J Surg Med. 2023;7(5):347-354.
DOI: 10.28982/josam.7669

Review

Journal of Surgery and Medicine
e-ISSN: 2602-2079
https://jsurgmed.com/

Graded motor imagery in orthopedic and neurological rehabilitation: A systematic review of clinical studies

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Ethics Committee Approval
This article is not a study with human participants. There are no experiments on animals. This article does not contain any studies on human participants or animals performed by the author. There is no identifying information of participants.

Conflict of Interest
No conflict of interest was declared by the authors.

Financial Disclosure
The authors declared that this study has received no financial support.

Published
2023 May 1

Abstract

Background/Aim: Graded motor imagery is an increasingly popular motion representation technique. However, treatment protocols for graded motor imagery vary depending on various diseases. This study aims to summarize the cases in which graded motor imagery therapy is used, study protocols, and outcome measures in studies.

Methods: The literature search was done with Web of Science, Pubmed, Scopus, and PEDro databases. The last search was carried out on September 13, 2022. A series-specific bias risk assessment tool was used with randomized, non-randomized, and case reports. All clinical studies that performed graded motor imagery, available in full text, describing their methods and findings, were included. The gender of the participants was not significant. The intervention was graded motor imagery. Outcome measures were mainly pain severity, other pain-related measures (e.g., pressure pain threshold, pain catastrophe), range of motion, strength, reaction time, kinesiophobia, neurophysiological measures, depression, function, or quality of life measures.

Results: Complex regional pain syndrome, distal radius fracture, phantom limb pain, stroke, cancer, pathological pain (phantom pain after amputation, pain after brachial plexus avulsion), elbow stiffness, frozen shoulder, chronic shoulder pain, and osteoarthritis conditions were included. The intervention duration in the studies varies from 2 to 8 weeks. A common outcome measure could not be determined among studies. The pain was assessed in 15 studies, although different rating scales were used. Graded motor imagery resulted in a reduction in pain in 14 of the 15 studies.

Conclusions: Due to the heterogeneity of the studies, a general conclusion regarding the effect of the disease-specific intervention was not possible. Based on pain outcome, graded motor imagery effectively decreased pain severity in various painful conditions.

Keywords: graded motor imagery, pain, chronic pain, motor imagery, rehabilitation

How to cite: Candiri B, Talu B, Karabicak GO. Graded motor imagery in orthopedic and neurological rehabilitation: A systematic review of clinical studies. J Surg Med. 2023;7(5):347-354.

Introduction

Graded motor imagery (GMI) is a movement representation technique used to achieve cortical reorganization through neuroplasticity, gradually activating cortical level activation and reducing cortical disinhibition [1,2]. GMI, which is used for definitions of "brain exercises" and "training the brain", basically consists of three stages [3,4]. These stages are implicit motor imagery (lateralization), explicit motor imagery, and mirror therapy [1]. The first of these stages, lateralization, activates the premotor cortex without activating the primary motor areas. The second stage causes the activation of motor areas similar to the realization of normal movement. The mirror therapy phase also provides input for normal movement [5]. The sequential implementation of these three phases is important [6]. The first known research on GMI started in 2004 with complex regional pain syndrome [7]. Looking at the literature, it is seen that it is used in various neurological and orthopedic conditions. Distal radius fracture [2], complex regional pain syndrome (CRPS) [3,6-13], pathological pain [4], post-amputation phantom limb pain [14], chronic shoulder pain [15], cancer [16], knee osteoarthritis [17], frozen shoulder [18], stroke [19,20], and elbow stiffness [21] are the conditions in which graded motor imagery has been used in all its stages in the literature. While the usage area of GMI is expanding, another issue is the different application protocols in the literature. Again, in the first known study, all three stages of GMI were applied at every waking hour of the day [7]. When the following literature was examined, different application forms were seen. For example, Lagueux et al. [8] suggested applying it three times a day because of their study's low feasibility of each waking hour.

