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Exploring pain interference with motor skill learning in humans: A Protocol for a systematic review

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Abstract

Introduction

Motor skill learning is intrinsic to living. Pain demands attention and may disrupt non-pain related goals such as learning new motor skills. Although rehabilitation approaches have utilised motor skill learning for individuals in pain, there is uncertainty on the impact of pain on learning motor skills.

Methods and analysis

The protocol of this systematic review has been designed and is reported in accordance with criteria set out by Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) guidelines. Web of Science, Scopus, Medline, EMBASE and CINAHL databases, key journals and grey literature will be searched up until December 2020, using subject specific searches. Two independent assessors will oversee searching, screening, extracting data and assessment of risk of bias. Both behavioural and activity-dependent outcome measures of motor learning will be synthesised and presented. The quality of evidence will be assessed using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach.

Ethics and dissemination

No patient data will be collected and therefore ethical approval was not required for this review. The results of this review will provide further understanding into the complex effects of pain and may guide clinicians in their use of motor learning strategies for the rehabilitation of individuals in pain. The results of this review will be published in a peer review journal and presented at scientific conferences.

PROSPERO registration number: TBC

Strengths and limitations of this study

- This is the first systematic review synthesising evidence exploring pain interference with motor learning in humans.
- The design of this study follows the recommendations laid out in the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocol guidelines.
- The meta-analysis will include only low and moderate risk of bias studies, assessed using appropriate risk of bias tools, for both randomized control and non-randomized studies.
- To provide consistency in reporting results, the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach will be utilised.
- Due to the potential for large methodological and clinical heterogeneity of the included studies sub-grouping will be explored to ensure useful conclusions for researchers and clinicians.

Introduction

In 2020 the international association of pain (IASP) revised its definition of pain to reflect the progress made over the last 30 years around the understanding of pain. The new definition states that pain is "an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage."[1 (p 2)] The new definition clearly notes that pain and nociception can be seen as different phenomena. Whereas nociception refers to activity that occurs in the nervous system in response to a noxious stimulus, pain is a 'personal experience that can be influenced by varying degrees by biological, psychological and social factors'.[1 (p 2)]

The experience of pain is considered primarily protective; it is perceived as aversive and motivates individuals to act.[2] Such action disrupts goal orientated behaviour.[3] For example, pain related goals, such as seeking relief, can conflict with non-pain goals,[4] such as learning a new skill or using an already acquired one. In short-lasting pain, brief disruption of functional goals is seen as beneficial or protective and is considered to have little impact on learning or memory of the disrupted functional goals.

In some cases, the presence of an ongoing perceived threat, despite the defensive action of a brief disruption of functional goals, results in persistent protective behaviour and persistence of a pain experience.[2] Such persistent pain is the leading cause of disability according to the 2016 Global Burden of disease review.[5] In individuals with persistent pain, prolonged defensive action and interruption of functional tasks may limit encoding of activity and task related information into memory.[6] Research has consistently demonstrated activities are performed with less accuracy and more slowly after being interrupted by pain.[7]

Pain disrupts the motor system at many levels.[8] One such change is an alteration in the ability of the motor system to adapt to repeated practice associated with impaired skill performance.[9] Boudreau and colleagues[9] demonstrated reduced motor performance following motor skill learning in the presence of pain and reduced motor cortex excitability in the primary motor cortex, a measure associated with cortical plasticity.[10]

Motor skill learning involves repeated task practice, resulting in effortless and efficient performance of movement sequences, as well as grouping together of motor actions, known as chunking.[11] Research has identified three stages of motor learning: early (acquisition), intermediate (consolidation) and late stage (retention). Early stage is within session learning, consolidation is learning that occurs offline or in between sessions and retention refers to learning across more than one session.[12] Motor skill learning is intrinsic to life. Novel life experiences, such as learning to walk or drive, require adaptations of the motor system to maintain efficient interactions with the environment requiring minimal attentional processes. Conversely, loss of function due to injury or disease requires relearning of previously well-established motor patterns or learning new motor skills within the limitations of function. Motor skill learning is common to many rehabilitation approaches used to help individuals manage their pain. Principles of motor skill learning applied to exercise for low back pain has been shown to reduce pain and improve muscle activity which is accompanied by activity dependent plasticity enhancing normalisation of networks of the primary motor cortex.[13]

The effectiveness of motor skill learning is commonly assessed using behavioural performance measures. These include assessing for reduction in reaction times, errors, requirements of attentional processes, changes in performance speed or movement synergies and kinematics.[14] A challenge for studies exploring the changes associated with motor skill learning is decoupling the performance improvements due to motor learning from performance speed changes associated with better motor execution.[15] Secondary outcome measures exploring neural correlates related to motor learning have been used to provide further insights into processes underlying the acquisition of motor skills.[15] Activity dependent plasticity can be demonstrated using neuroimaging techniques such as functional magnetic resonance imaging (fMRI) (changes in amplitude, temporal and spatial characteristics of blood oxygenation level dependent (BOLD) signals)[16] transcranial magnetic stimulation (TMS) (changes in amplitude, temporal and spatial characteristics of motor evoked potentials (MEP) and intra cortical excitability)[10] and electroencephalogram (EEG) (changes in amplitude of somatosensory evoked potentials (SEPs))[17].

Early animal studies demonstrated impaired adaptive learning in the presences of nociception in spinalized rats.[18 19] Subsequent research exploring this phenomenon in humans has provided mixed results. A within subject study design from 2007[9] explored pain interference in the acquisition phase of motor learning. The authors demonstrated an impairment of improvements in performance behaviour following 15mins of motor skill learning in the presence of capsaicin-induced pain. In contrast to the above study, Bouffard et al (2014)[20] demonstrated no impairment in acquisition of a locomotion motor skill when pain was experienced during the task. Instead they found impairments in the retention phase of learning 48hrs after the session. Differences in results may be explained in part due to the use of a tonic pain paradigm, not influenced by movement, and the choice of a motor adaptation intervention, reportedly dependent on different neural mechanisms compared to motor sequence learning.[21] Subsequent studies exploring impact of pain on behavioural measures following motor learning have demonstrated no change,[22-25] or an improvement in performance.[26-28]

No systematic review has synthesised the evidence for the impact of pain on behavioural performance measures and/or activity-dependent plasticity measures following motor skill learning in humans. The wide variety of motor learning paradigms (motor adaptation training versus motor sequence learning) and pain paradigms (tonic pain versus movement-related pain) has meant that comparisons and interpretation of results is not straightforward.

