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Critical Review

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

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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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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.

resonance spectroscopy (MRS), or positron emission tomography (PET; Table 1). Studies were excluded if: 1) included participants presented chronic pain associated with neurological disorders, cancer, or visceral pain, or 2) the study did not include a healthy control group or used the unaffected limb or body side as a control. Cross-sectional or prospective studies, including case-control and randomized controlled trials that provided baseline data with information relevant to the review objective and that met the eligibility criteria, were included.

Study Selection

Search results were imported into Endnote X7 (Clarivate Analytics, Philadelphia, PA). After removing duplicates, 2 reviewers independently screened titles and abstracts of all studies to remove those not relevant to the review objective. The full text of all remaining studies were retrieved and evaluated according to the eligibility criteria. If there was uncertainty or disagreement, a third reviewer was consulted.

Data Extraction

Two independent reviewers extracted the following data: pain condition, country of origin, study design and setting, inclusion/exclusion criteria, source of participants, sample size, participant demographic characteristics, duration and severity of chronic pain, neurophysiological methods, specifics of the investigative model, type and location of stimulation, and outcomes (ie, M1 excitability, representation, reactivity, neurochemical or glucose metabolism). Any disagreements were resolved in consensus with a third reviewer. If data were missing, authors were contacted a maximum of 3 times, after which the data were considered irretrievable.

Quality and Risk of Bias Assessment

Study quality and risk of bias were assessed by 2 independent reviewers using a modified version of the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) statement for cross-sectional and cohort studies.[67,103,104] Disagreements were resolved by consensus with a third reviewer. The modified STROBE statement investigated potential for bias in 5 domains: 1) source of participants, 2) participant selection, 3) methodology, 4) statistical analysis, and 5) funding (Supplementary Appendix 2). Each domain would be allocated 1 point if the risk of bias was low and no point if the risk of bias was considered high. The maximum score possible was 5 points. For studies using TMS, an additional methodological quality assessment was undertaken using an adapted version of the TMS methodological checklist.[14] Two items that were not relevant for this review were removed from the checklist (item 22—time between days of testing—and item 30—size of the unconditioned motor evoked potential [MEP] controlled). Each domain that was reported (*r*) and/or controlled (*c*) was allocated 1 point. In total, the maximum score possible for the reported and controlled items of the TMS methodological checklist were, respectively, 26 and 25 for single-pulse TMS, and 29 and 28 for paired-pulse TMS. The ratio of the summed score relative to the maximum score for the reported (r/[26 or 29] $\times$ 100) and controlled (c/[25 or 28] $\times$ 100) items was calculated. The median percentage for the reported and controlled items was then calculated. TMS studies received 1 point in the methodology category of the modified STROBE statement if the percentage of reported and controlled items were both greater than the median value.

Data Synthesis

Meta-analyses were performed to aggregate the data from TMS studies. Because of increased heterogeneity in the methodology of included studies, a narrative synthesis was used to summarize the findings of studies using other neurophysiological methods.[84] TMS outcome measures (resting and active motor threshold [aMT], MEP amplitude and latency, cortical silent period (CSP), map volume, intracortical inhibition and facilitation) were pooled and separate meta-analyses were performed using RevMan version 5.3 (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen). Cohen d effect sizes were used to analyze effect estimates (d $\leq$.2, small; .5, moderate; $\geq$.8, large).[16] Meta-analyses were performed using a random effects model when data from at least 2 studies addressing that outcome were accessible. Statistically significant heterogeneity was identified using the χ^2 test and was considered when χ^2 $P < .10$. The I^2 statistic was used to evaluate the degree of heterogeneity. Substantial heterogeneity was considered present when $I^2 > 50\%$.[35] Meta-analyzed data are presented as effect estimates (standardized mean difference [SMD] with 95% confidence intervals [CIs]).

Subgroup and Sensitivity Analysis

Preplanned subgroup analyses were conducted according to the type of musculoskeletal condition where significant heterogeneity was identified. The median value of the modified STROBE statement score of the TMS studies was used as a cutoff point to divide studies into either low or high risk of bias groups. The influence of high risk of bias studies was examined by rerunning the analysis with those studies excluded.

Results

The initial search identified 5,028 records, from which 120 full text articles were retrieved to assess eligibility. Sixty-nine studies met the inclusion criteria in the review. The authors of 14 studies were contacted to request additional data pertaining to M1 function. Two studies were excluded as a result of unsuccessful attempts to acquire these data.[18,106] Thus, a total of 67 studies were included in this review. The study flow chart can be seen in Fig 1.

Study Characteristics

The included studies encompassed 7 neurophysiological methods: TMS (n = 35 studies), functional MRI (fMRI;

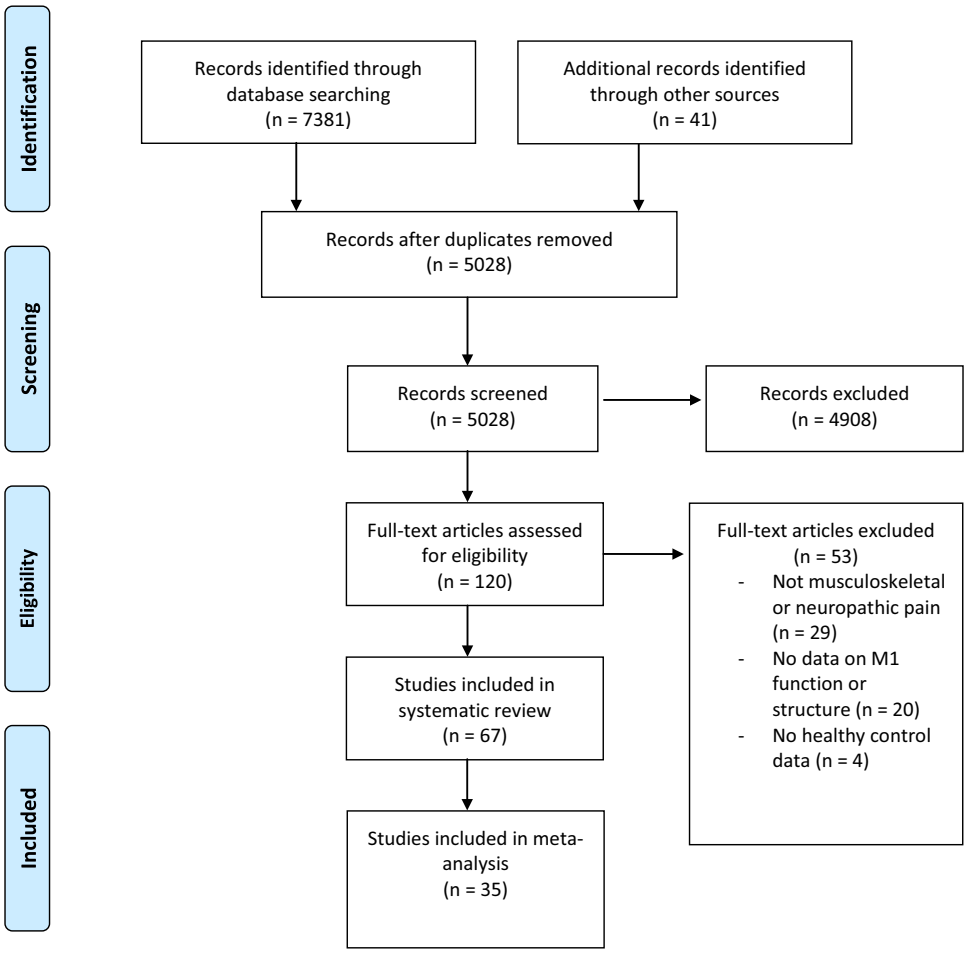

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram of the screening and inclusion of studies.

n = 16 studies), MRI (n = 6 studies), MEG (n = 3 studies), MRS (n = 3 studies), EEG (n = 1 study), and PET (n = 1 study). Two studies investigated functional as well as structural MRI changes.[95,101] In total, the included studies involved 1,248 chronic pain (20 different pain conditions) and 1,042 healthy participants. CRPS (n = 16 studies) and LBP (n = 16 studies) were the most frequently investigated conditions.

