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Protocol

Do brain activity patterns differ between chronic musculoskeletal pain patients and healthy controls as measured by functional neuroimaging techniques? A systematic review protocol

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ABSTRACT

Background: Chronic musculoskeletal pain has been associated with changes at various levels regarding pain processing. One of the fields that has highlighted such differences between healthy individuals and people suffering from chronic musculoskeletal pain is neuroimaging of the brain. The mixed results arising from the different pathologies in addition to the use of different imaging modalities do not offer a conclusive overview, implicating the interpretation of the findings and their relevance as a causal or a consequent factor to chronification of pain. The aim of this systematic review is to provide a comprehensive summary of the available evidence assessing chronic painful conditions against healthy populations per functional neuroimaging modality.
Methods: The protocol for this systematic review was informed and reported in line with the Preferred Reporting Items for Systematic Reviews. The databases that will be searched from inception to a prespecified date include PubMed, EMBASE (Ovid Interface), Scopus, Cochrane Library and Web of Science (Clarivate Analytics). Risk of bias will be assessed with the Newcastle-Ottawa tool and the quality of the cumulative evidence with the Grading of Recommendations, Assessment, Development and Evaluation guidelines.
Conclusions: The results of this review will provide an up-to-date report on what the main findings of brain neuroimaging per pathological population and imaging modality are, assessing at the same time the quality of the evidence and indicating future directions in the field of neuroimaging assessment of the musculoskeletal patient.
Trial Registration: Current control trial is CRD42024494813.

Keywords: Chronic pain, Brain neuroimaging, Case-control

INTRODUCTION

According to the World Health Organization (WHO), pain of musculoskeletal origin affects approximately 1.71 billion people worldwide (WHO, 2022). Despite being difficult to estimate due to the wide spectrum of conditions included in it, the rate of people suffering from chronic pain has been reported to be up to 47% of the general population.[1] Chronic musculoskeletal pain is generally defined as pain persisting for more than 3 months, related to the main musculoskeletal tissues,

usually accompanied by various levels of disability or distress.[2]

The disproportionate features of the painful experience beyond the natural history of many chronic musculoskeletal conditions or the abnormal pain processing during their presence have led to the description of central sensitization, a distinct entity in the pathophysiology of pain where an amplification of the neural signalling within the central nervous system is thought to take place.[3] Despite not being easily identifiable, neuroplastic changes have been described to underpin the CNS' increased responsiveness, without allowing to establish a causal effect though.[4]

Between the consistent findings which has served as one of the pathways to understand chronic musculoskeletal pain and central sensitization better, has been the alterations observed when exploring the structure and function of the chronic musculoskeletal pain patients' brain.[5,6] During the last 10 to 15 years, there has been a massive amount of research, mainly of observational nature, attempting to shed some light on what these associations mean and how they relate to the clinical symptomatology of the different musculoskeletal conditions.[7] Indeed, a plethora of studies have shown brain regions with distinct features when assessed structurally or functionally against healthy controls, or even in different stages of chronicity of the pathology the individuals seek help for.[8-11]

Among the studies that have mainly looked at the structure of the brain, key differences have been highlighted around the key measures usually assessed such as regional or whole brain volume, cortical thickness, grey matter (GM) morphology and white matter (WM) integrity.[5,6,12] As for the functional assessment of the brain, the establishment of the pain matrix concept as the network of pain processing as well as the records of resting state connectivity in different populations suffering from chronic pain, has further allowed to distinguish altered processing.[13] Previous literature has provided valuable insights into this by either comparing pain processing between healthy controls or acute pain patients versus chronic musculoskeletal pain patients under the provision of a noxious stimulus or even by directly monitoring functional brain activity and connectivity patterns during the transition from acute to chronic pain, pinpointing the dynamic nature of the pain experience.[8-11]

Nevertheless, as the imaging technologies used for structural and functional imaging of the brain are continually improving and different research settings have access to different equipment, it is becoming increasingly difficult to summarize all the available findings implicating brain regions or networks and determine their relevance with chronic musculoskeletal pain. More conclusive data is needed in order to set the basis on what future research focuses on while using a specific neuroimaging modality to investigate specific musculoskeletal populations.