The main objectives of the proposed systematic review are to 1) summarise existing literature to establish the evidence of pain interference on behavioural measures following motor skill learning, 2) summarise activity dependent plasticity measures assessed in the acquired literature in response to the observed pain interference, 3) identify and describe the different pain paradigms and motor skill learning paradigms used in research to explore pain interference of motor skill acquisition, 4) critically evaluate the methodological quality of the studies on pain interference of measures of motor performance following motor skill learning.

Methods

The protocol of this systematic review has been designed following a scoping literature search and is reported in accordance with criteria set out by Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) guidelines and Cochrane handbook.[29 30] The protocol was registered on PROSPERO (CRDXXXXX) on the 7th October 2020.

Eligibility criteria

Inclusion criteria

The PICOS framework (participants, interventions, comparators, outcomes and Study design) will be used to inform the eligibility criteria for the inclusion and exclusion of studies.[29]

Populations

Adults (age $\geq$ 18 years old) experiencing clinical or experimental pain. Including studies on both clinical and experimental pain will provide deeper insights into the interactions of pain with motor learning due to the complex nature of the pain experience. The location of pain will not be restricted. A control group including adults (age$\geq$ 18 years old) with no pain will make up a comparison group. This review will not limit studies by gender but demographic information including gender will be extracted from studies and will be considered in later discussions.

Intervention

Pain during motor skill learning is the experimental condition being analysed. As mentioned above, studies using healthy subjects experiencing experimentally induced pain and studies evaluating people with clinical pain will be included. All study participants will be required to complete a motor skill learning task.

Motor skill learning refers to 'the increasing spatial and temporal accuracy of movements with practice'.[31 (p 558)] Interventions consistent with definitions of motor skill learning used in the introduction of this systematic review will be the focus of this study. Interventions will involve repeated practice and characterised either by the ability of subjects to combine isolated movements into well-rehearsed and smooth sequences or to compensate in response to adaptations of body position or the environment.[12]

Comparators

To explore the impact of pain on the outcome of motor skill learning, an appropriate comparison group is essential. Studies included in this review are required to have a 'healthy, no pain' comparison group or condition. The comparison group or condition will be required to complete the same motor skill intervention as the experimental group.

Outcomes

Primary outcome measures will include behavioural measures related to motor learning. A broad range of behavioural performance measures are used to evaluate the impact of motor learning and will depend largely on the specifics of the motor training. Inclusion will require studies to use behavioural measures that include one or more of the following: speed, efficiency, accuracy, error measurements, attentional demand and effort, perceived effort or movement patterns, including EMG and biomechanical analysis.[14] Secondary outcome measures assessing activity dependent plasticity related to motor learning, will be discussed if available to provide further insight into the understanding of pain interference. These may include changes in amplitude, temporal or spatial characteristics of; BOLD fMRI signals or MEP, evoked by TMS, other TMS paradigms such as TMS -MEP response curves and intra cortical inhibition and/or changes in amplitude of Somatosensory evoked potentials from EEG.

Study design

Following a scoping review, randomised control studies were identified as the gold standard study design to demonstrate the impact of pain on the outcome of the intervention. Other study designs will be considered, including both within and between subject designs, provided that the interference of pain on study outcome measures following motor skill learning can be determined from the results. Clinical pain models make it difficult to randomize group allocation especially when the comparator is healthy subjects. As a result, quasi-experimental studies will be included in this study.

Study duration

Although study duration will not be limited, stages of motor learning will be considered as a scoping review has revealed potentially different interactions of pain with motor learning depending on the stage of learning.[9 20 32] Research has demonstrated potential different neural mechanisms[12] underlying the different stages of motor learning which may influence pain interactions.

Exclusion criteria

The study involves reviewing research exploring the impact of pain on motor learning in intact nervous systems. Therefore, studies exploring populations with known neurological disorders involving peripheral or central nervous system will be excluded. Any study including treatments as an adjunct to motor learning or utilising delayed onset muscle soreness (DOMS) experimental pain models, will be excluded based on the challenges of differentiating the impacts of pain from the impacts of physiological processes related to involved treatments or DOMS. Single case studies or case series along with any studies not published in English will be excluded.

Information sources

Comprehensive searches of the following databases will be completed by the lead reviewer, from inception until December 2020: Web of Science, Scopus, Medline, EMBASE and CINAHL. Hand searching of key journals (Brain sciences, Experimental Brain Research, Journal of Neurophysiology, Pain, Neural plasticity, The Journal of Neurosciences, European Journal of Pain) and preprint repositories, including PsyArxiv and BioArxiv, will be completed followed by a screening exercise of references and citations lists from the articles which meet the eligibility criteria. Authors lists of eligible articles will also be explored.

Search strategy

Search strategies will be designed, including MESH terms and natural language combinations, in conjunction with a health sciences librarian and agreed by all authors. This process will lead to keywords and their synonyms being identified and entered into databases using the Boolean terms AND/OR. The search process will be streamlined by piloting the search strategy with Medline, confirming MESH terms, and checking relevant article search terms. The strategy will then be adapted for use with other databases.

Example of search strategy used in Medline ((((((((pain [MESH]) OR nociception [MESH]) OR noxious stimuli [ALL FIELDS]) OR noxious [ALL FIELDS]) OR arthralgia [ALL FIELDS]) OR myalgia [MESH]) OR neuralgia [MESH]) OR dynia [ALL FIELDS])) AND (((((((((((motor training [ALL FIELDS]) OR motor learning [ALL FIELDS]) OR motor acquisition [ALL FIELDS]) OR skill training [ALL FIELDS]) OR skill learning [ALL FIELDS]) OR skill acquisition [ALL FIELDS]) OR task learning [ALL FIELDS]) OR task training [ALL FIELDS]) OR task acquisition [ALL FIELDS]) OR motor adaptation [All FIELDS]) OR motor sequence learning [ALL Fields])).