Five studies investigated 2 or more chronic pain conditions.[11,72,73,75,82] Participant sex (n = 4 studies) and age (n = 3 studies), pain intensity (n = 22 studies), and the duration of the pain (n = 7 studies) were not reported by some of the included studies. The characteristics of included studies are summarized in Tables 2 and 3.

Quality and Risk of Bias Within Studies

The average score for the methodological quality assessment was 3.1 of 5 (range = 1–5; Table 4), with 50 studies presenting a score of ≥3. For the TMS methodology checklist, the average score for the reported items was 64.8% (SD = 13) and for the controlled items 61.1% (SD = 13.8). All studies reported and controlled position and contact of electromyography electrodes and stimulation intensity. All studies that used paired-pulse paradigms (n = 16) reported the intensity of the test and conditioning pulse and the interstimulus interval. Participant age and sex, although reported, were not controlled. Items that were not consistently reported or controlled were: previous motor activity of the muscle to be tested, level of relaxation of the muscles other than those being tested, pulse shape, and participants' prescribed medication.

Is There Evidence of Altered M1 Function, Organization, and Structure in Chronic Pain?

We were unable to conduct meta-analyses of these data because of the heterogeneity of methodology across the included studies. Furthermore, the effect size of the differences between the pain and healthy participants were not reported in these studies.

In neuropathic pain, 3 studies reported statistically significant ($P < .05$) increases in M1 activation/connectivity in neuropathic pain populations from regional cerebral blood flow (rCBF)[47] (cluster level corrected $P < .05$, n = 22 participants, quality score = 2) and blood oxygen level-dependent (BOLD) contrast studies (n = 42 participants, quality score = 4[95]; n = 19 participants, quality score = 4[62]). Voxel-based morphometry (VBM) imaging showed 12% to 13% increase in bilateral M1 cortical thickness in

Table 2. Characteristics of Studies using TMS

			Chronic pain participants				Healthy participants					
Reference	Condition	Country	Study size (M/F), n	Age, years	Pain duration	Pain intensity (0–10)	Study size (M/F), n	Age, years	Modality	Stimuli	Target muscles	Outcome measures
Salerno et al[75]	Fibromyalgia; rheumatoid arthritis	France	13 (0/13); 5 (0/5)	50.1 ± 5.6; 50.0 ± 5.1 (SEM)	NA	NA	13 (NA)	49.1 ± 5 (SEM)	Double cone coil on cortical representation of the target muscles	Single and paired pulses	First dorsal interosseous, tibialis anterior	rMT, MEP amplitude, CSP, SICI, ICF, LICI
Schwenkreis et al[81]	CRPS I: hand	Germany	25 (9/16)	49.1 ± 13.8	26.1 ± 47 Months	NA	20 (10/10)	20 to 78 (95% CI)	Circular coil (14 cm) on vertex	Single and paired pulses, monophasic*	First dorsal interosseous	rMT, MEP amplitude, SICI, ICF
Strutton et al[91]	Chronic sciatica	United Kingdom	9 (NA)	NA	NA	NA	7 (NA)	NA	Double cone coil on hotspot	Single pulse, monophasic*	Tibialis anterior, lateral gastrocnemius	rMT, aMT
On et al[63]	Patello-femoral pain	Turkey	13 (0/13)	25 ± 8.1 (SEM)	3.46 ± 1.9 Years (SEM)	NA	13 (0/13)	25.1 ± 7.4 (SEM)	Circular coil (9 cm) on hotspot	Single pulse, monophasic	Vastus medialis obliques, vastus lateralis, extensor digitorum brevis	MEP amplitude
Eisenberg et al[21]	CRPS I: hand; CRPS I: foot	Israel	6 (4/2); 6 (5/1)	33 ± 12.7; 32 ± 9	31 ± 41 Months; 20 ± 21 months	7.3 ± 3.1; 6.7 ± 2.3	14 (10/4)	30.9 ± 12.7	Figure of 8 coil (9 cm) on hotspot	Single and paired pulses, monophasic*	Abductor pollicis brevis	SICI
Krause et al[43]	CRPS I: hand	Germany	12 (2/10)	55.9 ± 15.6	NA	NA	10 (NA)	42.4	Figure of 8 coil (9 cm) on hotspot	Single pulse, monophasic*	Long extensor muscle	rMT, MEP amplitude, CSP
Strutton et al[92]	LBP	United Kingdom	24 (15/9)	39.1 ± 2.2	NA	NA	11 (7/4)	35.9 ± 3.2	Double cone coil on vertex	Single pulse, monophasic*	Erector spinae	aMT, MEP latency, CSP
Krause et al[44]	CRPS: hand	Germany	14 (4/10)	37 (17–72)	>6 Months	NA	10	38 (24–63)	Figure of 8 coil (7 cm) on M1	Single pulse, monophasic*	Long extensor muscle	rMT, MEP amplitude, map volume
Turton et al[99]	CRPS I: hand	United Kingdom	8 (1/7)	45 ± 13	6.6 ± 4.9 Years	6.3 ± 1.4	8 (1/7)	45 ± 13	Figure of 8 coil (9.5 m) on hotspot	Single pulse, monophasic*	Abductor pollicis brevis	MEP amplitude
Tsao et al[97]	LBP	Australia	11 (5/6)	24 ± 7	5.6 ± 4.2 Years	5.5 ± 2	11 (4/7)	23 ± 3	Figure of 8 coil (7 cm) and double cone coil (11 cm) on hotspot and M1	Single pulse, monophasic	Transversus abdominus	rMT, aMT, map volume
Berth et al[5]	Rotator cuff tear	Germany	10 (10/0)	64.9 ± 4.6	>6 Months	NA	13 (10/3)	27.2 ± 8.1	Figure of 8 coil on hotspot	Single pulse, monophasic*	Deltoid	MEP amplitude