The aim of this systematic review is to collectively summarize the available data on functional neuroimaging studies assessing chronic musculoskeletal pain patients against healthy controls as well as provide a clear view of the findings by brain region or network per modality used to assess each of the different musculoskeletal conditions.

METHODS

The conduction of this systematic review will follow the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines.[14] Compliance with PRISMA item checklist when conducting a systematic review has been proposed to maximise transparency, accuracy and completeness of both the review process itself as well as the findings emerging from it.[15] According to the item checklist the following sections arise in advance: eligibility criteria (section 2.1), information sources (section 2.2), search strategy (section 2.3), selection process of the studies (section 2.4), data collection process (sections 2.5 and 2.6), risk of bias assessment (section 2.7).

Eligibility criteria

The inclusion criteria will be the following: Studies will be considered eligible when involving adult humans with chronic musculoskeletal pain assessed against a healthy control group while investigating brain activity with one or more of the following techniques: fMRI, ALS, PET, EEG, MEG, fNIRS, PET and SPECT scan. Incorporating these elements to the PICO acronym to frame the research question properly, the population of interest (P) will be participants with chronic pain, being assessed by a functional neuroimaging modality (I) compared to a control group of healthy controls (C) as for possible differences in brain activation patterns (O).[16,17] Studies that will be of case control design and whose primary objective was to examine possible post-intervention differences or during the provision of any type of treatment or stimulation will be taken into consideration by using exclusively their baseline measurement and only when a clear comparison or mention of the patient group versus the healthy group is made. Full-text studies, including in press or accepted studies and published only in English prior to a predetermined date.

The exclusion criteria will be studies including participants with acute or chronic pain which is not of musculoskeletal origin, for example, pain associated with spinal cord injury, stroke, cancer or visceral pain. Studies including participants with systemic local or auto-immune conditions, clinical depression or psychiatric disorders and studies that do not include a healthy control group or use the unaffected limb or body side as a control.

Information sources

The electronic databases that will be searched from inception to a prespecified date are the following: PubMed, EMBASE (Ovid Interface), Scopus, Cochrane Library and Web of Science (Clarivate Analytics). Database-specific search strategies will be developed including medical subject headings (MeSH) where appropriate in order to better inform the research strategy and make it more efficient.[18] Reference lists of relevant articles will be searched in order to expand the search strategy return and detect similar work not captured by the initial search strategy.

Search strategy

To achieve the maximum article retrieval, the initial search of the databases will be performed without restrictions (filters) on language or date of publication. Pilot testing of the strategy will take place in order to assess the ability of the strategy to identify a couple of indicative articles of the field of search before testing its repeatability. The article selection procedure will be presented in the PRISMA flowchart (Figure 1). A complete electronic search strategy for the PubMed database is presented as an example, which will then be adapted accordingly in order to search the rest of the databases.