The advantages of GMI are that it is suitable for home use, requires minimal equipment, and is low risk [20]. While the application areas of GMI are increasing, only two systematic reviews about GMI have been found. A systematic review focused on the effect of GMI on chronic pain and examined studies using any of the three stages of GMI [22]. Another systematic review investigated GMI or mirror therapy's effectiveness in patients with CRPS type 1 [23]. Only randomized controlled trials were selected in these reviews. There were three studies in total in which the three stages of GMI were used sequentially. Although the mechanism of GMI has not been fully elucidated, it has been applied to facilitate sensory and motor cortex reorganization and gradually activate cortical networks without causing a protective pain reaction [2,15]. For these, it is necessary to apply the stages of GMI sequentially [22]. Examining the studies in which the three stages of GMI are applied sequentially will be useful for future research. It is also necessary to examine GMI in situations other than CRPS and chronic pain conditions. We believe that a detailed literature review would be beneficial due to heterogeneous studies in different fields. Therefore, this review aims to examine in detail the different situations, application protocols, and outcome measures in studies in which all stages of GMI are applied sequentially.

Materials and methods

This systematic review has been prepared according to the rules of Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) [24].

1. Search strategy

The search was performed using Web of Science, Pubmed, Scopus, and PEDro databases. "Graded motor imagery" was used as a keyword, and no time or language filters were selected. The last search was carried out on September 13, 2022. Reference sections of included studies were also reviewed. Duplicates were removed using the Endnote 9 software program (Figure 1).

2. Eligibility criteria

In this review, accordance was made by considering the PICOS (population, intervention, control, outcomes, and study design) criteria [25].

2.1. Population

Studies, including the GMI program, were reviewed. Clinical trials using the three phases of the GMI program (implicit motor imagery, explicit motor imagery, and mirror therapy) sequentially, available in full text, and in which the article was particularly clear in terms of methods and findings, were included. The gender of the participants was not significant.

2.2. Intervention and control

The intervention was graded motor imagery. Only the three phases of the GMI (implicit motor imagery, explicit motor imagery, and mirror therapy) had to be applied sequentially. All studies with or without any comparison group were included.

2.3. Outcomes

Since the purpose of the review was to summarize the literature, no limitations were made. Outcome measures were mainly pain severity, other pain-related measures (e.g., pressure pain threshold, pain catastrophe), range of motion, strength, reaction time, kinesiophobia, neurophysiological measures, depression, function, or quality of life measures.

2.4. Study design

Randomized controlled trials, non-randomized studies, prospective studies, case reports, and case series were selected. The Jovell & Navarro-Rubio classification was used to assess the methodological quality of the included studies [26].

3. Selection criteria and data extraction

The first author reviewed the titles and abstracts of all studies to identify potentially relevant studies, and removed duplicated articles based on search results. The full texts of all potentially relevant studies were reviewed. Afterward, the articles were examined with other authors according to the inclusion and exclusion criteria, and the final articles were determined with a joint decision. The data described in the article's findings were extracted by a standardized data extraction form, which ensures that the most relevant information is obtained [27].

4. Risk of bias assessment

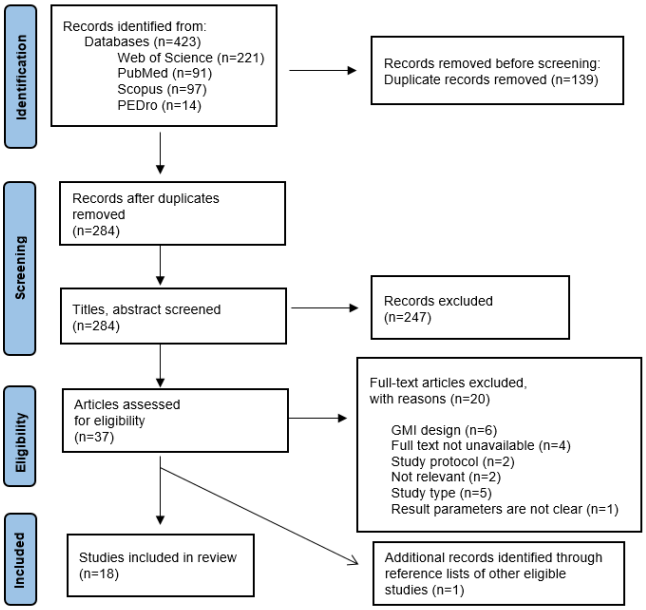
The risk of bias (ROB) for the non-randomized studies included was assessed using the Risk Of Bias In Non-randomized Studies of Interventions (ROBINS-I) tool [28]. Higgins et al.'s [29] risk of bias criteria (RoB 2) was used for the bias assessment of randomized controlled trials. Case reports and

case series were evaluated with a tool based on selection, ascertainment, causality, and reporting [30].