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Table 2. Continued

			Chronic pain participants				Healthy participants					
Reference	Condition	Country	Study size (M/F), n	Age, years	Pain duration	Pain intensity (0–10)	Study size (M/F), n	Age, years	Modality	Stimuli	Target muscles	Outcome measures
Turgut et al[98]	Diabetic neuropathic pain	Turkey	20 (5/15)	63.9 ± 7.3	12.4 ± 6.7 Years	8.1 ± 1.3	30 (14/16)	58.3 ± 6.5	Circular coil (14 cm) on hotspot	Single pulse, NA	First dorsal interosseous	rMT, MEP amplitude, MEP latency, CSP
Mhalla et al[57]	Fibromyalgia	France	21 (0/21)	52.2 ± 10.4	14.1 ± 11.9 Years	5.5 ± 1.3	21 (0/21)	46.7 ± 11.6	Figure of 8 coil	Single and paired pulses, NA	First dorsal interosseous	rMT, SICI, ICF
Schwenkreis et al[82]	Neuralgia: hand; OA: hand	Germany	26 (14/12); 20 (10/10)	50.9 ± 11.7; 56.6 ± 10.2	39.3 ± 44.8 Months; 35.6 ± 42.9 months	4.7 ± 2.1; 3.9 ± 2	14 (6/8)	58.8 ± 12.7	Circular coil (14 cm) on vertex	Single and paired pulses, monophasic	First dorsal interosseous	rMT, SICI, ICF
Clark et al[15]	LBP	United States	10 (5/5)	23.7 ± 6.1	3.2 ± 3.1 Years	2.6 ± 1.6	10 (5/5)	22.9 ± 1.9 (SEM)	Custom-modified 110-mm double cone coil on vertex	Single pulse, NA	Erector spinae	MEP amplitude
Schwenkreis et al[83]	Fibromyalgia	Germany	16 (2/14)	48.7 ± 8.4	NA	NA	23 (7/16)	37.7 ± 11.5	Circular coil (14 cm) on vertex	Single and paired pulses, mono-phasic*	Forearm superficial flexor	rMT, MEP amplitude, CSP, SICI, ICF
Tsao et al[96]	LBP	Australia	9 (4/5)	25 ± 3.4	3.6 ± 2.3 Years	4.7 ± 1.1	11 (5/6)	24 ± 5	Figure of 8 coil (7 cm) on M1	Single pulse, monophasic	Deep multifidus, erector spinae	Map volume
Masse-Alarie et al[54]	LBP	Canada	13 (6/7)	53.7 ± 7.4	16 ± 10 Years	2.9 ± 2.5	9 (4/5)	48.7 ± 6.8	Double cone coil (7 cm) on hotspot	Single and paired pulses, mono-phasic	Transversus abdominus, internal oblique	MEP amplitude, SICI
Vallence et al[105]	Chronic tension type headache	Australia	11 (5/6)	35 ± 13.2	NA	NA	18 (7/11)	28 ± 8 (unclear)	Figure of 8 (9 cm) on hotspot	Single pulse, mono-phasic*	Abductor pollicis brevis	rMT, MEP amplitude
Kittelson et al[41]	OA knee	United States	17 (8/9)	63.9 ± 1.8 (SEM)	NA	NA	20 (10/10)	58.3 ± 2.5 (SEM)	Double cone coil on hotspot	Single and paired pulses, mono-phasic*	Vastus lateralis	rMT, MEP amplitude, SICI, ICF
Marker et al[51]	Neck pain	United States	9 (2/7)	42.4 ± 11	>12 Months	1.7 ± 1.4	8 (4/4)	31.5 ± 14.5	Figure of 8 coil (7 cm) on hotspot	Single and paired pulses, mono-phasic	Upper trapezius	rMT, aMT, MEP amplitude, SICI
Rittig-Rasmussen et al[73]	Neck pain; knee pain	Denmark	20 (14/6); 15 (10/5)	29 ± 7; 27 ± 6	>3 Months	1.7 ± .6 1.5 ± .6	15 (12/3)	25 ± 3.5	Figure of 8 coil on hotspot	Single pulse, monophasic	Upper trapezius, abductor pollicis brevis	aMT, MEP amplitude, MEP latency
Bradnam et al[7]	Shoulder pain	Australia	8 (1/7)	64.9 (49–75)	>12 Months	4.4 ± 1.2	18 (9/8)	41.3 (20–68)	Figure of 8 (7 cm) on hotspot	Single pulse, monophasic*	Infraspinatus	aMT, MEP amplitude, CSP
Schabrun et al[78]	LBP	Australia	27 (13/14)	30 ± 9	5.3 ± 4 Years	4.6 ± 1.9	23 (12/11)	27 ± 5	Figure of 8 coil on M1	Single pulse, monophasic	L3 and L5 erector spinae	Map volume

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Table 2. Continued

			Chronic pain participants				Healthy participants					
Reference	Condition	Country	Study size (M/F), n	Age, years	Pain duration	Pain intensity (0–10)	Study size (M/F), n	Age, years	Modality	Stimuli	Target muscles	Outcome measures
Schabrun et al[79]	Lateral epicondylalgia	Australia	11 (5/6)	44 ± 11	9 ± 6 Months	2.7 ± 2	11 (5/6)	42 ± 11	Figure of 8 coil (7 cm) on M1	Single pulse, monophasic*	Extensor carpi radialis brevis, extensor digitorum	rMT, MEP amplitude, map volume
Van Velzen et al[101]	CRPS I: hand	Netherlands	12 (2/10)	51 ± 9.5	88 ± 26.9 Months	6.7 ± 1.8	12 (1/11)	52 ± 13	Figure of 8 coil on hotspot	Single pulse, biphasic*	First dorsal interosseous	rMT, MEP amplitude
Burns et al[8]	Lateral epicondylalgia	Australia	14 (4/10)	41.5 ± 9.9	37.3 ± 74.8 Months	3.5 ± 2.8	14 (4/10)	42.1 ± 11.1	Circular coil (9 cm) on hotspot	Single and paired pulses, monophasic*	Extensor carpi radialis brevis	rMT, aMT, MEP amplitude, SICI, ICF, LICI
Caumo et al[11]	Myofascial pain; fibromyalgia; OA knee	Brazil	54 (0/54); 19 (0/19); 27 (0/27)	46.1 ± 12.1; 50.4 ± 8.8; 64.4 ± 7.8	NA	7.2 ± 2.2; 7.9 ± 1.9; 6.3 ± 2.2	14 (0/14)	32.4 ± 10.8	Figure of 8 coil on M1	Single and paired pulses	First dorsal interosseous	MEP amplitude, CSP, SICI, ICF
Masse-Alarie et al[53]	LBP	Canada	35 (20/15)	38 ± 14.6	65.8 ± 72.8 Months	4.2 ± 2.1	13 (6/7)	37.6 ± 12.5	Double cone coil on hotspot	Single and paired pulses, monophasic	Multifidus	aMT, MEP amplitude, CSP, SICI, SICF
Masse-Alarie et al[52]	LBP	Canada	11 (6/5)	33.8 ± 12.5	NA	2 ± 1.9	13 (6/7)	37.6 ± 12.5	Double cone coil (7 cm) on hotspot	Single and paired pulses, monophasic*	Multifidus	aMT, MEP amplitude, CSP, SICI, SICF
Rio et al[72]	Patellar tendon pain; anterior knee pain	Australia	11 (10/1); 10 (6/4)	26 (18–37); 26.5 (18–37)	90 Months (5–192); 9 months (12–264) (median)	5.4 ± 2.0; 5.0 ± 2.4	8 (7/1)	26 (18–37) (median)	Double cone coil (110 mm) on hotspot	Single pulse, monophasic*	Rectus femoris	aMT
Tarrago et al[93]	OA knee	Brazil	21 (0/21)	64.5 ± 7.72	6.73 ± 2.53 Years	NA	10 (0/10)	34.1 ± 11.64	Figure of 8 coil on hotspot	Single and paired pulses	First dorsal interosseous	rMT, MEP amplitude, CSP, SICI, ICF
Morgante et al[60]	CRPS I: hand	United States	10 (1/9)	48.2 ± 5.5 (SE)	11.3 ± 1.8 Months (SE)	8.1 ± .73	10 (1/9)	48.3 ± 12.5 (SE)	Figure of 8 coil on hotspot	Single and paired pulses, monophasic	Abductor pollicis brevis	rMT, aMT, CSP, SICI, ICF
Parker et al[66]	OA hand	New Zealand	23 (6/17)	72 ± 6	13.5 ± 13.1 years	NA	20 (6/14)	71 ± 7	Figure of 8 coil on hotspot	Single and paired pulses, monophasic	First dorsal interosseous	rMT, MEP amplitude, CSP, SICI, LICI, SICF
Te et al[94]	Patello-femoral pain	Australia	11 (3/8)	21 ± 7	29 ± 6 months	2.3 ± 2.2	11 (3/8)	24 ± 6	Figure of 8 coil on M1	Single pulse, monophasic	Rectus femoris, vastus lateralis, vastus medialis	aMT, map volume

