain stimulation interventions for management of chronic central neuropathic pain: a scoping review protocol

Mei Lin Chen[1], Lin Yao[1], Jennifer Boger[1], Kathryn Mercer[2], Benjamin Thompson[3], Ning Jiang[1]*
[1]Department of Systems Design Engineering, Faculty of Engineering, University of Waterloo, Waterloo, Canada
[2]School of Pharmacy, University of Waterloo, Waterloo, Canada
[3]Optometry and Vision Science, University of Waterloo, Waterloo, Canada
mlchen@uwaterloo.ca, lin.yao@uwaterloo.ca, kmercer@uwaterloo.ca, ben.thompson@uwaterloo.ca, ning.jiang@uwaterloo.ca
*Corresponding author: Tel: +1 519 888 4567 x 33677; fax: +1 519 888 4567 x 32600. Postal code: N2L 3W8.

ABSTRACT

Introduction

Pain can affect people regardless of age, gender, or ethnicity. Chronic central neuropathic pain (CCNP) is a debilitating condition that affects populations such as stroke survivors, amputees, spinal cord injury patients, and multiple sclerosis patients, with prevalence rates between 30~80%. This condition can be caused by a lesion or disease affecting the somatosensory system. CCNP is notoriously drug resistant, and few effective CCNP treatment or management strategies exist. The emergence of non-invasive brain stimulation and neuromodulation techniques provide novel avenues for managing chronic central neuropathic pain. This scoping review aims to systematically identify the methods and effectiveness of non-invasive brain stimulation techniques for treating and managing chronic central neuropathic pain.

Methods and analysis

The following databases will be searched systematically: PubMed, EMBASE, Cumulative Index to Nursing and Allied Health Literature (CINAHL), IEEE, ACM, and Scopus. Additional literature will be identified by searching the reference lists of identified studies. Studies will include reviews and original research in both the published, and grey literature. Two reviewers will independently screen identified studies for final inclusion. A quantitative analysis on the intervention type, application and efficacy will be synthesized along with a qualitative analysis to describe the effectiveness of each intervention.

Ethics and dissemination

No primary data will be collected, hence formal ethics review is not required. The results of the scoping review will be presented at relevant national and international conferences, published in a peer-reviewed journal and provided to the stakeholders with plain language to be posted on their websites. This scoping review will provide a foundation to guide the development of future primary research on non-invasive brain stimulation and CCNP.

Strengths and limitations of this study

- This study protocol provides an overview of the current status of the field to inform the development of a scoping review of non-invasive brain stimulation interventions for the management of chronic central neuropathic pain
- The scoping review will identify gaps in research and in the translation of research results into clinical practice
- The scoping review is specific to active stimulation interventions, excluding pharmacotherapy interventions

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- A limitation is that this scoping review that aims to explore the field for existing methods rather than a systematic review that seeks to answer a specific question

Key Words: Brain-computer interface, neuropathic pain, non-invasive brain stimulation, pain management
Word count (abstract) – 269 words; (text) – 3602 words

INTRODUCTION

Pain is a critical mechanism for harm prevention. However, the experience of chronic pain can dramatically reduce one's quality of life, affecting the individual, their families and society at large [1], [2]. 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" [3]. Specifically, the IASP defined neuropathic pain as "pain caused by a lesion or disease of the somatosensory nervous system" [3]. Neuropathic pain is a clinical description (and not a diagnosis) which requires a demonstrable lesion or a disease that satisfies established neurological diagnostic criteria [3]. The term lesion is commonly used in diagnostic investigations (e.g. imaging, neurophysiology, biopsies, lab tests) to reveal an abnormality or obvious trauma. The term disease is commonly used when the underlying cause of the lesion is known (e.g. stroke, vasculitis, diabetes mellitus, genetic abnormality). Somatosensory refers to information about the body including visceral organs [3].

The burden of disability associated with neuropathic pain is substantial and includes healthcare costs, time and quality of life [4]. The health-related quality of life for people with neuropathic pain is comparable to cancer or chronic heart failure [5]. In Canada, chronic pain involves health care costs that exceed $6 billion per year, and productivity costs at $37 billion per year [6]. Further, an analysis of a large United States insurance database revealed that healthcare costs of patients with neuropathic pain were three times greater than those of age- and sex-matched claimants without neuropathic pain [7].

Currently, there exists no treatment to prevent the development of neuropathic pain following injury to the somatosensory system, neither is there a method to specifically control the pain when it is established. Pharmacotherapy for neuropathic pain has been generally disappointing [8]–[11]; neuropathic pain patients do not respond well to non-steroidal anti-inflammatory drugs, and resistance or insensitivity to opiates is common [2], [12], [13]. Examples of pharmacological treatments include tricyclic or serotonin and norepinephrine uptake inhibitors, antidepressants, and anticonvulsants, which all have limited efficacy and undesirable side-effects [2], [8]. Ancillary treatments such as physical and psychological interventions are often used to help patients cope with pain, although they are less effective for severe pain [9].

Alternatively, a number of invasive and non-invasive stimulation techniques are increasingly being proposed either as a substitute for or in combination with current medical therapies [9]. Peripheral stimulation techniques include: transcutaneous electrical nerve stimulation (TENS) and nerve root stimulation (NRS). TENS involves surface electrodes placed over the painful area or its associated nerve, delivers stimulation at high frequency and low intensity to activate the Aβ afferents and evoke paresthesia in the pain area, providing short term (20-30 min) pain relief in accordance with the gate-control theory [9]. NRS involves implantation of an electrode in the root exit from the spine. These peripheral stimulation techniques provide only temporary pain

relief which lasts for the duration of the stimulation [9]. Other invasive stimulation techniques include: spinal cord stimulation (SCS), deep brain stimulation (DBS), and motor cortex stimulation (MCS). These procedures involve the implantation of a stimulating device into their respective target areas: SCS targets the posterior thoracic space of the thoracic or cervical spine; DBS targets the sensory thalamus or periventricular gray matter; and MCS targets the motor cortex. The effectiveness of these invasive techniques varies significantly across patients [14] and their mechanisms of action are unclear [15]. Further, the techniques are only applicable to patients who can safely undergo surgery [9].