Results

The flow chart is shown in Figure 1. Eighteen studies were included in this review. The main characteristics of the included articles (author information, publication year, demographic information of the participants, pathological condition, number of study groups, and type of blinding) are given in Table 1.

Figure 1: Flow chart of participant selection according to PRISMA.



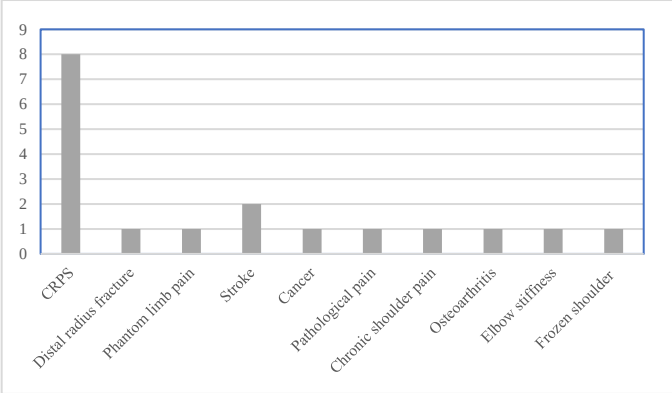
Study selection

As a result of the literature search made from databases, 423 articles were found. Of these, 139 copies were extracted, and 284 studies were reviewed. As a result, 37 articles were included in the review. Twenty studies were excluded because they did not meet the eligibility criteria. These studies included discrepancies or deficiencies in the order of the stages of GMI [18,31-35], lack of full-text access [36-39], protocol of the study [40,41], not fully implementing the GMI [42,43], study type (1 letter to the editor, 2 abstract conference papers, 2 reviews) [5,44-47] and were excluded due to unclear outcome parameters [13]. As a result, 17 eligible studies were reviewed, and after reviewing the reference sections of these studies, one more study [6] was added, and a total of 18 articles were included in this systematic review (Figure 1).

Study characteristics

These 18 studies included CRPS [3,6-12], distal radius fracture [2], phantom limb pain [14], stroke [19,20], cancer [16], pathological pain (phantom pain after amputation, post-brachial plexus avulsion, and CRPS) [4], chronic shoulder pain [15], osteoarthritis [17], frozen shoulder [48], and elbow stiffness [21] (Figure 2). Studies case report and patient series (n=4), randomized controlled (n=10) (two waiting list crossover), randomized (n=1), randomized parallel design (n=1), and a single-arm prospective (n=1) consisting of a non-randomized controlled trial (n=1). The sample of the studies included a total of 513 participants. The demographic information of the participants is given in Table 1. The methodological quality levels of the included studies based on the Jovell and Navarro-Rubio [26] classification are given in Table 2.

Figure 2: Distribution of diseases included in our systematic review. The x-axis is the number of studies included.



Risk of bias assessment

The ROB evaluation of randomized studies is summarized in Table 3. Of twelve randomized controlled studies, eight had “high” ROB, and the remaining four had “some concerns”. The ROB of non-randomized studies is shown in Table 4. Of the two included studies, a severe ROB was identified in one and a moderate ROB in the other. The evaluation of the case report and series are shown in Table 5.

Interventions

GMI was administered alone or in combination with any treatment. Since our aim in this review is also to reveal the different uses of GMI, all studies are included, even if they are used in addition to different treatments. First, when randomized studies were examined, GMI was applied together with traditional rehabilitation in four studies [2,17,20,48]. Three studies included GMI alone in the intervention group [4,7,14]. In one study, while GMI was applied sequentially to the intervention group, the order of the GMI was changed in the control groups [6]. In one study, 6 weeks of home exercise were applied after a 6-week GMI program [21]. Two of the studies were combined with the waiting protocol [9,10]. In another study, GMI with transcranial magnetic stimulation (tDCS) was compared with the group that received GMI with sham tDCS [11]. A non-randomized study used GMI with motor rehabilitation [19]. GMI alone was also included in a single-arm prospective study [15]. Considering case reports and patient series, one study used pain neuroscience education before GMI and graded functional exposure after GMI [3]. In another study, GMI was associated with neural mobilization [16]. It was used alone in two studies [8,12].