Abbreviations: M, male; F, female; SEM, standard error of the mean; NA, not available; rMT, resting motor threshold; SE, standard error.
NOTE. Values are mean ± SD unless otherwise stated.
*Information obtained from the stimulator manufacturer's website.

Table 3. Characteristics of Included Studies Using Other Neurophysiological Methods

			Chronic pain participants				Healthy participants				
Reference	Condition	Country	Study size (M/F)	Age	Pain duration	Pain intensity (0–10)	Study size (M/F)	Age	Modality	Stimuli	Outcome measures
Cook et al[17]	Fibromyalgia	United States	9 (0/9)	37 ± 5	NA	1.03 ± .7	9 (0/9)	35 ± 3	fMRI	Heat pain on left thenar eminence	BOLD at 1.5 T
Napadow et al[62]	Carpal tunnel syndrome	United States	10 (4/6)	51.1 (31–60)	4 months to 10 years	NA	9 (3/6)	46.9 (32–59)	fMRI	Innocuous electrical stimulation to digit 2, 3, and 5	BOLD at 3 T
Maihöfner et al[49]	CRPS I: hand	Germany	12 (2/10)	41.2 ± 2.5 (SEM)	52.2 ± 32 weeks (SEM)	3.9 ± .8 (SEM)	12 (2/10)	43.2 ± 2.5 (SEM)	fMRI	Finger tapping task	BOLD at 1.5 T
Gieteling et al[28]	CRPS I: hand with dystonia	Netherlands	8 (1/7)	46.4 ± 6	NA	NA	17 (2/15)	42.9 ± 9.2	fMRI	Imagining and performing wrist flexion/extension	BOLD at 3 T
Kobayashi et al[42]	LBP	Japan	8 (5/3)	33 (22–44)	>3 Months	NA	8 (8/0)	29 (22–42)	fMRI	Lumbar mechanical compression	BOLD at 3 T
Wasan et al[108]	LBP	United States	16 (5/11)	47.4 (95% CI = 40–54.8)	6.24 years (95% CI = 3.9–11.8)	4.8 (95% CI = 3.8–5.9)	16 (5/11)	46.7 (95% CI = 40.1–53.2)	fMRI	Rest state; clinical maneuver (pain exacerbation); heat pain (affected leg)	rCBF at 3 T
Barke et al[4]	LBP	Germany	30 (0/30)	NA	NA	NA	30 (0/30)	NA	fMRI	Photos (aversive and neutral movement/posture; general fear-inducing; neutral; spider)	BOLD at 3 T
Bolwerk et al[6]	CRPS I and II: hand and foot	Germany	12 (5/7)	61.1 ± 11.1	15.5 (4–406) Weeks	5.3 ± 2.1	12 (5/7)	60.9 ± 11	fMRI	Resting state	BOLD at 1.5 T
Liu et al[47]	Postherpetic neuralgia	China	11 (11/0)	66.2 ± 5.5	8.4 ± 6.2 Months	8.3 ± 1	11 (11/0)	64 (56–73)	fMRI	Resting state	rCBF at 3 T
Flodin et al[25]	Fibromyalgia	Sweden	16 (0/16)	48.3 (25–64)	7.6 ± 3.8 Years	NA	22 (0/22)	45.7 (20–63)	fMRI	Ankle, knee, and hand tasks	BOLD at 3 T
He et al[32]	Temporo-mandibular disorder	China	23 (9/14)	22.4 ± 3.6	14.8 ± 20.7 Months	NA	20 (9/11)	23.1 ± 2.4	fMRI	Resting state	BOLD at 3 T
Pijnenburg et al[69]	LBP	Belgium	17 (6/11)	33.3 ± 7.9	9.8 ± 8.2 Years	2 ± 2	17 (5/12)	31.8 ± 8.2	fMRI	Resting state	BOLD at 3 T
Shanahan et al[85]	OA knee	Australia	11 (6/5)	68.9 ± 6.4	NA	4.3 ± .8	7 (5/2)	64 ± 6.7	fMRI	15 Pressure stimuli (5 different pressure intensities) on left thumb	BOLD at 3 T
Flodin et al[24]	Rheumatoid arthritis	Sweden	24 (4/20)	53.8 ± 14.8	66 ± 34 Months	3.4 ± 2.9	19 (3/16)	50.4 ± 16.6	fMRI	Resting state	BOLD at 3 T
Hemington et al[34]	Ankylosing spondylitis, back pain	Canada	20 (17/3)	39.4 ± 12	12.8 ± 10.1 Years	NA	20 (17/3)	39.7 ± 12	fMRI	Resting state	BOLD at 3 T
Hotta et al[37]	CRPS I: hand	Finland	13 (0/13)	44.7 ± 6.9	5.2 ± 3.9 Years	7.7 ± 1.7	13 (0/13)	44.1 ± 8.6	fMRI	Viewing videos of hand actions	BOLD at 3 T
Tian et al[95]	Trigeminal neuropathic pain	China	20 (8/12)	52.6 ± 8.9	21.1 ± 16.2 Months	7.7 ± 1.6	22 (6/16)	52.2 ± 6.1	fMRI and MRI	Resting state	BOLD and DKI analysis at 3 T
Van Velzen et al[102]	CRPS: hand	Netherland	19 (0/19)	48.1 ± 11.6	110.8 ± 110.5 Years	7.1 ± 1.5	19 (0/19)	49.4 ± 11.6	fMRI and MRI	Resting state	BOLD, VBM and DTI analysis at 3 T

(*continued on next page*)

