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Neurophysiological Changes of Brain and Spinal Cord in Individuals with Patellofemoral Pain: a Systematic Review and Meta-analysis Protocol

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ABSTRACT

Introduction Reduced neuromuscular control due to altered neurophysiological functions of the central nervous system has been suggested to cause movement deficits in individuals with patellofemoral pain (PFP). However, the underlying neurophysiological measures of brain and spinal cord in this population remain to be poorly understood. The purpose of this systematic review is to evaluate the evidence for altered cortical and spinal cord functions in individuals with PFP.

Methods and analysis The protocol for conducting the review was prepared using the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols guidelines. We will systematically search the literature that examines cortical and spinal cord functions in individuals with PFP, aged 18–45 years. The studies for cross-sectional, prospective, longitudinal, case-control and randomised control trial designs will be included from the following databases: PubMed (MEDLINE), EMBASE and Web of Science. Only studies published in English prior to 1 February 2021 will be included. The risk of bias and quality assessment will be performed using National Institutes of Health's Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies. We will conduct meta-analysis of the data where appropriate. Narrative synthesis will be taken if a meta-analysis is not possible.

Ethics and dissemination This is a systematic review from the existing literature and does not require ethical approval. The results of this study will be published in a peer-reviewed journal in the field of rehabilitation medicine, sports/orthopaedic medicine or neurology, regardless of the outcome.

PROSPERO registration number CRD42020212128.

INTRODUCTION

Patellofemoral pain (PFP) is prevalent throughout the lifespan, affecting not only the general population but also specific populations such as adolescents, highly active individuals and the military, with an incidence rate of 9%–15%.¹ Furthermore, women are 2.23 times more likely to experience PFP than men, with a prevalence of 12%–13% in those

Strengths and limitations of this study

- This is the first systematic review of functional changes in brain and spinal cord from chronic patellofemoral pain.
- This protocol was written using the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols guidelines.
- Articles will be assessed for risk of bias and methodological quality by two independent researchers.
- Where appropriate, meta-analysis will be performed.
- One limitation is that studies not published in English will be excluded; thus, the review results may not represent all literature in this topic.

aged 18–35 years.² One hallmark symptom of PFP is pain around or behind the patella, which is often exacerbated by loading of the patellofemoral joint in a flexed knee position.^{3 4}

Individuals with PFP often exhibit difficulty performing weight-bearing tasks such as negotiating stairs, squatting and running.³ For example, an increase in dynamic knee valgus is a common movement deficit observed during those functional movements in this population.^{5 6} This atypical pattern is the result of excessive hip adduction and internal rotation, which causes excessive loading to the lateral aspect of patella and PFP.^{5 6} In addition, increased hip adduction during functional activities has been found to be a contributing factor of a higher level of pain and dysfunction in women with PFP.⁷ As weakness of hip musculature (ie, hip abductors and hip external rotators) is believed to attribute to excessive knee valgus during weight-bearing activities,⁵ addressing hip strength deficits is a commonly theorised treatment for such faulty movements.⁸ However, while hip muscle strengthening programmes have been shown to reduce pain and hip weakness deficits, the evidence supporting hip muscle strengthening

on improving dynamic knee valgus during functional activities is limited.^{8–10} A recent systematic review with meta-analysis further suggests that hip muscle weakness is not a risk factor of developing future PFP in adults.¹¹

In fact, as neuromuscular control is essential while performing functional movements, it has been found that a gait retraining protocol effectively corrects the frontal plane movement deficits during running in individuals with PFP, while a hip muscle strengthening programme alone does not.⁹ These gait retraining protocols often incorporate motor learning principles, such as faded feedback and external focus feedback designs.^{9,12} In addition, the skill of maintaining proper movements was found to be transferable to unlearned tasks, such as squatting and stair descent.¹² The recent literature supports the role of corticomotor excitability in hip kinematics during weight-bearing activities in healthy individuals.¹³ These findings highlight the needs for examining the role of neurophysiological measures of the brain and spinal cord in individuals with PFP, as the mechanisms underlying altered neuromuscular control in this population remain to be poorly understood.