Graded Motor Imagery

In all studies, the three stages of GMI, implicit motor imagery (lateralization), explicit motor imagery, and mirror therapy, were applied sequentially. Only one study had a modified GMI program. In this program, mirror therapy was first applied with mobilization of the unaffected hand, followed by mobilization of both hands [8].

Table 1: Characteristics of patients in studies.

	Author and year	Participants			Contents	Study Group	Blind
		N (I/C)	Age	Gender (F/M)			
1	Dilek et al. 2017	17/19	I: 52.59±9.8; C: 47.16±10.5	I: 12/5 C:12/7	Distal radius fracture	2	Assessor
2	Limakatso et al. 2019	11/10	Median: I:63 (53-65) C: 62 (59-67)	I: 3/8 C: 2/8	Phantom limb pain	2	Assessor
3	Moseley et al. 2004	7/6	I:35±15; C:38±14	I:5/2 C:4/2	Chronic CRPS1	2	Assessor
4	Moseley et al. 2006	25/25	Unspecified	NC	Phantom limb pain after amputation, brachial plexus avulsion, CRPS1	2	Assessor
5	Gurudut et al. 2020	5/5	I:45.80±8.44 C:55.80±6.83	Unspecified	Knee osteoarthritis	2	Unspecified
6	Moseley, 2005	7/6/7	G1:36±8 G2:27±7 G3:39±8	G1:5/2 G2:4/2 G3:5/2	CRPS1	3	Researcher
7	Ji et al. 2021	17/20	I: 53.29±17.09 C: 61.75±11.59	I: 8/9 C: 7/13	Chronic stroke	2	Unspecified
8	Birinci et al. 2022	25/25	I: 42.1±11.2 C: 41.7±10.5	I: 8/17 C: 10/15	Elbow stiffness	2	Assessor, patients
9	Gurudut et al. 2022	10/10	I: 57±7.24 C: 58±7.25	I: 7/3 C: 7/3	Frozen shoulder	2	Assessor
10	Strauss et al. 2021	21/21	I: 54.71±14.13 C: 52.19±14.76	I:17/4 C:17/4	CRPS	2	Unspecified
11	Lagueux et al. 2017	11/11	I: 41 ± 9 C: 53 ±10	I: 8/3 C: 6/5	CRPS	2	Patients
12	Strauss et al. 2021	20/20	I: 54.7±14.3 C: 52.2±14.7	I:17/3 C:16/4	CRPS	2	Assessor
13	Polli et al. 2017	14/14	I: 56.6±12.4 C: 58.75 ±13.3	I: 4/10 C: 3/11	Stroke	2	Assessors
14	Araya-Quintanilla et al. 2020	107/-	65.7±4.8	68/39	Chronic Shoulder Pain Syndrome	No	No
15	Shepherd et al. 2018	1/-	57	Female	CRPS1	No	Unspecified
16	Lagueux et al. 2012	7/-	45±9.36	6/1	CRPS1-acute phase	No	Unspecified
17	García et al. 2015	7	5-18	Unspecified	Cancer	No	Unspecified
18	Walz et al. 2013	1/1	37/37	F/F	CRPS	2	Unspecified

I: Intervention, C: Control, F: Female, M: Male, CRPS: Complex regional pain syndrome, NC: Not clear.

Table 2: Intervention, comparison, outcomes, and design of the studies.