Table 3. Continued

			Chronic pain participants				Healthy participants				
Reference	Condition	Country	Study size (M/F)	Age	Pain duration	Pain intensity (0–10)	Study size (M/F)	Age	Modality	Stimuli	Outcome measures
Moayedi et al[58]	Temporomandibular disorder	Canada	17 (0/17)	33.1 ± 11.9	9.8 ± 8.2 Years	4.3 ± 1.8	17 (0/17)	32.2 ± 10.1	MRI	Resting state	Cortical thickness analysis at 3 T
Desouza et al[19]	Trigeminal neuropathic pain	Canada	24 (9/15)	48.5 ± 12.7	6.3 ± 3 Years	NA	24 (9/15)	47.6 ± 12.3	MRI	Resting state	Cortical thickness analysis via 3 T
Maeda et al[48]	Carpal tunnel syndrome	United States	28 (8/20)	48.1 ± 9.6	8.5 ± 9.1 Years	2.5 ± .8 (0–5)	28 (11/17)	47.3 ± 9.9	MRI	Resting state	DTI analyses at 3 T
Wu et al[110]	Ankylosing spondylitis, neuropathic pain	Canada	17 (12/5)	34.4 ± 12.4	NA	6.1 ± 1.7	17 (12/5)	34.9 ± 10.1	MRI	Resting state	Cortical thickness analysis at 3 T
Pleger et al[70]	CRPS I: hand	Germany	20 (9/11)	41.8 ± 9.8	11.9 ± 14.3 Months	5.3 ± 2.4	20 (9/11)	41.6 ± 9.6	MRI	Resting state	VBM analysis (?) at 1.5 T
Ung et al[100]	LBP	United States	47 (25/22)	373. ± 12.2	8.6 ± 7.8 Years	NA	47 (25/22)	37.7 ± 7.8	MRI	Resting state	VBM (SVM) analysis at 3 T
Juottonen et al[39]	CRPS I: hand	Finland	6 (0/6)	44.5 (33–54)	42.2 ± 26.2 Months	5.6 ± 1.8	6 (0/6)	45.1 (34–55)	MEG	Tactile stimuli to the fingertips	Reactivity of 20-Hz motor cortex rhythm
Shibukawa et al[87]	Temporomandibular disorder	Japan	9 (4/5)	32.4	NA	NA	8 (4/4)	30	MEG	Observation tasks of jaw- and palm-opening movements	Neuromagnetic signals
Kirveskari et al[40]	CRPS I: hand	Finland	8 (0/8)	45.5 (26–57)	5.5 ± 3.1 Years	6.4 ± 1.8	8 (0/8)	46.3 28–57)	MEG	Noxious thulium laser stimulation of both hands	Reactivity of 20-Hz motor cortex rhythm
Grachev et al[29]	LBP	United States	9 (7/2)	45 ± 6	9 ± 5 Years	6.18 ± 1.72	11 (9/2)	44 ± 3	MRS	Resting state	Relative concentration of neurochemicals at 1.5 T
Fayed et al[23]	Fibromyalgia	Spain	10 (2/8)	40 ± 6.2	1.6 ± .3 Years	NA	10 (2/8)	37.8 ± 8.7	MRS	Resting state	Relative concentration of neurochemicals at 1.5 T
Sharma et al[86]	LBP	United States	19 (4/15)	46.1 ± 11.3	8.8 ± 7.2 Years	4.5 ± 1.9	14 (3/11)	44.6 ± 14.7	MRS	Resting state	Absolute concentration of neurochemicals at 3 T
Jacobs et al[38]	LBP	United States	10 (5/5)	39.2 ± 6.3 (95% CI)	>12 months	1.8 ± .26 (95%CI)	10 (5/5)	35.4 ± 5.3 (95%CI)	EEG	Arm raise	Alpha event-related desynchronization and Bereitschafts potentials
Shiraishi et al[88]	CRPS	Japan	18 (10/8)	40.7 (21–59)	49.8 (6–252) Months	NA	13 (11/2)	38.7 (27–58)	PET	Resting state	Cerebral glucose metabolism

Abbreviations: M, male; F, female; NA, not available; SEM, standard error of the mean; DKI, diffusion kurtosis imaging; DTI, diffusion tensor imaging; SVM, support vector machine.
NOTE. Values are mean ± SD unless otherwise stated.

Table 4. Risk of Bias Assessment for Included Studies

	Modified STROBE statement items						TMS methodology checklist	
Reference	Source of participants	Participant selection	Methodology	Statistical analysis	Funding	Total score	Reported	Controlled
Salerno et al[75]	0	1	0	0	1	2	41.4%	39.3%
Schwenkreis et al[81]	0	1	1	1	0	3	64.3%	63%
Strutton et al[91]	1	0	0	1	1	3	40%	41.7%
On et al[63]	0	1	0	1	0	2	53.8%	52%
Eisenberg et al[21]	1	1	1	1	0	4	72.4%	71.4%
Krause et al[43]	0	0	0	1	0	1	61.5%	48%
Strutton et al[92]	1	0	0	1	1	3	52%	45.8%
Krause et al[44]	1	0	0	1	0	2	52%	37.5%
Turton et al[99]	0	1	0	1	1	3	46.2%	44%
Tsao et al[97]	0	1	1	1	1	4	73.1%	76%
Berth et al[5]	0	0	1	1	1	3	77%	68%
Turgut et al[98]	0	1	1	1	0	3	69.2%	64%
Mhalla et al[57]	1	1	0	1	0	3	55.2%	53.6%
Schwenkreis et al[82]	0	1	1	1	1	4	64.3%	66.7%
Clark et al[15]	0	1	0	1	1	3	54.2%	52.2%
Schwenkreis et al[83]	0	0	0	1	1	2	64.3%	55.6%
Tsao et al[96]	0	0	1	1	1	3	79.2%	82.6%
Masse-Alarie et al[54]	0	0	1	1	1	3	69%	71.4%
Vallence et al[105]	0	0	1	0	1	2	77%	68%
Kittelson et al[41]	0	1	1	1	1	4	72.4%	71.4%
Marker et al[51]	1	0	1	1	1	4	90%	82.1%
Rittig-Rasmussen et al[73]	1	1	0	1	1	4	57.7%	56%
Bradman et al[7]	0	0	0	1	1	2	61.5%	52%
Schabrun et al[78]	0	1	0	1	1	3	43.5%	43.5%
Schabrun et al[79]	1	1	1	1	1	5	77%	76%
Van Velzen et al[101]	1	1	0	0	1	3	57.7%	52%
Burns et al[8]	0	1	1	1	1	4	79.3%	75%
Caumo et al[11]	1	0	0	1	1	3	62.1%	46.4%
Masse-Alarie et al[52]	0	1	0	1	1	3	62.1%	59.3%
Masse-Alarie et al[53]	0	1	1	1	1	4	69%	64.3%
Rio et al[72]	1	1	0	1	0	3	57.7%	60%
Tarrago et al[93]	1	1	0	1	1	4	69%	55.6%
Morgante et al[60]	0	1	1	1	1	4	72.4%	77.8%
Parker et al[66]	0	1	1	1	1	4	96.6%	88.9%
Te et al[94]	1	1	1	1	1	5	75%	79.2%
Grachev et al[29]	0	1	1	1	1	4	NA	NA
Juottonen et al[39]	0	1	1	0	1	3	NA	NA
Cook et al[17]	0	0	0	0	1	1	NA	NA
Napadow et al[62]	0	1	1	1	1	4	NA	NA
Shiraishi et al[88]	0	1	1	0	0	2	NA	NA
Maihöfner et al[49]	0	1	1	0	1	3	NA	NA
Shibukawa et al[87]	0	1	1	1	1	4	NA	NA
Gieteling et al[28]	0	1	1	0	1	3	NA	NA
Kobayashi et al[42]	0	0	1	0	1	2	NA	NA
Fayed et al[23]	1	0	0	1	1	3	NA	NA
Jacobs et al[38]	0	0	1	1	1	3	NA	NA
Kirveskari et al[40]	0	0	1	1	1	3	NA	NA
Moayedi et al[58]	0	1	0	1	1	3	NA	NA
Wasan et al[108]	0	1	0	0	1	2	NA	NA
Barke et al[4]	1	1	0	1	0	3	NA	NA
Sharma et al[86]	0	1	1	1	1	4	NA	NA
Bolwerk et al[6]	0	1	1	1	1	4	NA	NA
Desouza et al[19]	0	1	0	1	1	3	NA	NA
Liu et al[47]	0	1	0	0	1	2	NA	NA
Maeda et al[48]	0	1	0	1	1	3	NA	NA
Wu et al[110]	0	1	0	1	1	3	NA	NA
Flodin et al[25]	1	1	1	1	1	5	NA	NA
He et al[32]	0	1	1	0	1	3	NA	NA