Data management

Articles resulting from the search process will be downloaded to Endnote (V9 and later) software (Clarivate Analytics) and duplicates identified and deleted.

Study selection

Two reviewers (DM and EEC) will independently screen titles and abstracts against the predetermined inclusion and exclusion criteria. Studies will be categorised into include, exclude or undecided and full articles will be downloaded for articles meeting the inclusion criteria. For clarification full texts will be downloaded for studies where uncertainty still exists. Any disagreements will be first discussed by the two reviewers (DM and EEC) and where consensus is not reached an independent reviewer will be consulted (AK). Once the above procedure has been completed and full texts have been collated the screening process is repeated. Information on, and reasons for excluding studies will be reported.

Data extraction

Data extraction will be performed using a data extraction form developed from information gathered from early literature scoping activities (see Table 1). The data extraction form will initially be piloted to ensure relevant data is being extracted, and amendments made as appropriate prior to final data extraction. This will be completed independently by both reviewers (DM and EEC) to maintain autonomy.

Data items

Data items to be extracted are documented in Table 1. Authors will be contacted if clarity is required during extraction of data items. This could be due to missing data, ambiguity of results or to avoid duplication, i.e. if more than one article is identified representing a single data set. In such cases the lead and/or corresponding authors will be contacted by e-mail and a reminder will be sent one week later. Where the author does not respond within 4 weeks of the original e-mail, and the clarification impacts on the eligibility of the study, the study will be considered ineligible.

Risk of bias

Experimental randomized control trials (RCTs) and non-randomized studies are likely to be included in this systematic review. The Cochrane risk of bias tool (ROB2) has been the most commonly used tool for assessing risk of bias in RCTs and is now considered the gold standard.[33] Previous systematic reviews have used this same tool to assess risk of bias for non-randomised studies. Quigley et al (2019)[34] reported that risk of bias assessments designed for RCTs were inappropriately used for non-randomized studies, but there is no consensus on the best tool for these studies.[33] The ROBINS-1 will be used to assess risk of bias for non-randomized studies. This tool has been designed to assess risk of bias for non-randomized studies exploring the impacts of interventions and is becoming increasingly popular in recent years.[33] Each study will be independently assessed by the two reviewers (DM and EEC) using the appropriate tool and risk of bias judgements recorded for the study overall (see table 2 and 3). Where a consensus cannot be found a third author (AK) will be consulted. The Cohen Kappa coefficient will be calculated to explore agreement between the two reviewers.

Data synthesis

Where studies are sufficiently homogenous in populations (clinical heterogeneity) and motor learning intervention and outcome measures (methodological heterogeneity) a meta-analysis will be considered. Statistical heterogeneity will be assessed using the I^2 statistics. Due to the heterogeneity of motor training and pain paradigms, and the resulting likelihood of a range of mean effect sizes, the random effects model will likely be more appropriate for meta-analysis. In line with recommendations, the meta-analysis will report on mean effect size and heterogeneity of effect size.[35 36] Only 'low or moderate risk of bias' studies for non-randomized studies (ROBIN-1) and only RCTs categorised as 'Low risk of bias' or 'some concerns' (RoB2) will be included in the meta-analysis. A systematic narrative synthesis will be provided and a summary of the characteristics and findings in the studies will be presented in the text and tables. Studies will be grouped based on whether the studies explore clinical or experimental pain and whether they used a motor sequence learning or motor adaptation training paradigm. Further sub-grouping, due to the presence of either statistical and/or methodological heterogeneity, may be applied as appropriate. Both primary behavioural performance measures and secondary activity-dependent state outcome measures will be included in the synthesis.

Metabiases

Exploring reporting bias is an important part of a systematic review. This will be achieved by undertaking a search of unpublished studies. This will include accessing past conference proceedings of the last 10 years, for example, advances in motor learning and control, pain and progress in motor control, and comprehensive internet searches. Study protocols and resultant published studies will be scrutinised to assess for consistencies.

Confidence in cumulative evidence

To aid the communication of the results of this systematic review the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach will be utilised.[37] The GRADE approach suggests reporting on both the size of the effect and certainty of evidence. Reporting will use statements recommended by the GRADE working group.[38] The size of effect will be reported using 4 categories, *'large effect', 'moderate effect', 'small important effect' and 'trivial, small unimportant effect or no effect'*. Similarly, the 4 categories for certainty of evidence will be *'high', 'moderate', 'low' and 'very low'*. The quality of evidence will be assessed for each of the individual primary outcome measures included in the PICOS.[39] This review includes both RCTs and non-randomized studies. As per guidelines around assessing certainty of evidence initial assessment will begin by classifying the studies design. If relevant studies are RCTs the body of evidence begins as high certainty whereas for non-randomized studies the body of evidence will be considered as low certainty.[40] Ratings can then be lowered or raised based on further assessment of eight further domains. Risk of bias, inconsistency, indirectness, imprecision, and publication bias are reasons for lowering quality of evidence. Conversely, large effect size, dose– response gradient and plausible confounding biases that underestimate the effect size are reasons to upgrade the certainty of evidence.[41]

Patient and public involvement

The research question in this study forms part of a larger discussion within our patient and public involvement meetings. Patients and the public will not be involved in the data collection or data analysis of the review.

Clinical implications

Pain demands action. In acute pain this action is primarily protective such as seeking relief.[2] The resultant protective behaviour may impact on non-pain related functional goals.[3] Disruption of non-pain related functional goals can change our exposure to the environment. Limiting exposure to external stimuli can limit learning or adaptation, an intrinsic component of living. This could include, learning to respond to threat or social cues or learning how to perform a specific functional skill. Skill learning in the presence of pain is common in society. Motor skill learning is used regularly in rehabilitation for individuals in pain.[42-44] The results of studies exploring the impact of pain on motor learning remains conflicting and this may be due to factors that influence pain experience such as attention, cognition and motivation. This systematic review will provide insights into the interference of pain on motor learning and discuss characteristics of pain experience and of motor skill learning that may influence such interference. This may guide clinicians in the most effective approaches to motor skill learning for individuals experiencing pain.