At the cortical level, the motor cortex plays a critical role in motor output, and altered motor cortex structure and function underlie movement dysfunction in individuals with PFP. Motor evoked potentials of quadriceps muscles in response to transcranial magnetic stimulations revealed altered corticomotor control in individuals with chronic PFP compared with asymptomatic individuals.¹⁴ Furthermore, persistent PFP has been reported to induce reorganisation of the primary motor cortex, with shifts in motor representations of all three quadriceps muscles, increased overlap of motor cortex representations and reduced volume, compared with asymptomatic individuals.¹⁵ At the level of the spinal cord, the H-reflex is a commonly used electrophysiological test for quantifying the excitatory behaviour of monosynaptic Ia afferent volleys in the spinal cord circuitry. This assessment of the Ia afferent-motoneuronal pathway is used for investigating the role and transmission of the spinal circuitry underlying motor control and its adaptations in movement disorders, lesions or training.^{16–19} Women with chronic PFP had significantly lower H-reflex amplitudes in the vastus medialis muscle and lower patellar tendon reflexes compared with pain-free individuals. Furthermore, the altered H-reflex amplitudes were strongly associated with pain levels, where women with PFP who had larger amplitudes of H-reflexes in the vastus medialis muscle had lower pain.^{20–22} Understanding the pathological neurophysiology underlying PFP is thus important for the future design of rehabilitation protocols targeting neural control underlying movement dysfunction in the population.

OBJECTIVES

The objective of this study is to evaluate the evidence for altered cortical and spinal cord functions in individuals with PFP.

Table 1 Search themes and search terms

Search theme	Search terms
Patellofemoral pain	'patellofemoral pain' OR 'patellofemoral pain syndrome' OR 'patellofemoral syndrome' OR 'anterior knee pain' OR 'anterior knee pain syndrome'
Brain	'cortical reorganization' OR 'corticospinal excitability' OR 'transcranial magnetic stimulation' OR 'motor evoked potential' OR 'mapping' OR 'magnetic resonance imaging' OR 'functional magnetic resonance imaging'
Spinal cord	'spinal excitability' OR 'H-reflex' OR 'Hoffman reflex' OR 'spinal reflex' OR 'stretch reflex'

METHODS

Protocol

The protocol for conducting the review was prepared using the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols guidelines.²³ In addition, this systematic review protocol has been registered with the International Prospective Register of Systematic Reviews.

Search strategy

We will conduct the literature search using the following databases: PubMed (MEDLINE), EMBASE and Web of Science. Search strings and Medical Subject Headings keywords related to the theme of PFP and non-invasive assessments of brain and spinal cord functions will be used (table 1). All search themes will be combined using the Boolean operators 'AND' and 'OR'. In addition, reviewers will manually screen the reference list of each article yielded from the search for additional articles. Methods for conducting this systematic review were developed using the Guidelines for Meta-Analysis and Systematic Reviews of Observational Studies.²⁴

Eligibility criteria

The eligibility criteria for this study are shown in table 2.

Types of studies

Peer-reviewed studies from cross-sectional, prospective, longitudinal, case-control and randomised control trial designs that examine the neurophysiological measures of cortical and spinal cord functions in persons with PFP will be included. Cross-sectional studies will be included if they meet the eligibility criteria (table 2). Case-control and randomised control trials will be included if the baseline data provide relevant information to the objective of this review. Prospective and longitudinal studies will be included if relevant data are available in individuals who develop PFP during the course of the study.

Table 2 Inclusion and exclusion criteria for papers

Inclusion criteria	Exclusion criteria
1. Peer-reviewed, full-text studies published in English prior to 1 February 2021	1. Studies not published in English
2. Quantitative studies using cross-sectional, prospective, longitudinal, case-control or randomised control trial designs	2. Commentary, review or editorial/opinion papers
3. Participants are individuals aged between 18 and 45 years who have had PFP for at least 3 months	3. Theses, dissertation or conference proceedings
4. Studies including data from a control group of asymptomatic individuals	4. Participants younger than 18 years of age
5. Studies that investigate the functions of the brain and spinal cord using the following assessments: transcranial magnetic stimulation, magnetic resonance imaging (including structural and functional) and peripheral nerve stimulation to assess spinal circuit function (including H-reflex gain, recruitment curve slopes, amplitudes)	5. Participants older than 45 years of age
	6. Participants report PFP less than 3 months
	7. Studies that do not include a control group of individuals with no PFP or studies that use the asymptomatic limb as the control for comparisons

PFP, patellofemoral pain.

Types of participants

Participants are adults (aged between 18 and 45 years²⁵) who have PFP. PFP is a common, chronic musculoskeletal condition, presenting as pain around or behind the patella during patellofemoral joint loading activities (eg, squatting, stair ambulation and running).^{3,4} Pain experienced by the participants should be greater than 3 months in duration, which is the chronic phase of pain.²⁶ No restrictions will be placed on the sex. Studies with participants younger than 18 years will be excluded to avoid bias from including immature central nervous system function in paediatric/adolescent populations. Studies with participants older than 45 years will also be excluded to avoid the confounding findings related to patellofemoral joint osteoarthritis. Studies that do not include a control group of individuals with no PFP or studies that use the asymptomatic limb as the control for comparisons will also be excluded.