Examples of non-invasive brain stimulation techniques include: transcranial direct-current stimulation (tDCS) [14], [16], and repetitive transcranial magnetic stimulation (rTMS) [9], [17], [18]. Both stimulation techniques are adjustable and reversible [9]. tDCS has shown promising results in inducing cortical-plasticity with clinical benefits [19]. It passes a weak (commonly≤ 2mA) monophasic electric current to the cerebral cortex through the scalp, modifying neuron membrane excitability, leading to neuroplasticity [19]. A single tDCS session can induce transient cortical effects, but daily sessions may induce longer-lasting effects [19]. For rTMS, the stimulation is applied using a magnetic stimulation coil placed against the head. A rapidly changing magnetic field is induced in the coil that generates an electrical current in the cortical area below the coil. rTMS has been found to affect neuropathic pain processing [9], [20]. The clinical effects are modest and short-lasting from a single session, [9] but repeated sessions may cause greater and longer-lasting effects. There exists equivocal evidence and differing perspectives on the effects of rTMS – for instance, one study suggests that rTMS can produce long-lasting pain relief [17], while another states that its effects are uncertain and may be mediated by other factors such as mood [21]. Given that non-invasive brain stimulation may relieve neuropathic pain, and the effect size is modest, there is significant heterogeneity between studies that should be further investigated [22].

There is a need for a systematic overview of the existing evidence to support further research. Previous reviews have been done to gather the research evidence on isolated topics and NIBS techniques for specific conditions. However, a broad scoping review with a clear search strategy is needed to scope the wide-ranging evidence for non-invasive brain stimulation techniques for chronic central neuropathic pain. This scoping review will fill this gap by summarizing the breadth, depth, and clinical applications of current non-invasive brain stimulation interventions for chronic central neuropathic pain, distilling the existing research to support the future development of primary research [23], [24].

AIM

This article describes a protocol for a scoping review which will locate, summarize, and report literature that informs the current and proposed non-invasive brain stimulation interventions for chronic central neuropathic pain, as well as identify areas to direct future research.

The scoping review will:

1. Review the breadth and depth of peer reviewed literature that has examined or evaluated the application of non-invasive brain stimulation techniques to chronic central neuropathic pain in technology and medical databases;
2. Review the extent and nature of a sampling of non-peer reviewed non-invasive brain stimulation interventions for chronic central neuropathic pain from key organizational

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websites, professional regulatory bodies, and special interest organizations and disease specific groups.

METHODS AND ANALYSIS

Our scoping team of reviewers will be multi-disciplinary, comprising of clinician-researchers, engineering researchers and health researchers. The scoping review methodology laid out by Arksey and O'Malley [24] and further clarified by Levac *et al* [23] will be used. The approach will review the existing literature, and provide transparency, reproducibility and utility within this protocol [25].

Identifying the Research Question

The research question was framed by assimilating themes from preliminary searches and opinions were sought from experts in the field of pain rehabilitation and neurotechnology. Using a concept, target population and outcomes of interest approach, we formulated a broad research question: "What are the nature, adherence, extent, efficacy, exposure, quality of delivery and clinical application of non-invasive brain stimulation techniques currently used and proposed in managing chronic central neuropathic pain?".

Eligibility criteria

The following inclusion criteria were used to guide the search and will be used when reviewing articles:

- Published in the English language
- Human subjects with chronic central neuropathic pain
- Years of Publication: none specified
- All age groups
- Articles that include at least 1 non-invasive brain stimulation intervention

Exclusion criteria

- Commentaries
- Editorials
- Narrative reviews
- Books and book chapters
- Lectures and addresses
- Animal studies

Types of Study

Meta-analysis, systematic reviews, randomized control trials, cohort studies, case control studies, case series/case reports, and cross sectional trials.

Databases

Published studies will be identified from the following electronic database: PubMed, EMBASE, Cumulative Index to Nursing and Allied Health Literature (CINAHL), IEEE, ACM, and Scopus. Additional literature will be identified by hand searching the reference list of identified eligible studies and as well through identified grey literature sources.

Search Strategy

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The in-depth search strategy has been developed in each of the six databases to capture the broad literature on the topic. In order to maximize the sensitivity of the search, the following steps will be taken: consult with experts in the field; search in clinical trials registers, conference proceedings, selected grey literature such as PhD theses; perform forward and backward citation tracking; contact the websites of key organizations; and hand-search journal references.

Please see a sample search strategy in PubMed as follows:
("neuralgia"[MeSH Terms] OR "neuralgia"[All Fields] OR ("neuropathic"[All Fields] AND "pain"[All Fields]) OR "neuropathic pain"[All Fields]) AND ("therapy"[Subheading] OR "therapy"[All Fields] OR "treatment"[All Fields] OR "therapeutics"[MeSH Terms] OR "therapeutics"[All Fields]) OR ("Brain Stimul"[Journal] OR ("brain"[All Fields] AND "stimulation"[All Fields]) OR "brain stimulation"[All Fields]) OR (non[All Fields] AND invasive[All Fields]) AND (Clinical Trial[ptyp] AND "humans"[MeSH Terms] AND English[lang]).

Study Selection

Study screening will be reported and guided according to Levac *et al.*'s framework and the reporting will follow the Preferred Reporting Items for Systematics Reviews and Meta-analyses' (PRISMA) checklist, and will be performed in four major stages [26]. First, search results will be merged and duplicates will be removed via reference management software (EndNote V.X5). Second, a data extraction form based on the eligibility criteria described above will be developed by the research team. Third, a pilot test of this data extraction form will be performed: two reviewers will independently screen the first 25 titles, abstracts and grey literature of retrieved publications according to the eligibility criteria by using the data extraction form. Fourth, all eligible studies and those classified as unclear (needing more information) will be reviewed in full-text by each reviewer independently to determine if all inclusion criteria are met and if the article is to be included in the study. Inter-rater agreement will again be calculated on a random sample of 25 articles. Disagreement on study eligibility will be discussed and resolved with a third reviewer.

Data extraction

A customised data extraction form will be constructed to extract all relevant data from each study. Two reviewers will use the form to extract data from the first 15 eligible articles. Then they will meet to compare consistency of data extraction and coding. Clarification and updating of the extraction form will be an iterative process until all authors reach consensus on the final version. The data extraction form will be piloted on the first 5 eligible studies to evaluate its reliability in capturing the study data of interest. Data extraction will be undertaken independently by two reviewers.

