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Critical Review

Altered Primary Motor Cortex Structure, Organization, and Function in Chronic Pain: A Systematic Review and Meta-Analysis

Wei-Ju Chang,* Neil E. O'Connell,† Paula R. Beckenkamp,‡ Ghufran Alhassani,* Matthew B. Liston,* and Siobhan M. Schabrun*

*School of Science and Health, Western Sydney University, Penrith, New South Wales, Australia.
†Health Economics Research Group, Institute of Environment, Health and Societies, Department of Clinical Sciences, Brunel University, Uxbridge, United Kingdom.
‡The University of Sydney, Discipline of Physiotherapy, Faculty of Health Sciences, Sydney, New South Wales, Australia.

Abstract: **Chronic pain can be associated with movement abnormalities. The primary motor cortex (M1) has an essential role in the formulation and execution of movement. A number of changes in M1 function have been reported in studies of people with chronic pain. This review systematically evaluated the evidence for altered M1 structure, organization, and function in people with chronic pain of neuropathic and non-neuropathic origin. Database searches were conducted and a modified STrengthening the Reporting of OBservational studies in Epidemiology checklist was used to assess the methodological quality of included studies. Meta-analyses, including preplanned subgroup analyses on the basis of condition were performed where possible. Sixty-seven studies (2,290 participants) using various neurophysiological measures were included. There is conflicting evidence of altered M1 structure, organization, and function for neuropathic and non-neuropathic pain conditions. Meta-analyses provided evidence of increased M1 long-interval intracortical inhibition in chronic pain populations. For most measures, the evidence of M1 changes in chronic pain populations is inconclusive.**

Perspective: ***This review synthesizes the evidence of altered M1 structure, organization, and function in chronic pain populations. For most measures, M1 changes are inconsistent between studies and more research with larger samples and rigorous methodology is required to elucidate M1 changes in chronic pain populations.***

Key words: *Chronic pain, primary motor cortex, neuroplasticity, meta-analysis.*

Chronic pain conditions such as low back pain (LBP), neck pain, and knee osteoarthritis (OA) are leading causes of disability globally[107] and are associated with significant and rising health care and socioeconomic costs.[50] Despite this, effective treatment remains elusive.

People with chronic pain conditions commonly present with abnormalities of movement. For example, excessive finger flexion has been reported during grip release in chronic lateral elbow pain, greater hip adduction and internal rotation during stair climbing in lateral hip pain, and delayed onset of trunk muscle activation during

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Address reprint requests to Siobhan M. Schabrun, MD, School of Science and Health, Western Sydney University, Locked bag 1797, Penrith, New South Wales 2751, Australia. E-mail: s.schabrun@westernsydney.edu.au
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arm elevation in recurrent LBP.[3,33,97] As a result, rehabilitation to target movement dysfunction is a treatment for musculoskeletal pain. However, treatment success with this approach is limited[1,71] and there is debate regarding the type, quantity, and timing of interventions needed to effectively target movement dysfunction in chronic musculoskeletal pain or indeed whether such an approach is warranted.[2,30,31]

The physiological basis of movement dysfunction in pain is poorly understood. The primary motor cortex (M1) has an essential role in the formulation and execution of movement and is likely to have a role in movement abnormalities. Indeed, a recent systematic review provided evidence of reduced M1 output (ie, corticospinal excitability) in response to acute muscle pain that may represent an adaptive mechanism to protect against further pain or injury.[9] Similarly, studies investigating M1 in experimental models of progressively developing, sustained muscle pain show altered M1 organization (increased representations of painful muscles) and function (reduced M1 inhibition) 4 days after pain onset.[77] Studies have reported that changes in M1 structure, organization, and function may also be present when pain becomes chronic. For example, associations have been reported between the severity of pain and/or the degree of movement dysfunction in chronic musculoskeletal disorders such as low back, elbow, and patellofemoral pain and reorganization of the M1 representation (ie, greater representational overlap, reduced number of discrete peaks) of muscles in the region of pain.[78,79,94] However, it is unclear whether M1 reorganization presents in other chronic pain conditions and whether it can be observed via different neurophysiological methods.

Previous reviews examining changes in M1 in chronic pain have been restricted to specific pain conditions or by the neurophysiological method used to assess M1. For instance, a systematic review revealed limited evidence for bilateral M1 disinhibition in complex regional pain syndrome (CRPS) of the upper limb.[20] Whether similar alterations in M1 are present in other forms of chronic pain is unknown. Indeed, it has been suggested that M1 disinhibition may occur in chronic neuropathic but not chronic nociceptive pain.[82] A second systematic review reported similar findings of disinhibition across a range of chronic pain conditions (including migraine) but was restricted to data obtained using transcranial magnetic stimulation (TMS).[65] The integration of information on M1 structure, organization, and function across 1) a range of neuropathic and non-neuropathic conditions, and 2) using a range of complementary neurophysiological techniques, is necessary to provide comprehensive information on whether M1 is altered in chronic pain. This information is timely because of the range of treatment techniques being tested that target the M1 in chronic pain.[12,56,74,80]

The aim of this review was to systematically evaluate the evidence of altered M1 structure, organization, and function in chronic pain conditions of neuropathic and non-neuropathic origin across a range of neurophysiological methods.

Methods

The protocol of this review was prospectively registered with the International Prospective Register of Systematic Reviews (registration number CRD42015014823) and has been published elsewhere.[13] This review is reported following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement.[46]

Search Strategy

The search was conducted in 5 electronic databases (PubMed, MEDLINE, Embase, PsychINFO, and CINAHL) from inception to February 2017, using key words and medical subject headings terms related to chronic pain and M1 organization/function (Supplementary Appendix 1). The reference list of eligible studies and relevant reviews were manually searched for additional articles.

Eligibility Criteria

Inclusion criteria were: 1) full text studies published in English, including in press or accepted studies, 2) adult (aged older than 18 years) humans with non-neuropathic or neuropathic pain, 3) duration of pain >3 months,[64] 4) investigated and reported measures of the organization and/or function of the M1 (regardless of the anatomical or functional definition used) using TMS, magnetic resonance imaging (MRI), electroencephalography (EEG), magnetoencephalography (MEG), magnetic

Table 1. Summary of M1 Structural, Organizational, and Functional Constructs and Their Associated Neurophysiological Methods and Outcome Measures

	M1 STRUCTURE	*M1 ORGANIZATION*	*M1 FUNCTION*
Neurophysiological methods and outcome measures	MRI: cortical thickness (VBM); white matter structure (diffusion tensor imaging)	fMRI: activation/connectivity (rCBF, BOLD) TMS: M1 representation (map volume, CoG of M1 representation)	TMS: corticospinal excitability (rMT, aMT, MEP amplitude and latency, CSP); ICF/ intracortical inhibition EEG: cerebrocortical motor activity MEG: 20-Hz cortical rhythm (rebound amplitude/duration, reactivity) MRS: neurochemical metabolism PET: glucose metabolism

Abbreviation: rMT, resting motor threshold.