(continued on next page)

Table 4. Continued

	Modified STROBE statement items						TMS methodology checklist	
Reference	Source of participants	Participant selection	Methodology	Statistical analysis	Funding	Total score	Reported	Controlled
Pleger et al[70]	0	1	0	0	1	2	NA	NA
Ung et al[100]	0	1	0	0	1	2	NA	NA
Pijnenburg et al[69]	0	1	0	0	1	2	NA	NA
Shanahan et al[85]	0	1	0	0	1	2	NA	NA
Flodin et al[24]	1	1	1	0	1	4	NA	NA
Hemington et al[34]	0	1	0	0	1	2	NA	NA
Hotta et al[37]	1	1	0	0	1	3	NA	NA
Tian et al[95]	1	0	1	1	1	4	NA	NA
Van Velzen et al[102]	0	1	0	1	1	3	NA	NA

Abbreviations: STROBE, STrengthening the Reporting of OBservational studies in Epidemiology; NA not available.
NOTE: Each domain would be allocated 1 point if the risk of bias was low and zero point if the risk of bias was considered high. The maximum score possible was five points. NA: not applicable.

trigeminal neuralgia[19] (n = 48 participants, quality score = 3), and larger left M1 cortical thickness that were associated with stronger neuropathic pain symptoms in ankylosing spondylitis[110] (r = .8, n = 34 participants, quality score = 3). One diffusion tensor imaging study reported that enhanced myelination (lower radial diffusivity) in the microstructure of white matter connecting primary sensory cortex and M1 contralateral to the affected side was correlated with nerve conduction velocity in carpal tunnel syndrome[48] (r = .72, n = 56 participants, quality score = 3).

In LBP, 1 MRI study reported increased M1 gray matter (GM) density in people with chronic LBP[100] ($P < .001$ uncorrected for multiple comparisons, n = 94 participants, quality score = 2). Although 1 study reported decreased functional connectivity in the left M1, the left supplementary motor area, and the left cerebellum compared with healthy participants[69] (1.88 ± 0.89 SD vs 2.64 ± 0.8 SD, n = 34 participants, quality score = 2), the other reported increased rCBF in the left M1[108] (cluster-level $P < .01$, n = 32 participants, quality score = 2). Two studies reported no change in M1 activation/connectivity using BOLD contrast (n = 45 participants, quality score = 3,[42] and n = 16 participants, quality score = 2[4]). One EEG study reported altered cerebrocortical motor activity before an arm raise in chronic LBP participants[38] (n = 20 participants, quality score = 3). MRS studies reported conflicting findings for M1 neurochemical metabolism. One study reported no between group difference in sensorimotor cortex[29] (n = 20 participants, quality score = 4), whereas the other reported lower N-acetylasparate concentrations in the right M1 compared with healthy participants[86] (9 ± .9 mM vs 10.2 ± 1.2 mM, n = 33 participants, quality score = 4). For ankylosing spondylitis-related back pain, greater functional impairment was correlated with greater M1–precuneous resting functional connectivity and impaired spinal mobility was associated with weaker M1–rostral ventromedial medulla functional connectivity on BOLD contrast[34] (n = 40 participants, quality score = 2).

Findings in people with CRPS were inconsistent for M1 structure from VBM studies. One study showed increased M1 GM density[70] (cluster-level $P = .042$, corrected, n = 40 participants, quality score = 2), whereas the other showed no between group difference in GM volume and white matter connectivity in sensorimotor cortex[102] (n = 38 participants, quality score = 3). Similarly, findings for M1 activation/connectivity from BOLD contrast were inconsistent. Two studies showed increased activation in bilateral M1[49] (cluster-level $P < .0001$, uncorrected, n = 24 participants, quality score = 3) or connectivity[6] (cluster-level $P < .01$, corrected, n = 24 participants, quality score = 4), whereas 2 showed no changes compared with healthy participants (n = 25 participants, quality score = 3,[28] and n = 38 participants, quality score = 3[102]). There was a significant between group difference in activation of the sensorimotor cortex[37] ($P < .05$, corrected, n = 26 participants, quality score = 3).

In temporomandibular disorder (TMD), 1 VBM study reported that greater pain severity was associated with smaller GM thickness of the M1 region where the representation of the face was situated[58] (r = –.83, n = 34 participants, quality score = 3). BOLD contrast showed decreased intrinsic neural activity in the left M1 in individuals with TMD[32] ($P < .05$, corrected, n = 43 participants, quality score = 3). One MEG study reported that TMD participants had significantly smaller neuromagnetic signals in M1 during observation of jaw-opening movements[87] (1 ± 1 nano amp meter vs 16 ± 3 nano amp meter, n = 17 participants, quality score = 4).

In fibromyalgia, 1 MRS study showed a lower myoinositol to creatine ratio in the left sensorimotor cortex, indicating possible M1 neuronal metabolic dysfunction[23] ($P < .05$, n = 20 participants, quality score = 3). Two studies using BOLD contrast reported conflicting findings in M1 activation/connectivity. One reported no between group difference[17] (n = 18 participants, quality score = 3), whereas the other showed decreased sensorimotor cortex connectivity[25] ($P < .00031$, corrected, n = 38 participants, quality score = 4).

One fMRI study in people with knee OA reported that the M1 representation of the affected knee was shifted 4.1 mm anteriorly (SD or CI not reported) and the relative position of the knee and ankle representations were swapped when participants performed ankle and knee tasks[85] (n = 18 participants, quality score = 2). In

Table 5. Effect Sizes for Between Group Differences (People With and Without Pain) From Meta-Analyses of TMS Studies. Pooled Estimates for All Measures Revealed No Difference Between People With and Without Pain, With the Exception of LICI

Outcome measure	Number of included studies	Number of participants	Quality score range (maximum score = 5)	SMD (95% CI)
Resting motor threshold	19	604	1 to 5	.01 (–.29 to .31)
AMT	12	357	3 to 5	.11 (–.24 to .46)
MEP amplitude	24	788	1 to 5	–.15 (–.38 to .09)
MEP latency	4	181	2 to 4	.21 (–.11 to .52)
Cortical silent period	12	481	1 to 4	–42 (–.85 to .00)
Map volume: erector spinae	2	70	3	–.24 (–.72 to .23)
Map volume: wrist extensor	2	46	2 to 5	.35 (–.66 to 1.36)
SICI	15	572	2 to 4	.07 (–.36 to .50)
LICI	3	102	2 to 4	.78 (.37–1.19)
ICF	7	249	2 to 4	–.26 (–.65 to .14)
SICF	3	113	3 to 4	.23 (–.24 to .70)

addition, poorer performance of a knee task was associated with more anterior placement of the M1 loci in people with knee OA. In rheumatoid arthritis, 1 study using BOLD contrast reported increased connectivity of bilateral sensorimotor cortex with the supplementary motor and midcingulate cortex[24] ($P < .00031$, corrected, n = 43 participants, quality score = 4).