Descriptive summary tables will be produced to recapitulate the evidence base. The following data will be extracted:

- Author(s) and date;
- Geographical location;
- Research design;
- Aim;
- Research question;
- Methods;

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- Settings;
- Participants (total number, mean age, gender if available);
- Primary cause of pain;
- Pain characteristics;
- Intervention studied/proposed;
- Intervention rationale/mechanism;
- Intervention frequency, site, duration of stimulation and the delay between times of stimulation and the clinical effects;
- Attitude towards intervention (positive, negative feelings towards intervention – from the healthcare provider; positive or negative feelings towards treatment – from the participant/patient, etc);
- NIBS characteristic (intensity, number of pulses, montage, current pattern/waveform, duration);
- Length of follow up;
- Duration of effect;
- Patient response, participation, and enthusiasm in intervention;
- Simultaneous interventions (if applicable);
- Neuropathic pain comorbidities;
- Key findings;
- Research gaps identified;
- Potential biases in study.

Other variables may be added when revising and updating the data extraction form after analysis of the first 15 eligible articles.

Data Synthesis

An initial map will be developed to explore the interventions available for chronic central neuropathic pain. The findings will be quantitatively and qualitatively synthesized for all identified interventions. The quantitative synthesis will comprise of numerical counts such as number of interventions by setting, and by application. A qualitative description approach will be used to describe the characteristics of each intervention (i.e., definition of intervention, mechanism, efficacy, side-effects, frequency of use, feasibility). The specific metrics that will be included will be determined after the papers have been identified and reviewed.

ETHICS AND DISSEMINATION

There are no protected/private health information collected, hence there will be no need for formal ethical review. The results of the scoping review will be presented at relevant national and international conferences, published in a peer-reviewed journal, and proposed to relevant stakeholders.

CONCLUSION

This scoping review will map key concepts and empirical results relating to the use of non-invasive brain stimulation to treat and manage chronic central neuropathic pain. It will also provide a comprehensive evaluation of current methodologies and identify gaps for future research, and share the key research findings with relevant stakeholders.

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AUTHOR CONTRIBUTIONS

Designed the scoping review protocol: MLC KM. Performed literature search: MLC LY KM BT NJ. Contributed analysis tools: LY JB BT NJ. Wrote the paper: MLC. Proofread manuscript: MLC LY JB KM BT NJ.

We have read and understood BMJ policy on declaration of interests and declare that we have no competing interests.

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PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item
ADMINISTRATIVE INFORMATION		
Title: **(page 1)**		
Identification	1a	Identify the report as a protocol of a systematic review
Update	1b	If the protocol is for an update of a previous systematic review, identify as such
Registration **(none)**	2	If registered, provide the name of the registry (such as PROSPERO) and registration number
Authors: **(page 1)**		
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author
Contributions **(page 9)**	3b	Describe contributions of protocol authors and identify the guarantor of the review
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments
Support: **(none)**		
Sources	5a	Indicate sources of financial or other support for the review
Sponsor	5b	Provide name for the review funder and/or sponsor
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol
INTRODUCTION		
Rationale **(page 2-3)**	6	Describe the rationale for the review in the context of what is already known
Objectives **(page 3)**	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)
METHODS		
Eligibility criteria **(page 4)**	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage
Search strategy **(page 5)**	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated
Study records: **(page 5)**		
Data management **(page 5)**	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review

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Selection process **(page 5)**	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)
Data collection process **(page 5-6)**	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators
Data items **(page 6)**	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications
Outcomes and prioritization **(page 5-6)**	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale
Risk of bias in individual studies **(page 6)**	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis
Data synthesis **(page 6)**	15a	Describe criteria under which study data will be quantitatively synthesised
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned
Meta-bias(es) **(page 6)**	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)
Confidence in cumulative evidence **(n/a for scoping review)**	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

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Non-invasive brain stimulation interventions for management of chronic central neuropathic pain: a scoping review protocol

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Non-invasive brain stimulation interventions for management of chronic central neuropathic pain: a scoping review protocol

Mei Lin Chen[1], Lin Yao[1], Jennifer Boger[1], Kathryn Mercer[2], Benjamin Thompson[3], Ning Jiang[1]*
[1]Department of Systems Design Engineering, Faculty of Engineering, University of Waterloo, Waterloo, Canada
[2]School of Pharmacy, University of Waterloo, Waterloo, Canada
[3]Optometry and Vision Science, University of Waterloo, Waterloo, Canada
mlchen@uwaterloo.ca, lin.yao@uwaterloo.ca, kmercer@uwaterloo.ca, ben.thompson@uwaterloo.ca, ning.jiang@uwaterloo.ca
*Corresponding author: Tel: +1 519 888 4567 x 33677; fax: +1 519 888 4567 x 32600. Postal code: N2K 2W3.

ABSTRACT

Introduction

Pain can affect people regardless of age, gender, or ethnicity. Chronic central neuropathic pain (CCNP) is a debilitating condition that affects populations such as stroke survivors, amputees, spinal cord injury patients, and multiple sclerosis patients, with prevalence rates between 30~80%. This condition can be caused by a lesion or disease affecting the somatosensory system. CCNP is notoriously drug resistant, and few effective CCNP treatment or management strategies exist. The emergence of non-invasive brain stimulation and neuromodulation techniques provide novel avenues for managing chronic central neuropathic pain. This scoping review aims to systematically identify the methods and effectiveness of non-invasive brain stimulation techniques for treating and managing chronic central neuropathic pain.

Methods and analysis

The following databases will be searched systematically: PubMed, EMBASE, Cumulative Index to Nursing and Allied Health Literature (CINAHL), IEEE, ACM, and Scopus. Additional literature will be identified by searching the reference lists of identified studies. Studies will include reviews and original research in both the published, and grey literature. Two reviewers will independently screen identified studies for final inclusion. A quantitative analysis on the intervention type, application and efficacy will be synthesized along with a qualitative analysis to describe the effectiveness of each intervention.

Ethics and dissemination

No primary data will be collected, hence formal ethics review is not required. The results of the scoping review will be presented at relevant national and international conferences, published in a peer-reviewed journal and provided to the stakeholders with plain language to be posted on their websites. This scoping review will provide a foundation to guide the development of future primary research on non-invasive brain stimulation and CCNP.