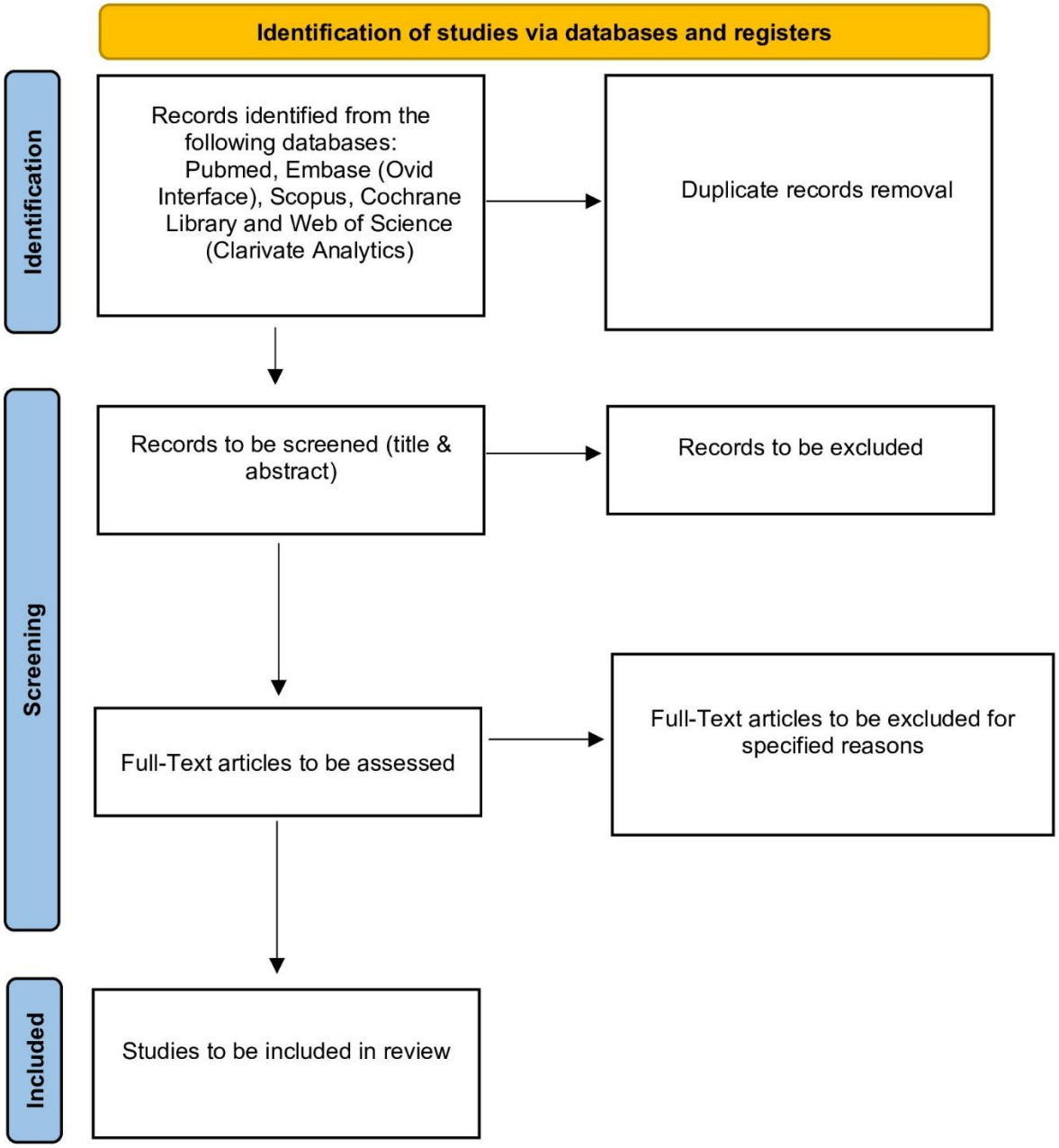

Figure 1: PRISMA flow chart systematic review protocol.

Table 1: Search strategy example for PubMed.

	Search strategy
1	"chronic pain" OR "chronic musculoskeletal pain" OR "musculoskeletal pain" OR "musculoskeletal disease*" OR "myofascial pain syndrom*" OR fibromyalgia OR "spinal pain" OR "neck pain" OR "back pain" OR "pelvic pain" OR headach* OR "temporomandibular pain" OR "shoulder pain" OR "elbow pain" OR "wrist pain" OR "hip pain" OR "knee pain" OR "ankle pain" OR "complex regional pain syndrom*" OR osteoarthr* OR "tendon pain" OR tendinopath* OR "nociceptive pain" OR "neuropathic pain" OR "nociplastic pain"
2	"brain imaging" OR "brain neuroimaging" OR "functional brain neuroimaging" OR FMRI OR "functional MRI" OR "functional magnetic resonance imaging" OR "resting-state FMRI" OR rsfmri OR "rs-fmri" OR "task-related fmri" OR "bold response" OR "blood oxygen-level dependent response" OR "blood oxygen-level dependent contrast" OR "haemodynamic response" OR haemodynamic* OR ASL OR "arterial spin labeling" OR MRS OR "magnetic resonance spectroscopy" OR PET OR "positron emission tomography" OR SPECT OR "single-photon emission computed tomography" OR EEG OR electroencephalogra* OR MEG OR magnetoencephalogra* OR "cortical activ*" OR "somatosensory evoked potential*" OR "neural activ*" OR NIRS OR FNIR* OR "near infrared spectroscopy" OR "functional near-infrared spectroscopy" OR hemoglobin* OR haemoglobin* OR oxyhemoglobin* OR oxyhaemoglobin*
3	"brain activ*" OR "brain network*" OR "brain connectivity" OR "brain chang*" OR "brain alteration*" OR "brain neuroplastic chang*" OR "brain plasticity" OR neuroplastic* OR "neural plasticity" OR "cortical chang*" OR "cortical alteration*" OR "cortical differenc*" OR "cortical reorganisation*" OR "functional connectivity"
4	#1 AND #2 AND #3