Ethics and dissemination

No research ethics is required since no patient data will be collected. Results of this review will be submitted to be published in a peer review journal and presented at conferences.

Protocol Amendments: Where amendments to the protocol are required, the date and a description and rationale for the changes will be documented.

Author contributions: DM, EEC, AK and DF were responsible for the conception of the research question, development of the protocol and drafting of the manuscript. DM and EEC will act as first and second reviewer. DM will complete searches and retrieve full text manuscripts. AK will be the third reviewer. All authors have approved the final manuscript and will contribute to data interpretation, conclusions and dissemination.

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Table 1: Overview of data items to be extracted from included studies

Content	Data items
General study information	Authors Title Year
Study characteristics	Study design, sample size (both groups), duration of follow up. Inclusion/exclusion criteria.
Participant information	Age, gender (experimental or clinical pain group and comparison group).
Type of intervention	**Pain paradigm**: Type of pain paradigm for experimental group/clinical groups, duration of pain including during training and/or data collection, location, pain intensity. **Motor skill learning paradigm**: Type of motor skill learning (motor sequence learning or motor adaptation learning), details of the type of learning including anatomical location, blocks, sets and duration.

Outcome of interest	**Primary Behavioural performance measures (as appropriate):**
	➢ Speed
	➢ Number of errors
	➢ Accuracy
	➢ Efficiency
	➢ Attentional demands
	➢ Effort/perceived effort
	➢ Movement patterns
	    ○ Electromyography (EMG)
	    ○ Biomechanical analysis
	Secondary neural correlates (as appropriate):
	➢ Somatosensory Evoked Potentials (SEPs).
	➢ Amplitude and temporal characteristics of Motor Evoked potentials (MEPs).
	➢ Motor thresholds.
	➢ Spatial characteristics of motor cortical maps
	➢ Transcranial Magnetic stimulation (TMS)-MEP curves
	➢ Cerebellar Inhibition (CBI).

	➢ Short-Interval intracortical inhibition (SICI). ➢ Change in blood oxygenation level dependent (BOLD) fMRI signals (spatial and temporal.
Results	Main findings, Statistical analysis methods

Judgement	Across Domains	Criterion
Low risk of bias	The study is comparable to a well performed randomised trial	The study is judged to be at low risk of bias for all domains
Moderate risk of bias	The study provides sound evidence for a nonrandomised study but cannot be considered comparable to a well performed randomised trial	The study is judged to be at low or moderate risk of bias for all domain
Serious risk of bias	The study has some important problems	The study is judged to be at serious risk of bias in at least one domain, but not at critical risk of bias in any domain
Critical risk of bias	The study is too problematic to provide any useful evidence and should not be included in any synthesis	The study is judged to be at critical risk of bias in at least one domain
No information	No information on which to base a judgement about risk of bias	There is no clear indication that the study is at serious or critical risk of bias and there is a lack of information in one or more key domains of bias (a judgement is required for this)

Table 2: Interpretation of overall risk of bias judgements in ROBINS-I (Adapted from Stern et al, 2016).[45]

Judgement	Criterion
Low risk of bias	The study is judged to be at low risk of bias for all domains for this result.
Some concerns	The study is judged to raise some concerns in at least one domain for this result, but not to be at high risk of bias for any domain.
High risk of bias	The study is judged to be at high risk of bias in at least one domain for this result. Or The study is judged to have some concerns for multiple domains in a way that

	substantially lowers confidence in the result.

Table 3: Interpretation of overall risk of bias judgements in ROB2 [46]

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Reporting checklist for protocol of a systematic review.

Based on the PRISMA-P guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

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		Reporting Item	Page Number
Title			
Identification	P1	Identify the report as a protocol of a systematic review	
Update	n/a	If the protocol is for an update of a previous systematic review, identify as such	

Registration		
	P2	If registered, provide the name of the registry (such as PROSPERO) and registration number
Authors		
Contact	P1	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author
Contribution	P10	Describe contributions of protocol authors and identify the guarantor of the review
Amendments		
	P10	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		
Sources	P10	Indicate sources of financial or other support for the review
Sponsor	P10	Provide name for the review funder and / or sponsor
Role of sponsor or funder	n/a	Describe roles of funder(s), sponsor(s), and / or institution(s), if any, in developing the protocol
Introduction		

Rationale	P3	Describe the rationale for the review in the context of what is already known
Objectives	P4	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)
Methods		
Eligibility criteria	P5	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	P6-7	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	P7	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 - data management	P7	Describe the mechanism(s) that will be used to manage records and data throughout the review
Study records - selection process	P7	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)

Study records - data collection process	P7	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	P8 and Table 1 P11	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	P6 and Table 1 P11	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	P8	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	P8	Describe criteria under which study data will be quantitatively synthesised
Data synthesis	P8	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 I2, Kendall's τ)
Data synthesis	P8	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)

Data synthesis	P8	If quantitative synthesis is not appropriate, describe the type of summary planned
Meta-bias(es)	P9	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)
Confidence in cumulative evidence	P9	Describe how the strength of the body of evidence will be assessed (such as GRADE)

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Exploring pain interference with motor skill learning in humans: A Protocol for a systematic review

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Exploring pain interference with motor skill learning in humans: A Protocol for a systematic review

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Abstract

Introduction

Motor skill learning is intrinsic to living. Pain demands attention and may disrupt non-pain related goals such as learning new motor skills. Although rehabilitation approaches have utilised motor skill learning for individuals in pain, there is uncertainty on the impact of pain on learning motor skills.

Methods and analysis

The protocol of this systematic review has been designed and is reported in accordance with criteria set out by Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) guidelines. Web of Science, Scopus, Medline, EMBASE and CINAHL databases, key journals and grey literature will be searched up until March 2021, using subject specific searches. Two independent assessors will oversee searching, screening, extracting data and assessment of risk of bias. Both behavioural and activity-dependent outcome measures of motor learning will be synthesised and presented. The quality of evidence will be assessed using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach.

Ethics and dissemination

No patient data will be collected and therefore ethical approval was not required for this review. The results of this review will provide further understanding into the complex effects of pain and may guide clinicians in their use of motor learning strategies for the rehabilitation of individuals in pain. The results of this review will be published in a peer review journal and presented at scientific conferences.