Strengths and limitations of this study

- This study protocol provides an overview of the current status of the field to inform the development of a scoping review of non-invasive brain stimulation interventions for the management of chronic central neuropathic pain
- The scoping review will identify gaps in research and in the translation of research results into clinical practice
- The scoping review is specific to active stimulation interventions, excluding pharmacotherapy interventions

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- A limitation is that this scoping review that aims to explore the field for existing methods rather than a systematic review that seeks to answer a specific question

Key Words: Brain-computer interface, neuropathic pain, non-invasive brain stimulation, pain management
Word count (abstract) – 269 words; (text) – 3659 words

INTRODUCTION

Pain is a critical mechanism for harm prevention. However, the experience of chronic pain can dramatically reduce one's quality of life, affecting the individual, their families and society at large [1], [2]. 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" [3]. Specifically, the IASP defined neuropathic pain as "pain caused by a lesion or disease of the somatosensory nervous system" [3]. Neuropathic pain is a clinical description (and not a diagnosis) which requires a demonstrable lesion or a disease that satisfies established neurological diagnostic criteria [3]. The term lesion is commonly used in diagnostic investigations (e.g. imaging, neurophysiology, biopsies, lab tests) to reveal an abnormality or obvious trauma. The term disease is commonly used when the underlying cause of the lesion is known (e.g. stroke, vasculitis, diabetes mellitus, genetic abnormality). Somatosensory refers to information about the body including visceral organs [3].

The burden of disability associated with neuropathic pain is substantial and includes healthcare costs, time and quality of life [4]. The health-related quality of life for people with neuropathic pain is comparable to cancer or chronic heart failure [5]. In Canada, chronic pain involves health care costs that exceed $6 billion per year, and productivity costs at $37 billion per year [6]. Further, an analysis of a large United States insurance database revealed that healthcare costs of patients with neuropathic pain were three times greater than those of age- and sex-matched claimants without neuropathic pain [7].

Currently, there exists no treatment to prevent the development of neuropathic pain following injury to the somatosensory system, neither is there a method to specifically control the pain when it is established. Pharmacotherapy for neuropathic pain has been generally disappointing [8]–[11]; neuropathic pain patients do not respond well to non-steroidal anti-inflammatory drugs, and resistance or insensitivity to opiates is common [2], [12], [13]. Examples of pharmacological treatments include tricyclic or serotonin and norepinephrine uptake inhibitors, antidepressants, and anticonvulsants, which all have limited efficacy and undesirable side-effects [2], [8]. Ancillary treatments such as physical and psychological interventions are often used to help patients cope with pain, although they are less effective for severe pain [9].

Alternatively, a number of invasive and non-invasive stimulation techniques are increasingly being proposed either as a substitute for or in combination with current medical therapies [9]. Peripheral stimulation techniques include: transcutaneous electrical nerve stimulation (TENS) and nerve root stimulation (NRS). TENS involves surface electrodes placed over the painful area or its associated nerve, delivers stimulation at high frequency and low intensity to activate the Aβ afferents and evoke paresthesia in the pain area, providing short term (20-30 min) pain relief in accordance with the gate-control theory [9]. NRS involves implantation of an electrode in the root exit from the spine. These peripheral stimulation techniques provide only temporary pain

relief which lasts for the duration of the stimulation [9]. Other invasive stimulation techniques include: spinal cord stimulation (SCS), deep brain stimulation (DBS), and motor cortex stimulation (MCS). These procedures involve the implantation of a stimulating device into their respective target areas: SCS targets the posterior thoracic space of the thoracic or cervical spine; DBS targets the sensory thalamus or periventricular gray matter; and MCS targets the motor cortex. The effectiveness of these invasive techniques varies significantly across patients [14] and their mechanisms of action are unclear [15]. Further, the techniques are only applicable to patients who can safely undergo surgery [9].

Examples of non-invasive brain stimulation techniques include: transcranial direct-current stimulation (tDCS) [14], [16], and repetitive transcranial magnetic stimulation (rTMS) [9], [17], [18]. Both stimulation techniques are adjustable and reversible [9]. tDCS has shown promising results in inducing cortical-plasticity with clinical benefits [19]. It passes a weak (commonly≤ 2mA) monophasic electric current to the cerebral cortex through the scalp, modifying neuron membrane excitability, leading to neuroplasticity [19]. A single tDCS session can induce transient cortical effects, but daily sessions may induce longer-lasting effects [19]. For rTMS, the stimulation is applied using a magnetic stimulation coil placed against the head. A rapidly changing magnetic field is induced in the coil that generates an electrical current in the cortical area below the coil. rTMS has been found to affect neuropathic pain processing [9], [20]. The clinical effects are modest and short-lasting from a single session, [9] but repeated sessions may cause greater and longer-lasting effects. There exists equivocal evidence and differing perspectives on the effects of rTMS – for instance, one study suggests that rTMS can produce long-lasting pain relief [17], while another states that its effects are uncertain and may be mediated by other factors such as mood [21]. Given that non-invasive brain stimulation may relieve neuropathic pain, and the effect size is modest, there is significant heterogeneity between studies that should be further investigated [22].

There is a need for a systematic overview of the existing evidence to support further research. Previous reviews have been done to gather the research evidence on isolated topics and NIBS techniques for specific conditions. However, a broad scoping review with a clear search strategy is needed to scope the wide-ranging evidence for non-invasive brain stimulation techniques for chronic central neuropathic pain. This scoping review will fill this gap by summarizing the breadth, depth, and clinical applications of current non-invasive brain stimulation interventions for chronic central neuropathic pain, distilling the existing research to support the future development of primary research [23], [24].

AIM

This article describes a protocol for a scoping review which will locate, summarize, and report literature that informs the current and proposed non-invasive brain stimulation interventions for chronic central neuropathic pain, as well as identify areas to direct future research.

The scoping review will:

1. Review the breadth and depth of peer reviewed literature that has examined or evaluated the application of non-invasive brain stimulation techniques to chronic central neuropathic pain in technology and medical databases;
2. Review the extent and nature of a sampling of non-peer reviewed non-invasive brain stimulation interventions for chronic central neuropathic pain from key organizational

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websites, professional regulatory bodies, and special interest organizations and disease specific groups.