A clarification has to be taken into consideration regarding the search terms 'neuropathic' and 'headache'. More specifically, according to 11th edition of International Classification of Diseases (ICD-11), neuropathic pain is a distinct entity from chronic musculoskeletal pain.[2] However, due to close interplay between the structures being considered responsible for primary or secondary musculoskeletal pain as a possible pain driver and not a source of symptoms which in case is the neural tissue, we thought meaningful to include the cases of radiculopathies and peripheral neuropathies as part of the search strategy. On a similar basis, among the different headache types, only cervicogenic headache and tension-type headache will be considered for analysis, due to their proposed pathophysiological mechanisms.[19,20] Thus, the extended search strategy using these two terms was adopted to achieve maximal retrieval for both fields will be 'filtered' in article inclusion.

Study selection

The screening forms will be pilot tested first by both reviewers on a small number of articles, to ensure their effectiveness. The screening process will begin with the two reviewers (PA and BP) checking thoroughly the titles/abstracts of the identified studies independently against the inclusion/exclusion criteria. Using the screening forms, the reviewers will subcategorise the studies into definitely eligible, definitely ineligible or doubtful. Therefore, any obviously irrelevant studies and relevant studies will be excluded and included respectively. In the event of doubtful categorisation, the reviewer will read the full text for further clarification. If uncertainty still exists, a meeting will be arranged between the two reviewers to discuss and decide whether this study should be included or not. In the event that the two reviewers cannot reach an agreement after discussion or that a study's eligibility is unclear, a third independent reviewer (SK) will be consulted to mediate the dispute. In cases that further information is required to support the screening process, the authors of the study will be contacted. The two reviewers will then independently examine the full text of all remaining studies for compliance with the eligibility criteria. Once again, the third reviewer will support the process if necessary. Information regarding the excluded studies will be reported within the PRISMA flow diagram.

Data management

The search results will be imported into the EndNote X9 (Clarivate Analytics) reference manager software. Duplicates will be removed after screening from the main reviewer (PA). The remaining studies will be exported to the Rayyan web-based systematic review software, where the two reviewers (PA and BP) blinded between them will be able to screen the abstracts and classify them as 'included', 'maybe included/excluded' and 'excluded' following the screening form guidance on the eligibility criteria. By the end of the process the reviewers will check disagreements and the third reviewer will intervene in cases of non-resolution.

Data extraction

Appropriate data collection forms will be developed including the patient and control group details (i. e., number of participants and pathology), imaging method details such as the modality and technique used (resting state or task related) as well as the main findings, in order to capture the information of interest. The second reviewer will check the accuracy of the procedure. In cases of incomplete data, authors will be contacted, attempting to obtain the missing information,

encouraging this to take place within two weeks. If this is not possible, the study will be excluded under the justification of 'ambiguity'.

