INPLASY PROTOCOL

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The authors have no conflicts of interest to disclose.

Structural and functional alterations in the brain of chronic low back pain: A systematic review and multimodal meta-analysis

Cheng, S[1]; Xin, M[2]; Zhou, J[3]; Wang, Z[4]; Sun, R[5]; Liang, F[6].

Review question / Objective: **Would chronic low back pain patients show both structural and functional alterations in the same brain regions?**
Condition being studied: **Chronic low back pain is the most common and important public health problem of all chronic pain disorders across the world. Patients with chronic low back pain often suffer from non-negligible pain, depression and anxiety, concentration difficulties that significantly impair the quality of life. The exact underlying central mechanism is still uncertain.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 28 May 2020 and was last updated on 28 May 2020 (registration number INPLASY202050103).

INTRODUCTION

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significantly impair the quality of life. The exact underlying central mechanism is still uncertain.

METHODS

Search strategy: A PubMed, Web of Science, Cochrane Library and Embase search will be performed to identify putative studies reporting structural or functional imaging studies in subjects with chronic low back pain. The search is conducted up to June 20, 2020, with no time span specified for date of publication. The following search terms will be used: (1) “chronic low back pain", "back pain”; (2) “MRI" (magnetic resonance imaging), "fMRI" (functional MRI), "VBM" (voxel-based morphometry), "voxel wise" and "gray matter", "ReHo" (regional homogeneity), "ALFF" (amplitude of low-frequency fluctuation), "fALFF" (fractional amplitude of low-frequency fluctuation); (3) "resting state". Second, the reference lists of the articles included in the review will be manually checked for any studies not identified by the computerized literature search.

Participant or population: Inclusion: adults with chronic low back pain (as diagnosed using any recognized diagnostic criteria). Exclusion: adolescents (under 18 years of age) and elderly people (over 70).

Intervention: Chronic low back pain patients. A group of people who were diagnosed as chronic low back pain without other diseases.

Comparator: Healthy Adults. A group of people who were not diagnosed with chronic low back pain and other diseases.

Study designs to be included: Structural or functional MRI studies of patients with chronic low back pain and healthy controls.

Eligibility criteria: The included studies will meet the following criteria: (1) involved whole-brain structural or functional imaging of both groups; (2) results of x-y-z coordinates were reported in Montreal Neurological Institute (MNI) or Talairach coordination; and (3) a 1.5T or 3.0T MRI scanner was used.

Information sources: Electronic databases including MEDLINE, EMBASE, the Cochrane Library, Web of Science will be searched. Unpublished or ongoing trial data will also be searched from the following clinical trial registries: The National Institutes of Health clinical registry Clinical Trials, the Chinese clinical registry, the Australian New Zealand Clinical Trials Registry, the International Clinical Trials Registry Platform. Ambiguous literatures and reference lists of identified publications will be checked manually. If the data of the primary studies is missing, the authors will be contact for the information. If the missing data cannot be obtained, the studies will only be included for narrative analysis.

Main outcome(s): Significant altered cerebral regions (described with MNI/Talairach coordinates, cluster sizes, statistic magnitudes, and statistical threshold) in chronic low back pain patients compared with HCs.

Additional outcome(s): To localize brain areas both structurally and functionally altered in chronic low back pain patients, the structural and functional findings were cross-validated in a single meta-analytic map by computing the union of the structural and functional p - values.

Quality assessment / Risk of bias analysis: Two raters will independently assess the risk of bias and the quality of evidence of the included studies using the 12 items from the Cochrane Collaboration's tool. The following areas will be assessed: sequence generation; allocation concealment; blinding of participants, personnel and outcome assessment; incomplete outcome data; selective reporting and other sources of bias. Each item will be scored as yes (low risk of bias), no (high risk of bias) or unclear. A low risk of bias study will be defined as fulfilling six or more of the criteria items. Any disagreements will be discussed and

resolved by consensus or consulting a third reviewer.

Strategy of data synthesis: Aggregate data on participants' demographic characteristics will be conducted in the form of mean±SD for outcome variables. Separate voxel-based meta-analysis of regional gray matter volume and functional brain response abnormalities will be conducted using the latest SDM software, statistical analysis will include: (a) Pre-processing; (b) Mean-analysis; (c) Subgroup-analysis for assessment of heterogeneity; (d) Jackknife sensitivity analysis; (e) Meta-regression. Data for outcome measures will be used to calculate standardised mean difference (Hedge's g) values including 95% CIs and to compute Forest plots using the Meta-Essentials workbook4 toolbox. Based on study heterogeneity, we will use a random-effects meta-analysis for quantitative comparison. Heterogeneity between studies will be assessed using I^2 statistics, with an I^2 >50% regarded as an indicator of substantial heterogeneity.

Subgroup analysis: If the necessary data are available, subgroup analyses will be done for people with short and long durations separately. Within the duration, and overall, we also plan to do a subgroup analysis by age (40 years). This is a qualitative synthesis and while subgroup analyses may be undertaken it is not possible to specify the groups in advance.

Sensibility analysis: A leave-one-out jackknife sensitivity analysis was used to test the reproducibility of MRI study findings, which consisted of repeating the mean analysis after systematically removing each study.

Country(ies) involved: China.

Keywords: meta-analysis; chronic low back pain; multimodal; neuroimaging; signed differential mapping; voxel-based morphometry.

Contributions of each author:

Author 1 - Shirui Cheng - Author 1 provided statistical expertise and drafted the manuscript.

Author 2 - Ming Xin - Author 2 drafted the manuscript.

Author 3 - Jun Zhou - The author contributed to the development of the selection criteria, serach strategy.

Author 4 - Ziwen Wang - The author read, provided feedback and approved the final manuscript.

Author 5 - Ruirui Sun - The author read, provided feedback and approved the final manuscript.

Author 6 - Fanrong Liang - The author read, provided feedback and approved the final manuscript.