METHODS AND ANALYSIS

Our scoping team of reviewers will be multi-disciplinary, comprising of clinician-researchers, engineering researchers and health researchers. The scoping review methodology laid out by Arksey and O'Malley [24] and further clarified by Levac *et al* [23] will be used. The approach will review the existing literature, and provide transparency, reproducibility and utility within this protocol [25].

Identifying the Research Question

The research question was framed by assimilating themes from preliminary searches and opinions were sought from experts in the field of pain rehabilitation and neurotechnology. Using a concept, target population and outcomes of interest approach, we formulated a broad research question: "What are the nature, adherence, extent, efficacy, exposure, quality of delivery and clinical application of non-invasive brain stimulation techniques currently used and proposed in managing chronic central neuropathic pain?".

Eligibility criteria

The following inclusion criteria were used to guide the search and will be used when reviewing articles:

- Published in the English language
- Human subjects with chronic central neuropathic pain
- Years of Publication: none specified
- All age groups
- Articles that include at least 1 non-invasive brain stimulation intervention

Exclusion criteria

- Commentaries
- Editorials
- Narrative reviews
- Books and book chapters
- Lectures and addresses
- Animal studies

Types of Study

Meta-analysis, systematic reviews, randomized control trials, cohort studies, case control studies, case series/case reports, and cross sectional trials.

Databases

Published studies will be identified from the following electronic database: PubMed, EMBASE, Cumulative Index to Nursing and Allied Health Literature (CINAHL), IEEE, ACM, and Scopus. Additional literature will be identified by hand searching the reference list of identified eligible studies and as well through identified grey literature sources.

Search Strategy

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The in-depth search strategy has been developed in each of the six databases to capture the broad literature on the topic. In order to maximize the sensitivity of the search, the following steps will be taken: consult with experts in the field; search in clinical trials registers, conference proceedings, selected grey literature such as PhD theses; perform forward and backward citation tracking; contact the websites of key organizations; and hand-search journal references.

Please see a sample search strategy in PubMed as follows:
("neuralgia"[MeSH Terms] OR "neuralgia"[All Fields] OR ("neuropathic"[All Fields] AND "pain"[All Fields]) OR "neuropathic pain"[All Fields]) AND ("therapy"[Subheading] OR "therapy"[All Fields] OR "treatment"[All Fields] OR "therapeutics"[MeSH Terms] OR "therapeutics"[All Fields]) OR ("Brain Stimul"[Journal] OR ("brain"[All Fields] AND "stimulation"[All Fields]) OR "brain stimulation"[All Fields]) OR (non[All Fields] AND invasive[All Fields]) AND (Clinical Trial[ptyp] AND "humans"[MeSH Terms] AND English[lang]).

Study Selection

Study screening will be reported and guided according to Levac *et al.*'s framework and the reporting will follow the Preferred Reporting Items for Systematics Reviews and Meta-analyses' (PRISMA) checklist, and will be performed in four major stages [26]. First, search results will be merged and duplicates will be removed via reference management software (EndNote V.X5). Second, a data extraction form based on the eligibility criteria described above will be developed by the research team. Third, a pilot test of this data extraction form will be performed: two reviewers will independently screen the first 25 titles, abstracts and grey literature of retrieved publications according to the eligibility criteria by using the data extraction form. Fourth, all eligible studies and those classified as unclear (needing more information) will be reviewed in full-text by each reviewer independently to determine if all inclusion criteria are met and if the article is to be included in the study. Inter-rater agreement will again be calculated on a random sample of 25 articles. Disagreement on study eligibility will be discussed and resolved with a third reviewer.

Data extraction

A customised data extraction form will be constructed to extract all relevant data from each study. Two reviewers will use the form to extract data from the first 15 eligible articles. Then they will meet to compare consistency of data extraction and coding. Clarification and updating of the extraction form will be an iterative process until all authors reach consensus on the final version. The data extraction form will be piloted on the first 5 eligible studies to evaluate its reliability in capturing the study data of interest. Data extraction will be undertaken independently by two reviewers.

Descriptive summary tables will be produced to recapitulate the evidence base. The following data will be extracted:

- Author(s) and date;
- Geographical location;
- Research design;
- Aim;
- Research question;
- Methods;

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- Settings;
- Participant characteristics (total number, mean age, gender, pathology if available);
- Primary cause of pain;
- Pain characteristics;
- Intervention studied/proposed;
- Intervention rationale/mechanism;
- Intervention frequency, site, duration of stimulation and the delay between times of stimulation and the clinical effects;
- Attitude towards intervention (positive, negative feelings towards intervention – from the healthcare provider; positive or negative feelings towards treatment – from the participant/patient, etc);
- NIBS characteristic (intensity, number of pulses, montage, current pattern/waveform, duration);
- Length of follow up;
- Duration of effect;
- Patient response, participation, and enthusiasm in intervention;
- Simultaneous interventions (if applicable);
- Neuropathic pain comorbidities;
- Key findings;
- Research gaps identified;
- Potential biases in study (assessed using The Cochrane Collaboration's 'Risk of bias' tool for assessing risk of bias) [26];
- Pain outcome (visual analogue scale if available);
- Daily functioning outcome.

Other variables may be added when revising and updating the data extraction form after analysis of the first 15 eligible articles.

Data Synthesis

An initial map will be developed to explore the interventions available for chronic central neuropathic pain. The findings will be quantitatively and qualitatively synthesized for all identified interventions. The quantitative synthesis will comprise of numerical counts such as number of interventions by setting, and by application. A qualitative description approach will be used to describe the characteristics of each intervention (i.e., definition of intervention, mechanism, efficacy, side-effects, frequency of use, feasibility) as well as pain outcome using the visual analogue scale (VAS). The change in VAS, for example, will be used to review the effectiveness of the intervention. The specific metrics that will be included will be determined after the papers have been identified and reviewed.

ETHICS AND DISSEMINATION

There are no protected/private health information collected, hence there will be no need for formal ethical review. The results of the scoping review will be presented at relevant national and international conferences, published in a peer-reviewed journal, and proposed to relevant stakeholders.