	Intervention		Control	Outcomes		Study Design	
	Exercise Type	Exercise Content/ Duration/ Frequency/ Time		Outcome	Results	D	Q
1	GMI and traditional rehabilitation	Traditional rehabilitation and lateralization, motor imagery and mirror therapy 8 wk/ twice on the wk/ 60 min L: 3 wk/3 times every waking hour (about 10 min) MI: 3 wk/3 times every waking hour (about 15 min) MT: 2 wk/10 times each waking hour.	Traditional rehabilitation including ROM and strengthening exercises 8 wk/ twice on the wk/60 min	VAS, active ROM, grip strength, DASH, MHQ	The GMI group showed greater improvement in pain intensity, wrist ROM and forearm ROM, and functional status (DASH, MHQ).	RCT	III
2	GMI, routine physiotherapy	Left/right judgements, imagined movements, mirror therapy 6 wk/ 2 supervised exercises (30 min) in the first week of each phase L: 2 wk MI: 2 wk MT: 2 wk Each phase 10 min each waking hour (12 sessions per day)	Routine physiotherapy (NC) 6 wk/NC	Brief Pain Inventory (Pain severity scale and pain interference scale), VAS of the EuroQol EQ-5D-5L	Significant improvements have been demonstrated in the interaction of pain and pain with function.	RCT	III
3	GMI, physical therapy	Recognition of hand laterality, imagined hand movements and mirror therapy 6 wk/ Unspecified L: 2 wk/three times each waking hour (<10 min) MI: 2 wk/ three times each waking hour (<15 min) MT: 2 wk/(Repeat 20 movements 10 times each waking hour)	Physical therapy 12 wk/ 2- 3 times per week.	Neuropathic pain scale, finger circumference, response time	In the GMI group, a reduction in pain, edema and response time was demonstrated.	RCT	III
4	GMI, standard rehabilitation	Limb laterality recognition, movement imagery, mirror movements 6 wk/ NC L: 2 wk/NC MI: 2 wk/NC MT: 2 wk/NC	Standard physiotherapy 6 wk/NC	Patient-specific task-related numerical rating scale, VAS	Improvements in pain and function were maintained at 6 months.	RCT	III
5	Progressive muscle relaxation, GMI, traditional rehabilitation	Left/right discrimination, explicit therapy, mirror therapy, traditional rehabilitation 2 wk/5 sessions per wk/ 20 min L and MI: First week MT: Second week	Jacobson's relaxation technique, traditional rehabilitation 2 wk/5 sessions per wk/ 20min	WOMAC, Knee flexion ROM	Knee flexion range of motion and WOMAC scores were significantly better in the GMI group than in the PMR group.	RCT	III
6	GMI	G1: Respectıvely (L, MI, MT) L: 2 wk/3 times every waking hour (~10 min) MI: 2 wk/ Twice every waking hour (~10 min) MT: 2 wk/Repeat each picture 5 times at each wake-up time (~10 min)	G2: Respectıvely (MI, L, MI) G3: Respectıvely (L, MT, L) L: 2 wk/3 times every waking hour (~10 min) MI: 2 wk/ Twice every waking hour (~10 min) MT: 2 wk/Repeat each picture 5 times at each wake-up time (~10 min)	Neuropathic pain scale, 11-point numerical rating scale (activity difficulties)	Sequential administration of GMI (G1) produced further reductions in pain and disability.	RCT	III
7	GMI, conventional therapy	Implicit motor imagery, explicit motor imagery, and mirror therapy, conventional therapy 8 wk/30 min a day L: NC MI: NC MT: NC	Conventional therapy (Task-oriented active/passive range of motion training) 8 wk/30 min a day	MFT, Fugl-Meyer Assessment, Modified Barthel Index	The MFT arm motion score was significantly better in the GMI group than in the controls.	RCT	III
8	GMI, structured exercise program	Left-right discrimination, motor imagery, and mirror therapy Home exercises (6 weeks after GMI) 6 wk/ twice a wk (GMI) L: 2 wk (1-2 wk) MI: 2 wk (2-3 wk) MT: 4 wk (3,-6 wk)	Structured exercise program Home exercise (6 weeks after exercise program) 6 wk/ twice a wk	DASH, ROM, VAS, Tampa Scale, muscle strength, left-right , discrimination, Global Rating of Change scale.	Function, elbow AROM, pain, fear of movement-related pain, and muscle strength were significantly different in the GMI group compared to the control group.	RCT	III
9	GMI, conventional physiotherapy	Laterality recognition, movement visualization, mirror therapy, conventional physiotherapy 3 wk/ three times a wk L: 1 wk/NC MI: 1 wk MT: 1 wk	Conventional physiotherapy 3 wk/ three times a wk	ROM, fear avoidance belief questionnaire, VAS, SPADI.	Pain, functional disability, fear of movement, and abduction ROM, in the GMI group, was significantly better than in the control group	RCT	III