Types of outcome measures

Measures of neurophysiological changes should be reported in the eligible studies. These measures include cortical excitability as measured by transcranial magnetic stimulation, magnetic resonance imaging (including structural and functional) and peripheral nerve

stimulation for assessment of spinal circuit function (ie, H-reflex gain and/or recruitment curve slopes and/or amplitudes elicited via nerve stimulations). The units of variables associated with H-reflex assessments are likely to vary and may include, but not limited to, millivolts, volts or ratios.

Data management

Two reviewers will evaluate the titles and abstracts of all studies yielded by the search with the inclusion and exclusion criteria, independently. Full texts of all eligible articles will be obtained and organised using EndNote X9 (Clarivate Analytics, Massachusetts) software. Duplicate studies will be removed. Should there be uncertainty or disagreement about the eligibility of a study between the two reviewers, we will consult an additional reviewer to reach a consensus.

Data extraction

The main data to be analysed within the abstract include descriptive information regarding the study (study design) and neurophysiological assessments that examine the functions of the brain and spinal cord using transcranial magnetic stimulation, magnetic resonance imaging (including structural and functional) and peripheral nerve stimulation for assessing spinal circuit function (H-reflex assessments).

Risk of bias and quality assessment

Two researchers will perform the assessment of risk of bias and quality independently. In the case of any disagreement, we will consult an additional reviewer. Eligible studies will be assessed by two investigators independently for methodological quality using National Institutes of Health's Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies.²⁷ This 14-item assessment tool included 'yes', 'no', 'not applicable' and 'not reported' as possible responses. A score of 0 was given for 'no' and 1 for 'yes'. The methodological quality for each study will be categorised as good, fair or poor.²⁷

Strategy for data synthesis

Effect size and 95% CI will be calculated. We will use Cohen's d for analysis of effect size estimates, with d=0.2 representing small effect size, d=0.5 representing medium effect size and d=0.8 representing large effect size.²⁸ Quantitative data will be presented as effect estimates. Statistical heterogeneity will be assessed using the I² statistics, where I²<25% represents low heterogeneity, I² of 25%–50% represents medium heterogeneity and I²>50% represents high heterogeneity.²⁹ Statistical significance will be set at p<0.05. Narrative synthesis will be taken if a meta-analysis is not possible.

Patient and public involvement

The development of the research question and outcome measures was informed by the fact that patients with PFP often exhibit movement deficits, likely from changes in their neurophysiological function of the central nervous

system. In this systematic review, we aim to examine the cortical and spinal cord functions in adult patients with PFP, as PFP is a common disorder in this population. We plan to submit our findings to a peer-reviewed journal in the field of rehabilitation medicine, sports/orthopaedic medicine or neurology. As such, in addition to obtaining the research findings on their own, patients with PFP may receive the information from the healthcare professionals (eg, sports/orthopaedic physicians, physical therapists and athletic trainers).

DISCUSSION

This study will play an important role in evidence-based practice as it provides rich, in-depth understanding of the cortical and spinal cord functions in individuals with PFP through a thorough review and appraisal process. The analyses from the review findings will provide insight into the neurophysiological mechanisms underlying patellofemoral joint dysfunction, which in turn may be useful in improving movement patterns and symptoms in individuals with PFP. Efforts will also be made to conduct a meta-analysis; however, whether a synthesis of data can be made will depend on the variation between papers.

In addition to thorough analyses of findings in this topic, the strength and quality of the literature will be carefully examined. This information will guide future research in this field to better provide high-quality design and evidence in understanding the neurophysiological functions in individuals with PFP. We anticipated that the findings of this review will be of interest to various healthcare professionals, such as sports/orthopaedic physicians, physical therapists and athletic trainers, as well as to individuals who experience PFP.

Ethics and dissemination

This review meets the criteria for waiver of ethical approval, as defined by the Institutional Review Board at the University of Nevada, Las Vegas. The results of this study will be published in a peer-reviewed journal in the field of rehabilitation medicine, sports/orthopaedic medicine or neurology, regardless of the findings.

Contributors JNL and KH conceived and designed the study. JNL, SB, AM, KM, DN and KH developed the search strategies and analysis of the study. JNL, SB, AM, KM, DN and KH were involved in writing and editing of the study protocol. All authors approved the final manuscript.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

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