

INPLASY PROTOCOL

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**Review Stage at time of this
submission:** Piloting of the
study selection process.

Conflicts of interest:
The authors report no
competing interests.

INTRODUCTION

Review question / Objective: Are there consistent cortical thickness alterations in chronic pain?

Rationale: The results of cortical thickness alterations in chronic pain across studies

Cortical thickness in chronic pain: a protocol for systematic review and meta-analysis

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Review question / Objective: Are there consistent cortical thickness alterations in chronic pain?

Condition being studied: Chronic pain is a common health care problem. The pathophysiological mechanisms remain poorly understood. There is cumulative evidence that chronic pain is associated with common brain structural and functional reorganizations. Brain cortical thickness (CTh) analysis is a sensitive technique to feature cortical gray matter morphometry. A growing number of studies have investigated cortical thickness in chronic pain. However, their results are inconsistent. Establishing consistency across different studies and chronic pain conditions represents a critical step in the development of a reliable biomarker.

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 17 May 2020 and was last updated on 17 May 2020 (registration number INPLASY202050069).

are divergent and have not been quantitatively reviewed.

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METHODS

Search strategy: Three electronic databases: PubMed, Web of Science, and Embase were searched for eligible studies published in English from each database's inception to April 3rd, 2020. The following terms were used for the searches: ((chronic pain) OR (chronic myofascial pain) OR (chronic headache*) OR (chronic migraine*) OR (burning mouth syndrome) OR (temporomandibular joint disorder*) OR (neck pain) OR (shoulder pain) OR (phantom limb pain) OR (chronic thoracic pain) OR (chronic chest pain) OR (chronic back pain) OR (chronic knee pain) OR (chronic ankle pain) OR (chronic epicondylalgia*) OR (chronic abdominal pain) OR (chronic visceral pain) OR (chronic pelvic pain syndrome) OR (neuropathic pain) OR (trigeminal neuralgia) OR neuralgia OR (postherpetic neuralgia) OR (complex regional pain syndrome) OR fibromyalgia OR (ankylosing spondylitis) OR (chronic epigastric pain syndrome) OR (irritable bowel syndrome) OR (inflammatory bowel disease) OR (Crohn's disease) OR (chronic bladder pain syndrome) OR (chronic testicular pain) OR (functional dyspepsia) OR (musculoskeletal pain) OR (chronic widespread pain) OR (chronic whiplash-associated disorder) OR arthritis OR (somatoform pain) AND ((cortical thickness) OR (cortical thinning) OR (surface-based morphometry)).

Participant or population: Patients with chronic pain.

Intervention: Cortical thickness differences between patients with chronic pain and matched pain-free controls.

Comparator: Cortical thickness.

Study designs to be included: Case-controlled studies.

Eligibility criteria: Inclusion criteria: The articles have to satisfy following inclusion criteria: (1) case-controlled studies that investigated regional CTh differences between patients with chronic pain and matched pain-free controls at the whole-brain cortical level; (2) studies with non-significant results and studies with significant findings that reported brain clusters in standard Montreal Neurological Institute (MNI) or Talairach space; (3) an original article published in English in a peer-reviewed journal. Exclusion criteria: Reports were excluded if they met the following criteria: (1) the sample size was fewer than seven either in the chronic pain group or the pain-free group; (2) three-dimensional coordinates of significant CTh results were not reported; (2) the studies only employed regions of interest analysis or global CTh analysis; (3) a direct pain-free compassion group was lacked; (4) the patient sample was overlapped with the another one with a larger sample size. (5) no baseline comparison was performed in case of a longitudinal study;(6) the pain duration was less than three months; (7) studies investigated experimental pain; (8) the publications were conference abstracts, research protocols, case reports, letters, reviews, and editorials.

Information sources: Three electronic databases: PubMed, Web of Science, and Embase were searched for eligible studies published in English from each database's inception to April 3rd, 2020. The reference lists of the included articles and any relevant review articles were manually reviewed other potentially qualified studies.

Main outcome(s): Cortical thickness differences between patients with chronic pain and matched pain-free controls.

Additional outcome(s): None.

Quality assessment / Risk of bias analysis:

A 12-point checklist, which was based on a previous CTh meta-analysis (Li Q, Zhao Y, Chen Z, et al. Meta-analysis of cortical thickness abnormalities in medication-free patients with major depressive disorder. *Neuropsychopharmacology*. 2020; 45(4):703-712. doi:10.1038/s41386-019-0563-9), will be utilized for the quality assessment of the included studies.

Strategy of data synthesis: This meta-analysis will be performed using SDM-PSI (version 6.21, <http://www.sdmproject.com>).

Subgroup analysis: Subgroup meta-analyses will be performed if at least 10 datasets were available based on patient types, sample characteristics, and image methodology.

Sensitivity analysis: To assess the stability of the results identified in the main CBMA, a sensitivity analysis was performed by repeating the same analyses by consecutively removing one study at a time.

Language: English.

Country(ies) involved: China.

Keywords: chronic pain; cortical thickness; coordinate-based meta-analysis; gray matter.

Contributions of each author:

Author 1 - HaiRong Ma - Author 1 drafted the manuscript.

Author 2 - LiQin Sheng - The author provided statistical expertise.

Author 3 - Fei Chen - The author contributed to the development of the selection criteria, the risk of bias assessment strategy, and data extraction.

Author 4 - CongHu Yuan - The author contributed to the development of the selection criteria, the risk of bias assessment strategy, and data extraction; and drafted the manuscript.

Author 5 - ZhenYu Dai - The author reviewed and edited the manuscript.

Author 6 - PingLei Pan - The author reviewed and edited the manuscript.