Is There Evidence of Altered Corticospinal Excitability in Chronic Pain?

Data for resting motor threshold, aMT, MEP amplitude and latency, CSP, and map volume were pooled to perform separate meta-analyses from studies using single-pulse TMS. Pooled effect estimates for all measures revealed no difference between people with and without pain (Table 5; Supplementary Figs 1–6). There was substantial heterogeneity across all measures with the exception of MEP latency and map volume of erector spinae.

For comparisons in which significant heterogeneity was observed, we conducted subgroup analysis according to condition. A moderate reduction in aMT in people with chronic knee pain (3 studies, 73 participants, SMD = –.52, 95% CI = –1.02 to –.02, $P = .04$, χ^2 $P = .68$, $I^2 = 0\%$; all studies have quality score >3; Supplementary Fig 2) was detected, indicating increased M1 corticospinal excitability.

Seven of 35 TMS studies[7,43,44,63,75,83,105] scored lower than 3 (median value) on the modified STROBE statement and were categorized as high risk of bias. Meta-analyses rerun after removing the high risk of bias TMS studies detected a large reduction in the CSP for CRPS but left only a single small study (n = 20 participants) in that subgroup.

Is There Evidence for Altered Intra-Cortical Facilitation and/or Inhibition in Chronic Pain?

Sixteen studies investigated intracortical inhibitory and facilitatory networks using paired-pulse TMS paradigms with several different measures. A moderate increase in long-interval intracortical inhibition (LICI) was detected in people with pain (3 studies, 102 participants, SMD = .78, 95% CI = .37–1.19, $P < .001$, χ^2 $P = .84$, $I^2 = 0\%$; Fig 2), indicating increased M1 intracortical inhibition. No difference between people with and without pain was found for short-interval intracortical inhibition (SICI), intra-cortical facilitation (ICF) or short-interval ICF (SICF; Table 5, Supplementary Figs 7–9). One study appeared to mislabel ICF as SICF on the basis of the experimental protocol and was not included in the meta-analysis.[11] There was substantial heterogeneity in the pooled effect estimates for SICI (χ^2 $P < .01$, $I^2 = 80\%$) and ICF (χ^2 $P = .04$, $I^2 = 51\%$). The subgroup analysis showed a moderate reduction in SICI in people with CRPS (4 studies, 100 participants, SMD = –.77, 95% CI = –1.21 to –.34, $P < .01$, χ^2 $P = .72$, $I^2 = 0\%$; Supplementary Fig 7), indicating reduced M1 intracortical inhibition, and a moderate reduction in ICF in people with non-neuropathic

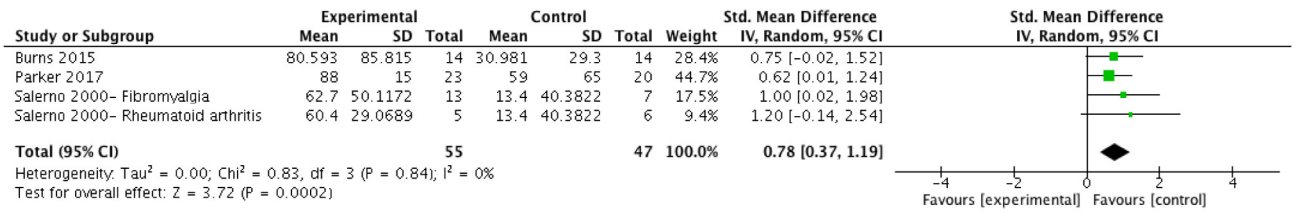

Figure 2. Meta-analysis forest plot for LICI.

pain (6 studies, 151 participants, SMD = –.53, 95% CI = –.94 to –.13, $P = .01$, χ^2 $P = .24$, $I^2 = 26\%$; Supplementary Fig 8), indicating reduced M1 ICF.

Evidence of reduced M1 intracortical inhibition in people with CRPS is complemented by the findings of attenuated activities of the 20-Hz cortical rhythm (which reflects decreased M1 cortical inhibition) from 2 MEG studies. The 20-Hz rebound duration in the right hemisphere was significantly shorter[39] (357 vs 458 ms, $P < .03$, n = 18 participants, quality score = 3), and the rebound amplitude (1 ± 1 SD vs 7 ± 3 SD femtotesla/cm, $P = .05$) and the reactivity (4 ± 2 SD vs 16 ± 5 SD femtotesla/cm, $P = .03$) to painful hand stimuli were significantly smaller[40] (n = 18 participants, quality score = 3) compared with healthy participants. One PET study (n = 31 participants, quality score = 2) showed reduced glucose metabolism in the contralateral M1 in CRPS[88] ($P < .005$, uncorrected), suggesting possible M1 inhibition.

Discussion

To our knowledge, this systematic review is the first to provide a comprehensive and critical review of studies investigating M1 structure, organization, and function in people with chronic pain. For a range of neurophysiological parameters, published studies provided conflicting evidence. Meta-analyses identified a moderate increase in M1 LICI in people with chronic pain. Our findings suggest that the evidence for M1 changes in chronic pain populations is inconclusive for most measures.

Evidence for Altered ICF and/or Inhibition in Chronic Pain

Pooled data from 3 studies investigating non-neuropathic pain provided evidence of increased LICI, indicating increased M1 intracortical inhibition. Increased LICI reflects upregulated γ-aminobutyric acid $(GABA)_B$-mediated intracortical inhibition.[55] Subgroup analyses showed reduced ICF in non-neuropathic pain, suggesting decreased ICF of glutamatergic interneurons through N-methyl-D-aspartate receptors,[111] and reduced SICI in CRPS, suggesting M1 intracortical disinhibition driven by downregulated $GABA_A$-receptors.[55,109] However, although our subgroup analyses were preplanned, interpretation of these findings requires caution because there are no overall effects in the pooled estimates for SICI and ICF.