PROSPERO registration number: CRD42020213240

Strengths and limitations of this study

- This is the first systematic review synthesising evidence exploring pain interference with motor learning in humans.
- The design of this study follows the recommendations laid out in the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocol guidelines.
- The meta-analysis will include only low and moderate risk of bias studies, assessed using appropriate risk of bias tools, for both randomized control and non-randomized studies.
- To provide consistency in reporting results, the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach will be utilised.
- Due to the potential for large methodological and clinical heterogeneity of the included studies sub-grouping will be explored to ensure useful conclusions for researchers and clinicians.

Introduction

In 2020 the International Association of Pain (IASP) revised its definition of pain to reflect the progress made over the last thirty years around the understanding of pain. The new definition states that pain is "an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage."[1 (p 2)] The new definition clearly notes that pain is a "personal experience that can be influenced by varying degrees by biological, psychological and social factors."[1 (p 2)]

The experience of pain is considered primarily protective; it is perceived as aversive and motivates individuals to act.[2] Such action disrupts goal orientated behaviour.[3] For example, pain related goals, such as seeking relief, can conflict with non-pain goals,[4] such as learning a new skill or using an already acquired one. In short-lasting pain, brief disruption of functional goals is seen as beneficial or protective and is considered to have little impact on learning or memory of the disrupted functional goals.

In some cases, the presence of an ongoing perceived threat, despite the defensive action of a brief disruption of functional goals, results in persistent protective behaviour and persistence of a pain experience.[2] Such persistent pain is the leading cause of disability according to the 2016 Global Burden of Disease Review.[5] In individuals with persistent pain, prolonged defensive action and interruption of functional tasks may limit encoding of activity and task related information into memory.[6] Research has consistently demonstrated activities are performed with less accuracy and more slowly after being interrupted by pain.[7]

Pain disrupts the motor system at many levels.[8] There is a wealth of behavioural and neurophysiological evidence that pain effects the motor system.[9] One such change is an alteration in the ability of the motor system to adapt to repeated skilled practice associated with impaired skill performance.[10] Boudreau and colleagues[10] demonstrated reduced motor performance following motor skill learning in the presence of pain and reduced motor cortex excitability in the primary motor cortex, a measure associated with cortical plasticity.[11]

In contrast to the above, research demonstrating the neural substrate for such an interaction is less conclusive. Neuroimaging studies have identified a cerebral signature of pain,[12] including areas associated with motor planning and execution, such as the anterior cingulate cortex, premotor and primary motor cortex, cerebellum and basal ganglia.[13 14] Misra (2015)[15] reported an increase in BOLD activity in the mid cingulate cortex in response to pain or movement and when they occurred simultaneously. In the same research group, Coombes (2016)[9] identified areas of the cerebellum (left lobules VI and VIIb) that demonstrate overlapping roles during motor activity and pain and continue to be active in the presence of both. Both these areas have been associated with motor adaptation and have anatomical and functional connections with the motor cortex.[16] Connections from the striatum (basal ganglia) and the cerebellum to the motor cortex have been found to play a key role in early stages of motor skill learning.[17 18]

Motor skill learning involves repeated task practice, resulting in effortless and efficient performance of a movement.[19] Research has identified three stages of motor learning common across all motor learning tasks: early (acquisition), intermediate (consolidation) and late stage (retention). Early stage is within session learning, consolidation is learning that occurs offline or in between sessions and retention refers to learning across more than one session.[18] Motor skill learning is intrinsic to life. Novel life experiences, such as learning to walk or drive, require adaptations of the motor system to maintain efficient interactions with the environment requiring minimal attentional processes. Conversely, loss of function due to injury or disease requires relearning of previously well-established motor patterns or learning new motor skills within the limitations of function. Motor skill learning is common to many rehabilitation approaches used to help individuals manage their pain. Principles of motor skill learning applied to exercise for low back pain has been shown to reduce pain and improve muscle activity which is accompanied by activity dependent plasticity enhancing normalisation of networks of the primary motor cortex.[20]

The effectiveness of motor skill learning is commonly assessed using measures of task performance and activity-dependent plasticity measures. Typical measures of post learning task performance include the number of errors or measurement of spatial errors, measures of accuracy, such as distance away from ideal performance, or temporal measures, such as speed of performance, acceleration or reaction/response times.[17] Measures exploring neural correlates related to motor learning have been used to provide further insights into processes underlying the acquisition of motor skills.[21] Activity dependent plasticity can be demonstrated using neuroimaging techniques such as functional magnetic resonance imaging (fMRI) (changes in amplitude, temporal and spatial characteristics of blood oxygenation level dependent (BOLD) signals)[22] transcranial magnetic stimulation (TMS) (changes in amplitude, temporal and spatial characteristics of motor evoked potentials (MEP) and intra cortical excitability)[11] and electroencephalogram (EEG) (changes in amplitude of somatosensory evoked potentials (SEPs)).[23] Methods of analysing movement strategies people use when learning a motor skill has included but are not limited to end point errors, motor activity using EMG and biomechanical analysis.

Early animal studies demonstrated impaired adaptive learning in the presences of nociception in spinalized rats.[24 25] Subsequent research exploring this phenomenon in humans has provided mixed results. A within subject study design from 2007[10] explored pain interference in the acquisition phase of motor learning during a motor tracing task. The authors demonstrated an impairment of improvements in performance behaviour following fifteen mins of motor skill learning in the presence of capsaicin-induced pain. In contrast to the above study, Bouffard et al (2014)[26] demonstrated no impairment in acquisition of a locomotion motor skill when pain was experienced during the task. Instead, they found impairments in the retention phase of learning forty-eight hours after the session. Differences in results may be explained in part due to the use of a tonic pain paradigm, not influenced by engagement in the task, and the choice of a motor adaptation intervention, reportedly dependent on different neural mechanisms compared to motor sequence learning.[27] Subsequent studies exploring impact of pain on behavioural measures following motor learning have demonstrated no change,[28-31] or an improvement in performance.[32-34]

No systematic review has synthesised the evidence for the impact of pain on task performance measures and/or activity-dependent plasticity measures following motor skill learning in humans. The wide variety of motor learning paradigms, pain paradigms and outcome measures has meant that comparisons and interpretation of results is not straightforward. It is possible that due to varying cognitive and attentional demands of different motor learning tasks the interaction with pain will vary.[35]

The main objectives of the proposed systematic review are to 1) summarise existing literature to establish the evidence of pain interference on task performance measures following motor skill learning, 2) summarise activity dependent plasticity measures associated with the cerebellum, corticospinal tract and primary motor area assessed in the acquired literature in response to the observed pain interference, 3) describe the different pain paradigms and motor skill learning paradigms used in the research to explore pain interference of motor skill acquisition, and discuss how and possible reasons why the resultant interaction varies, 4) critically evaluate the methodological quality of the studies on pain interference of measures of motor performance following motor skill learning.