CONCLUSION

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This scoping review will map key concepts and empirical results relating to the use of non-invasive brain stimulation to treat and manage chronic central neuropathic pain. It will also provide a comprehensive evaluation of current methodologies and identify gaps for future research, and share the key research findings with relevant stakeholders.

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AUTHOR CONTRIBUTIONS
Designed the scoping review protocol: MLC KM. Performed literature search: MLC LY KM BT NJ. Contributed analysis tools: LY JB BT NJ. Wrote the paper: MLC. Proofread manuscript: MLC LY JB KM BT NJ.

We have read and understood BMJ policy on declaration of interests and declare that we have no competing interests.

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PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item
ADMINISTRATIVE INFORMATION		
Title: **(page 1)**		
Identification	1a	Identify the report as a protocol of a systematic review
Update	1b	If the protocol is for an update of a previous systematic review, identify as such
Registration **(none)**	2	If registered, provide the name of the registry (such as PROSPERO) and registration number
Authors: **(page 1)**		
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author
Contributions **(page 9)**	3b	Describe contributions of protocol authors and identify the guarantor of the review
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments
Support: **(none)**		
Sources	5a	Indicate sources of financial or other support for the review
Sponsor	5b	Provide name for the review funder and/or sponsor
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol
INTRODUCTION		
Rationale **(page 2-3)**	6	Describe the rationale for the review in the context of what is already known
Objectives **(page 3)**	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)
METHODS		
Eligibility criteria **(page 4)**	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage
Search strategy **(page 5)**	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated
Study records: **(page 5)**		
Data management **(page 5)**	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review

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Selection process **(page 5)**	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)
Data collection process **(page 5-6)**	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators
Data items **(page 6)**	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications
Outcomes and prioritization **(page 5-6)**	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale
Risk of bias in individual studies **(page 6)**	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis
Data synthesis **(page 6)**	15a	Describe criteria under which study data will be quantitatively synthesised
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned
Meta-bias(es) **(page 6)**	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)
Confidence in cumulative evidence **(n/a for scoping review)**	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

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Non-invasive brain stimulation interventions for management of chronic central neuropathic pain: a scoping review protocol

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Non-invasive brain stimulation interventions for management of chronic central neuropathic pain: a scoping review protocol

Mei Lin Chen[1], Lin Yao[1], Jennifer Boger[1], Kathryn Mercer[2], Benjamin Thompson[3], Ning Jiang[1]*
[1]Department of Systems Design Engineering, Faculty of Engineering, University of Waterloo, Waterloo, Canada
[2]School of Pharmacy, University of Waterloo, Waterloo, Canada
[3]Optometry and Vision Science, University of Waterloo, Waterloo, Canada
mlchen@uwaterloo.ca, lin.yao@uwaterloo.ca, kmercer@uwaterloo.ca, ben.thompson@uwaterloo.ca, ning.jiang@uwaterloo.ca
*Corresponding author: Tel: +1 519 888 4567 x 33677; fax: +1 519 888 4567 x 32600. Postal code: N2K 2W3.

ABSTRACT

Introduction

Pain can affect people regardless of age, gender, or ethnicity. Chronic central neuropathic pain (CCNP) is a debilitating condition that affects populations such as stroke survivors, amputees, spinal cord injury patients, and multiple sclerosis patients, with prevalence rates between 30~80%. This condition can be caused by a lesion or disease affecting the somatosensory system. CCNP is notoriously drug resistant, and few effective CCNP treatment or management strategies exist. The emergence of non-invasive brain stimulation and neuromodulation techniques provide novel avenues for managing chronic central neuropathic pain. This scoping review aims to systematically identify the methods and effectiveness of non-invasive brain stimulation techniques for treating and managing chronic central neuropathic pain.

Methods and analysis

The following databases will be searched systematically: PubMed, EMBASE, Cumulative Index to Nursing and Allied Health Literature (CINAHL), IEEE, ACM, and Scopus. Additional literature will be identified by searching the reference lists of identified studies. Studies will include reviews and original research in both the published, and grey literature. Two reviewers will independently screen identified studies for final inclusion. A quantitative analysis on the intervention type, application and efficacy will be synthesized along with a qualitative analysis to describe the effectiveness of each intervention.

Ethics and dissemination

No primary data will be collected, hence formal ethics review is not required. The results of the scoping review will be presented at relevant national and international conferences, published in a peer-reviewed journal and provided to the stakeholders with plain language to be posted on their websites. This scoping review will provide a foundation to guide the development of future primary research on non-invasive brain stimulation and CCNP.

Strengths and limitations of this study

- This study protocol provides an overview of the current status of the field to inform the development of a scoping review of non-invasive brain stimulation interventions for the management of chronic central neuropathic pain
- The scoping review will identify gaps in research and in the translation of research results into clinical practice
- The scoping review is specific to active stimulation interventions, excluding pharmacotherapy interventions

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- A limitation is that this scoping review that aims to explore the field for existing methods rather than a systematic review that seeks to answer a specific question

Key Words: Brain-computer interface, neuropathic pain, non-invasive brain stimulation, pain management
Word count (abstract) – 269 words; (text) – 3659 words

INTRODUCTION

Pain is a critical mechanism for harm prevention. However, the experience of chronic pain can dramatically reduce one's quality of life, affecting the individual, their families and society at large [1], [2]. 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" [3]. Specifically, the IASP defined neuropathic pain as "pain caused by a lesion or disease of the somatosensory nervous system" [3]. Neuropathic pain is a clinical description (and not a diagnosis) which requires a demonstrable lesion or a disease that satisfies established neurological diagnostic criteria [3]. The term lesion is commonly used in diagnostic investigations (e.g. imaging, neurophysiology, biopsies, lab tests) to reveal an abnormality or obvious trauma. The term disease is commonly used when the underlying cause of the lesion is known (e.g. stroke, vasculitis, diabetes mellitus, genetic abnormality). Somatosensory refers to information about the body including visceral organs [3].

The burden of disability associated with neuropathic pain is substantial and includes healthcare costs, time and quality of life [4]. The health-related quality of life for people with neuropathic pain is comparable to cancer or chronic heart failure [5]. In Canada, chronic pain involves health care costs that exceed $6 billion per year, and productivity costs at $37 billion per year [6]. Further, an analysis of a large United States insurance database revealed that healthcare costs of patients with neuropathic pain were three times greater than those of age- and sex-matched claimants without neuropathic pain [7].