Risk of bias

Two reviewers (PA and PB) will independently appraise the included studies for risk of bias (ROB) using the Newcastle-Ottawa Scale (NOS).[21] Conducting a systematic review does always require to ensure a thorough assessment of the possible types of bias the primary studies may concede to, which in turn could easily result in conclusions of doubtful validity. Although a variety of appraisal tools are widely available for the assessment of observational studies, previous literature does not establish any superiority among them.[22,23] Hence, the choice of the suitable tool could be controversial. The choice of NOS for this review was mainly based on the fact that is the most commonly used tool in observational studies, with previous utilisation in the field of chronic pain, as well as its adaptability as it allows the author to modify it accordingly in cases needed.[7]

According to the published criteria of the NOS scale, studies are rated in three main domains by using eight items overall: four items constitute the 'selection' domain, one item the 'comparability' domain and three items the exposure domain.[21] Rating includes attributing one star to the first and third categories, while up to two stars can be awarded for comparability.

Therefore, the NOS scores range from 0 to 9 with the latter representing the highest quality.[21] In the adapted version of the NOS scale for case-control studies we will use, the same star ranking system will be followed apart from the 'exposure' domain of the original scale, which will be modified to 'outcome' to be more compatible with the context of the study.[7]

In accordance with the standards of the Agency for Healthcare Research and Quality, a study's quality will be categorized as 'good', 'fair' or 'poor' based on the number of stars assigned. The conversion thresholds used for this will be based on previous studies.[24]

Table 2: Criteria for evaluating the methodological quality according to the NOS scale.

Selection				Comparability		Exposure		Brain neuroimaging tool data quality and preprocessing		Total score	Level of evidence
1	2	3	4	5	6	7	8	9	10		
-	-	-	-	-	-	-	-	-	-	-	-

Scoring symbols

Criterion fulfilled: +, criterion not fulfilled: - and unclear answer: /. 1=Is the definition adequate, 2=Representativeness of the cases, 3=Selection of controls, 4=Definition of controls, 5=Study controls for age or sex, 6=Study controls for any additional factor, 7=Ascertainment of exposure, 8=Same method of ascertainment for cases, 9=Visual Inspection of data quality and 10=Manual exclusion in case of low data quality and/or automated data adjustment included in preprocessing pipeline.

Synthesis of data

A descriptive summary of the data will be presented by grouping the main findings for the ROIs per neuroimaging modality for each of the chronic musculoskeletal pain conditions. In cases of provided stimulation (e. g., cognitive or sensory) during assessment, this will be highlighted accordingly. Apart from the descriptive synthesis per musculoskeletal pathology and based on similar studies of the field, an analytical table with the main findings of each single study will be created where samples' characteristics, neuroimaging modality and methods as well as the key observations of the cases-controls comparison will be presented.[6,7] A meta-analysis is not expected to be feasible upon the data expected to be retrieved mainly due to the qualitative nature of the data in addition to wide spectrum of neuroimaging protocols per imaging modality. The level of evidence of the studies will be determined according to the 2005 classification system of the Dutch Institute for Healthcare Improvement (CBO), taking into consideration the methodological quality and study design as indicated by previous literature.[6,7]

DISCUSSION

To our knowledge, this will be the first systematic review attempting to summarize all the available evidence regarding functional neuroimaging and chronic musculoskeletal pain, including the whole spectrum of imaging modalities along with the different chronic musculoskeletal pathologies that have been investigated to date. The results of this review could provide a framework for future studies serving as a baseline and guiding future research on either primarily assessing a musculoskeletal population against healthy controls using the neuroimaging modality of preference having a reference summary to compare against, or even indicating an indirect path to look for treatment outcomes after the provision of different types of therapy. To date, different systematic reviews have provided valuable knowledge consisting of the best available evidence around chronic

pain and brain functional neuroimaging comparison in health and pathology. Nevertheless, the inclusion of chronic pain populations of various pathologies other than solely musculoskeletal, the exploration of a single musculoskeletal pathology or even a single imaging modality and the consideration of a specific imaging approach may reflect only part of the scenery within the entire spectrum of musculoskeletal conditions.[25-28]

CONCLUSION

Thus, the conduction of this systematic review is thought to contribute in bridging this gap in the contemporary neuroscience field.

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