Methods

The protocol of this systematic review has been designed following a scoping literature search and is reported in accordance with criteria set out by the Cochrane handbook and Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) guidelines.[36 37] The protocol was registered on PROSPERO (CRD42020213240).

Eligibility criteria

Inclusion criteria

The PICOS framework (participants, interventions, comparators, outcomes and Study design) will be used to inform the eligibility criteria for the inclusion and exclusion of studies.[36]

Populations

Adults (age $\geq$ 18 years old) experiencing clinical or experimental pain. Including studies on both clinical and experimental pain will provide deeper insights into the interactions of pain with motor learning due to the complex nature of the pain experience. Clinical pain will be any symptoms of pain included in the IASP definition for pain mentioned above excluding those occurring in the presence of neurological disease or muscular delayed onset of muscle soreness (DOMS). The location of pain will not be restricted. Confounding factors known to impact on the outcome of interventions, such as duration of pain, anxiety, depression, low mood and associated motor and sensory disturbances will be extracted from the studies where appropriate. A control group including adults (age$\geq$ 18 years old) with no pain will make up a comparison group.

Intervention

Pain during motor skill learning is the experimental condition being analysed. As mentioned above, studies using healthy subjects experiencing experimentally induced pain and studies evaluating people with clinical pain will be included. All study participants will be required to complete a motor skill learning task, with the explicit intention to improve their performance across the session.

Motor skill learning refers to "the increasing spatial and temporal accuracy of movements with practice."[38 (p 558)] Implicit and explicit learning interventions consistent with definitions of motor skill learning used in the introduction of this systematic review will be the focus of this study. Interventions will involve repeated practice and characterised either by simple repeated movements, the ability of subjects to combine isolated movements into well-rehearsed and smooth sequences (motor sequence learning, both simple and complex) or to compensate in response to a mechanical perturbation (motor adaptation).[18] Prism adaptation paradigms will be excluded from this review in an attempt to reduce confounding variables, such as the impact of visual perception, focusing on the impact of pain on motor learning. Further variations in the motor learning paradigms will be extracted from the studies and included in the discussions.

Comparators

To explore the impact of pain on the outcome of motor skill learning, an appropriate comparison group is essential. Studies included in this review are required to have a "healthy, no pain" comparison group or condition. A "healthy, no pain" comparison group was defined as subjects with no acute or chronic pain, no history of recurrent pain and no history of psychiatric, neurological or musculoskeletal disease or injury. The comparison group or condition will be required to complete the same motor skill intervention as the experimental group.

Outcomes

Outcome measures will include measures of task performance related to motor learning and activity-dependent plasticity measures. Measures of task performance will include, the number of errors, or measurement of spatial errors, measures of accuracy, such as distance away from ideal performance, or temporal measures, such as speed of performance, acceleration or reaction/response times. Activity dependent plasticity measures related to motor learning will be discussed if available to provide further insight into the understanding of pain interference. These may include changes in amplitude, temporal or spatial characteristics of; BOLD fMRI signals or MEP, evoked by TMS, other TMS paradigms such as TMS -MEP response curves and intra cortical inhibition and/or changes in amplitude of Somatosensory evoked potentials from EEG. A further requirement of included studies is that within-session gains have been established using appropriate data analysis of outcome measures.

Study design

Following a scoping review, randomised control studies were identified as the gold standard study design to demonstrate the impact of pain on the outcome of the intervention. Other study designs will be considered, including both within and between subject designs, provided that the interference of pain on study outcome measures following motor skill learning can be determined from the results. Clinical pain models make it difficult to randomize group allocation especially when the comparator is healthy subjects. As a result, quasi-experimental studies will be included in this study.

Study duration

Although study duration will not be limited, stages of motor learning will be considered as a scoping review has revealed potentially different interactions of pain with motor learning depending on the stage of learning.[10 26 39] Research has demonstrated potential different neural mechanisms[18] underlying the different stages of motor learning which may influence pain interactions.

Exclusion criteria

The study involves reviewing research exploring the impact of pain on motor learning in intact nervous systems. Therefore, studies exploring populations with known neurological disorders involving peripheral or central nervous system will be excluded. Any study including treatments as an adjunct to motor learning or utilising delayed onset muscle soreness (DOMS) experimental pain models, will be excluded based on the challenges of differentiating the impacts of pain from the impacts of physiological processes related to involved treatments or DOMS. Single case studies, case series and review papers along with any studies not published in English will be excluded.

Information sources

Comprehensive searches of the following databases will be completed by the lead reviewer, from inception until March 2021: Web of Science, Scopus, Medline, EMBASE and CINAHL. Hand searching of preprint repositories, including PsyArxiv and BioArxiv, will be completed followed by a screening exercise of references and citations lists from the articles which meet the eligibility criteria. Authors lists of eligible articles will also be explored.

Search strategy

Search strategies were designed (See supplementary file), including MESH terms and natural language combinations, in conjunction with a health sciences librarian and agreed by all authors. Keywords and their synonyms were identified and entered into databases using the Boolean terms AND/OR. The search process was streamlined by piloting the search strategy with Medline, confirming MESH terms, and checking relevant article search terms. The strategy was adapted for use with other databases.

Data management

Articles resulting from the search process will be downloaded to Endnote (V9 and later) software (Clarivate Analytics) and duplicates identified and deleted.