Currently, there exists no treatment to prevent the development of neuropathic pain following injury to the somatosensory system, neither is there a method to specifically control the pain when it is established. Pharmacotherapy for neuropathic pain has been generally disappointing [8]–[11]; neuropathic pain patients do not respond well to non-steroidal anti-inflammatory drugs, and resistance or insensitivity to opiates is common [2], [12], [13]. Examples of pharmacological treatments include tricyclic or serotonin and norepinephrine uptake inhibitors, antidepressants, and anticonvulsants, which all have limited efficacy and undesirable side-effects [2], [8]. Ancillary treatments such as physical and psychological interventions are often used to help patients cope with pain, although they are less effective for severe pain [9].

Alternatively, a number of invasive and non-invasive stimulation techniques are increasingly being proposed either as a substitute for or in combination with current medical therapies [9]. Peripheral stimulation techniques include: transcutaneous electrical nerve stimulation (TENS) and nerve root stimulation (NRS). TENS involves surface electrodes placed over the painful area or its associated nerve, delivers stimulation at high frequency and low intensity to activate the Aβ afferents and evoke paresthesia in the pain area, providing short term (20-30 min) pain relief in accordance with the gate-control theory [9]. NRS involves implantation of an electrode in the root exit from the spine. These peripheral stimulation techniques provide only temporary pain

relief which lasts for the duration of the stimulation [9]. Other invasive stimulation techniques include: spinal cord stimulation (SCS), deep brain stimulation (DBS), and motor cortex stimulation (MCS). These procedures involve the implantation of a stimulating device into their respective target areas: SCS targets the posterior thoracic space of the thoracic or cervical spine; DBS targets the sensory thalamus or periventricular gray matter; and MCS targets the motor cortex. The effectiveness of these invasive techniques varies significantly across patients [14] and their mechanisms of action are unclear [15]. Further, the techniques are only applicable to patients who can safely undergo surgery [9].

Examples of non-invasive brain stimulation techniques include: transcranial direct-current stimulation (tDCS) [14], [16], and repetitive transcranial magnetic stimulation (rTMS) [9], [17], [18]. Both stimulation techniques are adjustable and reversible [9]. tDCS has shown promising results in inducing cortical-plasticity with clinical benefits [19]. It passes a weak (commonly≤ 2mA) monophasic electric current to the cerebral cortex through the scalp, modifying neuron membrane excitability, leading to neuroplasticity [19]. A single tDCS session can induce transient cortical effects, but daily sessions may induce longer-lasting effects [19]. For rTMS, the stimulation is applied using a magnetic stimulation coil placed against the head. A rapidly changing magnetic field is induced in the coil that generates an electrical current in the cortical area below the coil. rTMS has been found to affect neuropathic pain processing [9], [20]. The clinical effects are modest and short-lasting from a single session, [9] but repeated sessions may cause greater and longer-lasting effects. There exists equivocal evidence and differing perspectives on the effects of rTMS – for instance, one study suggests that rTMS can produce long-lasting pain relief [17], while another states that its effects are uncertain and may be mediated by other factors such as mood [21]. Given that non-invasive brain stimulation may relieve neuropathic pain, and the effect size is modest, there is significant heterogeneity between studies that should be further investigated [22].

There is a need for a systematic overview of the existing evidence to support further research. Previous reviews have been done to gather the research evidence on isolated topics and NIBS techniques for specific conditions. However, a broad scoping review with a clear search strategy is needed to scope the wide-ranging evidence for non-invasive brain stimulation techniques for chronic central neuropathic pain. This scoping review will fill this gap by summarizing the breadth, depth, and clinical applications of current non-invasive brain stimulation interventions for chronic central neuropathic pain, distilling the existing research to support the future development of primary research [23], [24].

AIM

This article describes a protocol for a scoping review which will locate, summarize, and report literature that informs the current and proposed non-invasive brain stimulation interventions for chronic central neuropathic pain, as well as identify areas to direct future research.

The scoping review will:

1. Review the breadth and depth of peer reviewed literature that has examined or evaluated the application of non-invasive brain stimulation techniques to chronic central neuropathic pain in technology and medical databases;
2. Review the extent and nature of a sampling of non-peer reviewed non-invasive brain stimulation interventions for chronic central neuropathic pain from key organizational

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websites, professional regulatory bodies, and special interest organizations and disease specific groups.

METHODS AND ANALYSIS

Our scoping team of reviewers will be multi-disciplinary, comprising of clinician-researchers, engineering researchers and health researchers. The scoping review methodology laid out by Arksey and O'Malley [24] and further clarified by Levac *et al* [23] will be used. The approach will review the existing literature, and provide transparency, reproducibility and utility within this protocol [25].

Identifying the Research Question

The research question was framed by assimilating themes from preliminary searches and opinions were sought from experts in the field of pain rehabilitation and neurotechnology. Using a concept, target population and outcomes of interest approach, we formulated a broad research question: "What are the nature, adherence, extent, efficacy, exposure, quality of delivery and clinical application of non-invasive brain stimulation techniques currently used and proposed in managing chronic central neuropathic pain?".

Eligibility criteria

The following inclusion criteria were used to guide the search and will be used when reviewing articles:

- Published in the English language
- Human subjects with chronic central neuropathic pain
- Years of Publication: none specified
- All age groups
- Articles that include at least 1 non-invasive brain stimulation intervention

Exclusion criteria

- Commentaries
- Editorials
- Narrative reviews
- Books and book chapters
- Lectures and addresses
- Animal studies

Types of Study

Meta-analysis, systematic reviews, randomized control trials, cohort studies, case control studies, case series/case reports, and cross sectional trials.

Databases

Published studies will be identified from the following electronic database: PubMed, EMBASE, Cumulative Index to Nursing and Allied Health Literature (CINAHL), IEEE, ACM, and Scopus. Additional literature will be identified by hand searching the reference list of identified eligible studies and as well through identified grey literature sources.

Search Strategy

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The in-depth search strategy has been developed in each of the six databases to capture the broad literature on the topic. In order to maximize the sensitivity of the search, the following steps will be taken: consult with experts in the field; search in clinical trials registers, conference proceedings, selected grey literature such as PhD theses; perform forward and backward citation tracking; contact the websites of key organizations; and hand-search journal references.