Consistent with a previous review of CRPS,[20] our review also found M1 disinhibition on the basis of MEG outcomes from 2 studies. The 20-Hz cortical rhythm measured in MEG is initially decreased (suppression; reflecting an activated M1) and subsequently increased (rebound; reflecting inhibited M1) and represents the functional state of M1.[68,76] Combined MEG and MRS showed a positive correlation between 20-Hz rebound amplitude and the concentration of the inhibitory neurotransmitter GABA, indicating the rebound period represents GABAergic inhibition in M1.[27] MEG studies reported a significantly shorter rebound duration of 20-Hz rhythm in both hemispheres,[39] and weaker rebound amplitude and reactivity of 20-Hz rhythm in the hemisphere contralateral to the affected side,[40] indicating M1 disinhibition in CRPS. These findings suggest M1 disinhibition in CRPS, reflecting downregulated GABAergic inhibition. The MEG findings of reduced M1 inhibition in CRPS are inconsistent with the findings of increased LICI in chronic pain from TMS studies. These inconsistencies could be explained because none of these TMS studies investigated CRPS. Although 1 PET study reported reduced glucose metabolism in the contralateral M1 for CRPS in the group analysis, indicating possible M1 inhibition, only 3 (of 18) CRPS participants showed this finding in the individual analysis.[88] Future larger trials are needed to elucidate M1 glucose metabolism in CRPS.

Evidence of Altered M1 Structure, Organization, and Function in Chronic Pain

There is conflicting evidence for M1 changes in chronic pain, which may be explained by the heterogeneity of the underlying neurophysiological mechanisms, methodological differences, internal study biases, reporting biases, and the random play of chance, because of the small sample sizes of the included studies. For example, heterogeneity of underlying neurophysiological mechanisms in nonspecific chronic LBP has been reported.[89] A mixture of neuropathic and non-neuropathic pain components were identified not only in chronic nonspecific LBP,[90] but ankylosing spondylitis back pain,[110] and knee and hip OA.[26,36,59,61] However, it is unclear whether a neuropathic pain subgroup exists in other pain conditions. Future studies should investigate whether distinct pain subgroups exist within chronic pain conditions and whether these subgroups present with different M1 changes.

Evidence from several different measures suggests increased M1 activation/connectivity in neuropathic pain. M1 disinhibition has been attributed to increased M1 activation (carpal tunnel syndrome), increased M1 rCBF (postherpic neuralgia), and increased M1 functional connectivity (trigeminal neuralgia)[47,62,95] though M1 disinhibition in neuropathic pain was not supported by the finding of a reduction in MEP amplitude from a single study in people with diabetic neuropathy[98] (Supplementary Fig 3). More research is needed to elucidate the neurophysiological mechanisms driving M1 functional changes in neuropathic pain populations.

Several studies reported that impaired motor control in chronic pain was associated with M1 reorganization or altered corticomotor physiology.[38,85,97] For example, delayed activation of the trunk muscles when performing an arm raise in chronic LBP patients was associated with smaller amplitudes of Bereitschafts potential, an EEG potential generated by M1 and the supplementary motor cortex representing movement preparation,[38] and with increased map volume and the posterolaterally shifted M1 representation of transversus abdominis.[97] This supports the role of altered M1 in motor control impairment in musculoskeletal disorders. However, the causal relationship and the interaction between M1 changes, motor

control impairment, and symptom persistence in chronic pain requires further investigation.

A previous review on M1 function in CRPS could not draw a definite conclusion on M1 functional changes.[20] Two recent MRI studies investigating M1 function and structure for CRPS were included in this review, which reported conflicting findings, likely because of different experimental protocols (resting state vs observational tasks).[37,102] Taken together with the other neurophysiological evidence, no conclusion on M1 changes in CRPS can be drawn from our findings.

Evidence of Altered Corticospinal Excitability in Chronic Pain

Meta-analyses of TMS data revealed no significant change in any measure of corticospinal excitability in people with chronic pain. Although subgroup analysis found a reduction in aMT in chronic knee pain, suggesting increased excitability in the motor system particularly in relation to neuronal and interneuronal membrane excitability,[112] interpretation of this finding requires caution because there is no overall effect in the pooled estimate for aMT.

A previous review on corticomotor excitability in chronic pain reported evidence of M1 disinhibition that was more prominent in neuropathic pain populations.[65] However, our review did not find compelling evidence of M1 disinhibition when people with and without pain were compared. This discrepancy is likely because of our inclusion of more recent studies[7,11,52,53,60,66,72,79,85,93,94] and exclusion of studies containing neurological populations.[45] Also, CRPS studies were separated from neuropathic pain in our subgroup analyses because they have different diagnostic criteria and pathophysiology.

Altered M1 representation of erector spinae muscles (reduced map volume) in chronic LBP has been reported,[96] but not supported by a larger study.[78] Pooled map volume data from these studies found no significant difference between LBP and healthy participants. The differences between the studies in sample size and methodology such as different electromyography electrodes (fine wire needle vs superficial, surface electrodes), the sizes of grid used to measure the map (5×7 cm versus 6×7 cm), and different coils used to deliver TMS could contribute to the contradictory findings of M1 reorganization of erector spinae in LBP. Although some small single studies reported increased map volume of the wrist extensor (lateral epicondylalgia) and transversus abdominis (LBP) muscles, and decreased map volume of quadriceps (patellofemoral pain; Supplementary Fig 5), meta-analyses do not support the changes in M1 representations.

Limitations and Recommendations

Several limitations should be considered when interpreting the findings of this review. First, most included studies were small, and may be affected by low statistical power as well as conversely, the propensity for small published studies to return positive and often inflated effect sizes.[10] Additionally, subgroup analyses are regarded as exploratory and interpretation of these findings requires caution, particularly when there is no overall effect in the pooled estimates. False positive significance tests also increase in likelihood rapidly as more subgroup analyses are performed.

TMS studies investigating M1 representations of the affected muscles in chronic pain reported the center of gravity (CoG) as the location of M1 representation. Smudged M1 representations of affected muscles (measured by the distance between the CoG of neighboring muscles) has been reported in chronic LBP and lateral epicondylalgia, suggesting M1 reorganization.[78,79,96] However, we were unable to meta-analyze CoG data because studies reported either the coordinates of the CoG or the absolute distance between the averaged CoG for each group. Future research using TMS to investigate M1 representation of the affected muscles should report the coordinates of CoG for meta-analysis of the data. We also acknowledge that 4 included TMS studies were published by 1 of the coauthors of this review.[8,78,79,94] To minimize the bias, reviewers who were not involved in these studies performed the risk of bias assessment.

A recent study reported that the errors of software commonly used for data analysis in fMRI studies may result in a false positive rate of up to 70% and questioned the validity of some fMRI studies.[22] It is beyond the scope of this review to discuss how these statistical issues may influence the findings of this review. However, the fMRI findings of M1 activation/connectivity and organization for chronic pain in this review should be interpreted with caution. Several studies included in this review investigated the sensorimotor cortex rather than the M1.[23-25,37,102] It is possible that heterogeneity in the brain region being investigated (ie, sensorimotor vs M1) contributed to the inconclusive findings of this review.

Conclusions

This review provides the current evidence on M1 structure, organization, and function in chronic pain and identifies areas where further research is required. EEG, MEG, MRS, and PET techniques have been rarely used to investigate M1 function in chronic pain. Data pertaining to M1 changes for conditions such as TMD, rheumatoid arthritis, neck, shoulder, and neuropathic pain are still lacking. Additionally, more research using paired-pulse TMS paradigms to investigate M1 ICF/and inhibition in chronic pain is required because data are still lacking for measures of LICI and SICF. Future studies with larger sample sizes are warranted to elucidate M1 changes in chronic pain conditions and to inform treatments targeting M1.

Supplementary Data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.jpain.2017.10.007.

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