Study selection

Two reviewers (DM and EEC) will independently screen titles and abstracts against the predetermined inclusion and exclusion criteria. Studies will be categorised into include, exclude or undecided and full articles will be downloaded for articles meeting the inclusion criteria. For clarification full texts will be downloaded for studies where uncertainty still exists. Any disagreements will be first discussed by the two reviewers (DM and EEC) and where consensus is not reached an independent reviewer will be consulted (AK). Once the above procedure has been completed and full texts have been collated the screening process is repeated. Information on, and reasons for excluding studies will be reported.

Data extraction

Data extraction will be performed using a data extraction form developed from information gathered from early literature scoping activities (see Table 1). The data extraction form will initially be piloted to ensure relevant data is being extracted, and amendments made as appropriate prior to final data extraction. This will be completed independently by both reviewers (DM and EEC) to maintain autonomy.

Data items

Data items to be extracted are documented in Table 1. Authors will be contacted if clarity is required during extraction of data items. This could be due to missing data, ambiguity of results or to avoid duplication, i.e., if more than one article is identified representing a single data set. In such cases the lead and/or corresponding authors will be contacted by e-mail and a reminder will be sent one week later. Where the author does not respond within four weeks of the original e-mail, and the clarification impacts on the eligibility of the study, the study will be considered ineligible.

Risk of bias

Experimental randomized control trials (RCTs) and non-randomized studies are likely to be included in this systematic review. The Cochrane risk of bias tool (ROB2) has been the most commonly used tool for assessing risk of bias in RCTs and is now considered the gold standard.[40] Previous systematic reviews have used this same tool to assess risk of bias for non-randomised studies. Quigley et al (2019)[41] reported that risk of bias assessments designed for RCTs were inappropriately used for non-randomized studies, but there is no consensus on the best tool for these studies.[40] The ROBINS-1 will be used to assess risk of bias for non-randomized studies. This tool has been designed to assess risk of bias for non-randomized studies exploring the impacts of interventions and is becoming increasingly popular in recent years.[40] Each study will be independently assessed by the two reviewers (DM and EEC) using the appropriate tool and risk of bias judgements recorded for the study overall (see table 2 and 3). Where a consensus cannot be found a third author (AK) will be consulted. The Cohen Kappa coefficient will be calculated to explore agreement between the two reviewers.

Data synthesis

Where studies are sufficiently homogenous in populations (clinical heterogeneity) and motor learning intervention and outcome measures (methodological heterogeneity) a meta-analysis will be considered. Statistical heterogeneity will be assessed using the I^2 statistics. Due to the heterogeneity of motor training and pain paradigms, and the resulting likelihood of a range of mean effect sizes, the random effects model will likely be more appropriate for meta-analysis. In line with recommendations, the meta-analysis will report on mean effect size and heterogeneity of effect size.[42 43] Only "low or moderate risk of bias" studies for non-randomized studies (ROBIN-1)[44] and only RCTs categorised as "Low risk of bias" or "some concerns" (RoB2)[45] will be included in the meta-analysis. A systematic narrative synthesis will be provided and a summary of the characteristics and findings in the studies will be presented in the text and tables. Sub-grouping will be used, as appropriate, to ensure clarity of data analysis and presentation of results. Possible sub-groupings may include different pain paradigms, motor training paradigms or the presence of statistical heterogeneity. Both behavioural performance measures and activity-dependent state outcome measures will be included in the synthesis.

Meta-biases

Exploring reporting bias is an important part of a systematic review. This will be achieved by undertaking a search of unpublished studies. This will include accessing past conference proceedings of the last 10 years, for example, advances in motor learning and control, pain and progress in motor control, and comprehensive internet searches. Study protocols and resultant published studies will be scrutinised to assess for consistencies.

Confidence in cumulative evidence

To aid the communication of the results of this systematic review the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach will be utilised.[46] The GRADE approach suggests reporting on both the size of the effect and certainty of evidence. Reporting will use statements recommended by the GRADE working group.[47] The size of effect will be reported using 4 categories, *"large effect," "moderate effect," "small important effect" and "trivial, small unimportant effect or no effect."* Similarly, the 4 categories for certainty of evidence will be *"high," "moderate," "low" and "very low."* The quality of evidence will be assessed for each of the individual primary outcome measures included in the PICOS.[48] This review includes both RCTs and non-randomized studies. As per guidelines around assessing certainty of evidence initial assessment will begin by classifying the studies design. If relevant studies are RCTs the body of evidence begins as high certainty whereas for non-randomized studies the body of evidence will be considered as low certainty.[49] Ratings can then be lowered or raised based on further assessment of eight further domains. Risk of bias, inconsistency, indirectness, imprecision, and publication bias are reasons for lowering quality of evidence. Conversely, large effect size, dose– response gradient and plausible confounding biases that underestimate the effect size are reasons to upgrade the certainty of evidence.[50]

Patient and public involvement

The research question in this study forms part of a larger discussion within our patient and public involvement meetings. Patients and the public will not be involved in the data collection or data analysis of the review.

Clinical implications

Pain demands action. In acute pain this action is primarily protective such as seeking relief.[2] The resultant protective behaviour may impact on non-pain related functional goals.[3] Disruption of non-pain related functional goals can change our exposure to the environment. Limiting exposure to external stimuli can limit learning or adaptation, an intrinsic component of living. This could include, learning to respond to threat or social cues or learning how to perform a specific functional skill. Skill learning in the presence of pain is common in society. Motor skill learning is used regularly in rehabilitation for individuals in pain.[51-53] The results of studies exploring the impact of pain on motor learning remains conflicting and this may be due to factors that influence pain experience such as attention, cognition and motivation. This systematic review will provide insights into the interference of pain on motor learning and discuss characteristics of pain experience and of motor skill learning that may influence such interference. This may guide clinicians in the most effective approaches to motor skill learning for individuals experiencing pain.

Ethics and dissemination

No research ethics is required since no patient data will be collected. Results of this review will be submitted to be published in a peer review journal and presented at conferences.

Protocol Amendments: Where amendments to the protocol are required, the date and a description and rationale for the changes will be documented.