Please see a sample search strategy in PubMed as follows:
("neuralgia"[MeSH Terms] OR "neuralgia"[All Fields] OR ("neuropathic"[All Fields] AND "pain"[All Fields]) OR "neuropathic pain"[All Fields]) AND ("therapy"[Subheading] OR "therapy"[All Fields] OR "treatment"[All Fields] OR "therapeutics"[MeSH Terms] OR "therapeutics"[All Fields]) OR ("Brain Stimul"[Journal] OR ("brain"[All Fields] AND "stimulation"[All Fields]) OR "brain stimulation"[All Fields]) OR (non[All Fields] AND invasive[All Fields]) AND (Clinical Trial[ptyp] AND "humans"[MeSH Terms] AND English[lang]).

Study Selection

Study screening will be reported and guided according to Levac *et al.*'s framework and the reporting will follow the Preferred Reporting Items for Systematics Reviews and Meta-analyses' (PRISMA) checklist, and will be performed in four major stages [26]. First, search results will be merged and duplicates will be removed via reference management software (EndNote V.X5). Second, a data extraction form based on the eligibility criteria described above will be developed by the research team. Third, a pilot test of this data extraction form will be performed: two reviewers will independently screen the first 25 titles, abstracts and grey literature of retrieved publications according to the eligibility criteria by using the data extraction form. Fourth, all eligible studies and those classified as unclear (needing more information) will be reviewed in full-text by each reviewer independently to determine if all inclusion criteria are met and if the article is to be included in the study. Inter-rater agreement will again be calculated on a random sample of 25 articles. Disagreement on study eligibility will be discussed and resolved with a third reviewer.

Data extraction

A customised data extraction form will be constructed to extract all relevant data from each study. Two reviewers will use the form to extract data from the first 15 eligible articles. Then they will meet to compare consistency of data extraction and coding. Clarification and updating of the extraction form will be an iterative process until all authors reach consensus on the final version. The data extraction form will be piloted on the first 5 eligible studies to evaluate its reliability in capturing the study data of interest. Data extraction will be undertaken independently by two reviewers.

Descriptive summary tables will be produced to recapitulate the evidence base. The following data will be extracted:

- Author(s) and date;
- Geographical location;
- Research design;
- Aim;
- Research question;
- Methods;

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- Settings;
- Participant characteristics (total number, mean age, gender, pathology if available);
- Primary cause of pain;
- Pain characteristics;
- Intervention studied/proposed;
- Intervention rationale/mechanism;
- Intervention frequency, site, duration of stimulation and the delay between times of stimulation and the clinical effects;
- Attitude towards intervention (positive, negative feelings towards intervention – from the healthcare provider; positive or negative feelings towards treatment – from the participant/patient, etc);
- NIBS characteristic (intensity, number of pulses, montage, current pattern/waveform, duration);
- Length of follow up;
- Duration of effect;
- Patient response, participation, and enthusiasm in intervention;
- Simultaneous interventions (if applicable);
- Neuropathic pain comorbidities;
- Key findings;
- Research gaps identified;
- Potential biases in study (assessed using The Cochrane Collaboration's 'Risk of bias' tool for assessing risk of bias) [26];
- Pain outcome (visual analogue scale if available);
- Daily functioning outcome.

Other variables may be added when revising and updating the data extraction form after analysis of the first 15 eligible articles.

Data Synthesis

An initial map will be developed to explore the interventions available for chronic central neuropathic pain. The findings will be quantitatively and qualitatively synthesized for all identified interventions. The quantitative synthesis will comprise of numerical counts such as number of interventions by setting, and by application. A qualitative description approach will be used to describe the characteristics of each intervention (i.e., definition of intervention, mechanism, efficacy, side-effects, frequency of use, feasibility) as well as pain outcome using the visual analogue scale (VAS). The change in VAS, for example, will be used to review the effectiveness of the intervention. The specific metrics that will be included will be determined after the papers have been identified and reviewed.

ETHICS AND DISSEMINATION

There are no protected/private health information collected, hence there will be no need for formal ethical review. The results of the scoping review will be presented at relevant national and international conferences, published in a peer-reviewed journal, and proposed to relevant stakeholders.

CONCLUSION

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This scoping review will map key concepts and empirical results relating to the use of non-invasive brain stimulation to treat and manage chronic central neuropathic pain. It will also provide a comprehensive evaluation of current methodologies and identify gaps for future research, and share the key research findings with relevant stakeholders.

ACKNOLWEDGEMENT
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AUTHOR CONTRIBUTIONS
Designed the scoping review protocol: MLC KM. Performed literature search: MLC LY KM BT NJ. Contributed analysis tools: LY JB BT NJ. Wrote the paper: MLC. Proofread manuscript: MLC LY JB KM BT NJ.

We have read and understood BMJ policy on declaration of interests and declare that we have no competing interests.

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PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item
ADMINISTRATIVE INFORMATION		
Title: **(page 1)**		
Identification	1a	Identify the report as a protocol of a systematic review
Update	1b	If the protocol is for an update of a previous systematic review, identify as such
Registration **(none)**	2	If registered, provide the name of the registry (such as PROSPERO) and registration number
Authors: **(page 1)**		
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author
Contributions **(page 9)**	3b	Describe contributions of protocol authors and identify the guarantor of the review
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments
Support: **(none)**		
Sources	5a	Indicate sources of financial or other support for the review
Sponsor	5b	Provide name for the review funder and/or sponsor
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol
INTRODUCTION		
Rationale **(page 2-3)**	6	Describe the rationale for the review in the context of what is already known
Objectives **(page 3)**	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)
METHODS		
Eligibility criteria **(page 4)**	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage
Search strategy **(page 5)**	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated
Study records: **(page 5)**		
Data management **(page 5)**	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review

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Selection process **(page 5)**	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)
Data collection process **(page 5-6)**	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators
Data items **(page 6)**	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications
Outcomes and prioritization **(page 5-6)**	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale
Risk of bias in individual studies **(page 6)**	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis
Data synthesis **(page 6)**	15a	Describe criteria under which study data will be quantitatively synthesised
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned
Meta-bias(es) **(page 6)**	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)
Confidence in cumulative evidence **(n/a for scoping review)**	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

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