Author contributions: DM, EEC, AK and DF were responsible for the conception of the research question, development of the protocol and drafting of the manuscript. DM and EEC will act as first and second reviewer. DM will complete searches and retrieve full text manuscripts. AK will be the third reviewer. All authors have approved the final manuscript and will contribute to data interpretation, conclusions and dissemination.

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Table 1: Overview of data items to be extracted from included studies

Content	Data items
General study information	Authors Title Year
Study characteristics	Study design, sample size (both groups), duration of follow up. Inclusion/exclusion criteria.
Participant information	Age, gender (experimental or clinical pain group and comparison group).
Type of intervention	**Pain paradigm**: Type of pain paradigm for experimental group/clinical groups, duration of pain including during training and/or data collection, location, pain intensity, duration of pain, anxiety, depression, low mood and associated motor and sensory disturbances. **Motor skill learning paradigm**: Type of motor skill learning, details on the type of learning including anatomical location, explicit or implicit, discrete or continuous, internally/externally paced, number of blocks, sets and duration, feedback given, familiarisation, sleep diary (retention).
Outcome of interest	**Task performance measures (as appropriate):** ➢ Speed ➢ Number of errors ➢ Accuracy/error measure. ➢ Reaction /response times **Neural correlates (as appropriate):** ➢ Somatosensory Evoked Potentials (SEPs). ➢ Amplitude and temporal characteristics of Motor Evoked potentials (MEPs). ➢ Motor thresholds. ➢ Spatial characteristics of motor cortical maps ➢ Transcranial Magnetic stimulation (TMS)-MEP curves ➢ Cerebellar Inhibition (CBI). ➢ Short-Interval intracortical inhibition (SICI). ➢ Change in blood oxygenation level dependent (BOLD) fMRI signals (spatial and temporal.

Results	Main findings, Statistical analysis methods

Judgement	Across Domains	Criterion
Low risk of bias	The study is comparable to a well performed randomised trial.	The study is judged to be at low risk of bias for all domains
Moderate risk of bias	The study provides sound evidence for a nonrandomised study but cannot be considered comparable to a well performed randomised trial	The study is judged to be at low or moderate risk of bias for all domain
Serious risk of bias	The study has some important problems	The study is judged to be at serious risk of bias in at least one domain, but not at critical risk of bias in any domain
Critical risk of bias	The study is too problematic to provide any useful evidence and should not be included in any synthesis	The study is judged to be at critical risk of bias in at least one domain.
No information	No information on which to base a judgement about risk of bias.	There is no clear indication that the study is at serious or critical risk of bias and there is a lack of information in one or more key domains of bias (a judgement is required for this)

Table 2: Interpretation of overall risk of bias judgements in ROBINS-I.

Judgement	Criterion
Low risk of bias	The study is judged to be at low risk of bias for all domains for this result.
Some concerns	The study is judged to raise some concerns in at least one domain for this result, but not to be at high risk of bias for any domain.
High risk of bias	The study is judged to be at high risk of bias in at least one domain for this result. Or The study is judged to have some concerns for multiple domains in a way that substantially lowers confidence in the result.

Table 3: Interpretation of overall risk of bias judgements in ROB2.

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Search Strategy

Example of MEDLINE search;

((TITLE-ABS-KEY (((pain OR nociception OR noxious OR *algia OR athralgia OR myalgia OR neuralgia OR *dynia) W/10 (interfere* OR *ffect* OR impair* OR impact* OR associat* OR imped* OR change* OR alter* OR disturb* OR influence* OR modif* OR determine* OR reduc*)))) AND (TITLE-ABS-KEY ((performance OR *plasticity OR *excitability) W/10 (training OR learning OR acquisition OR practice))) AND (TITLE-ABS-KEY ((performance OR *plasticity OR *excitability) W/10 (*motor OR skill OR task)))) OR ((TITLE-ABS-KEY (((pain OR nociception OR noxious OR *algia OR athralgia OR myalgia OR neuralgia OR *dynia) W/10 (interfere* OR *ffect* OR impair* OR impact* OR associat* OR imped* OR change* OR alter* OR disturb* OR influence* OR modif* OR determine* OR reduc*)))) AND ((TITLE-ABS-KEY ("*motor training" OR "*motor learning" OR "*motor acquisition" OR "*motor practice" OR "Skill training" OR "Skill learning" OR "Skill acquisition" OR "Skill practice" OR "Task learning" OR "task training" OR "Task acquisition" OR "Task practice")) OR (TITLE-ABS-KEY ("*motor adaptation" OR "motor sequence learning" OR "repeated practice"))))

Reporting checklist for protocol of a systematic review.

Based on the PRISMA-P guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the PRISMA-Preporting guidelines, and cite them as:

Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart LA. Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) 2015 statement. Syst Rev. 2015;4(1):1.

		Reporting Item	Page Number
Title			
Identification	P1	Identify the report as a protocol of a systematic review	
Update	n/a	If the protocol is for an update of a previous systematic review, identify as such	

Registration		
	P2	If registered, provide the name of the registry (such as PROSPERO) and registration number
Authors		
Contact	P1	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author
Contribution	P10	Describe contributions of protocol authors and identify the guarantor of the review
Amendments		
	P10	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		
Sources	P10	Indicate sources of financial or other support for the review
Sponsor	P10	Provide name for the review funder and / or sponsor
Role of sponsor or funder	n/a	Describe roles of funder(s), sponsor(s), and / or institution(s), if any, in developing the protocol
Introduction		

Rationale	P3	Describe the rationale for the review in the context of what is already known
Objectives	P4	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)
Methods		
Eligibility criteria	P5	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	P6-7	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	P7	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 - data management	P7	Describe the mechanism(s) that will be used to manage records and data throughout the review
Study records - selection process	P7	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)

Study records - data collection process	P7	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	P8 and Table 1 P11	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	P6 and Table 1 P11	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	P8	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	P8	Describe criteria under which study data will be quantitatively synthesised
Data synthesis	P8	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 I2, Kendall's τ)
Data synthesis	P8	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)

Data synthesis	P8	If quantitative synthesis is not appropriate, describe the type of summary planned
Meta-bias(es)	P9	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)
Confidence in cumulative evidence	P9	Describe how the strength of the body of evidence will be assessed (such as GRADE)