GMI: Graded motor imagery, L: Lateralization, MI: Motor imagery, MT: Mirror therapy, VAS: Visual Analog Scale, ROM: Range of motion, DASH: Disabilities of the Arm, Shoulder and Hand, MHQ: Michigan Hand Outcomes Questionnaire, MFT: Manual Function Test, tDCS: Transcranial Magnetic Stimulation, fMRI: Functional Magnetic Resonance Imaging, FMA: Fugl-Meyer Assessment, PCS: Pain catastrophizing scale, WMFT: Wolf Motor Function Test, RCT: Randomized Controlled Trials, WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index, SPADI: Shoulder Pain And Disability Index, G1: Group 1, G2: Group 2, G3: Group 3, NC: Not Clear, min: minute, wk: week, D: design, Q: quality.

Table 2: Continues.

	Intervention		Control	Outcomes		Study Design	
	Exercise Type	**Exercise Content/ Duration/ Frequency/ Time**		**Outcome**	**Results**	**D**	**Q**
10	GMI	Left/right judgments, imagined movements, mirror therapy 6 wk GMI followed by 6 wk wait L: 2 wk/10 min every waking hour MI: 2 wk/10 min every waking hour MT: 2 wk/10 min every waking hour	6 wk wait followed by 6 wk GMI	CRPS severity score (CSS), QuickDASH, VAS, cutaneous sensory threshold, spatiotactile resolution, Roeder Manipulative Aptitude Test, cortical excitability	Without waiting, GMI resulted in a minor effect on movement pain, reduction in CSS, increased use of the affected hand, and an improvement in motor function and spatial tactile performance .	Randomized controlled crossover study	III
11	GMI, Transcranial Direct Current Stimulation	GMI: Limb laterality recognition, imagined movements, mirror therapy L: 2 wk/6 times a wk/ 3 times per day/10 min MI: 2 wk/6 times a wk/ 3 times per day/10 min MT: 2 wk/6 times a wk/ 3 times per day/10 min tDCS: Constant current with a intensity of 2 mA (30 seconds ramp up, 30 seconds ramp down), (20 min) 1-2 wk: 5 days a wk 3-6 wk: 1 time per wk	GMI+ shamtDCS	Brief pain inventory shortform, SF-12, Tampa Scale, Pain catastrophizing scale, State-Trait Anxiety Inventory, Beck Depression Inventory	GMI + tDCS did not cause a significant change in pain compared to the sham group. There were significant group differences in kinesiophobia, catastrophizing pain, and anxiety.	Randomized parallel design	III
12	GMI	Mental rotation, movement imagery, mirror movements 6 wk GMI followed by 6 wk wait L: 2 wk/ 10 min every waking hour MI: 2 wk/ 10 min every waking hour MT: 2 wk/10 min every waking hour	6 wk wait followed by 6 wk GMI	VAS, response Time, fMRI Representation	GMI treatment alone, but not waiting, showed an effect on motion pain and hand reasoning task performance.	Randomized wait-list crossover design	III
13	GMI, motor rehabilitation	Implicit Motor Imagery, Explicit Motor Imagery and Mirror Therapy and motor rehabilitation (GMI 1 hour and motor rehabilitation 1 hour) 4 wk/5 days a wk L: 6-8 session/ 1 hour MI: 6-8 session/ 1 hour MT: 6-8 session/ 1 hour	C: Motor rehabilitation 4 wks/5 days a wk/ 2 hours	WMFT, FMA for Upper Limb, Tardieu Rating Scale, VAS, Functional Independence Measure, Satisfaction questionnaire	In FMA and WMFT, improvements have been shown in motor function, as well as in the pain section of FMA.	Non-randomized controlled trial	IV
14	GMI	Laterality training, imagined movements, and mirror therapy 6 wk/ 3 times a wk L: NC/1 hour a day MI: NC/3 times per day MT: NC/30 min	No	VAS, Tampa Scale, PCS, active ROM	A decrease in VAS, Tampa Scale and PCS and an increase in active ROM were shown.	Single-Arm Prospective Study	VI
15	Pain neuroscience education, Graded motor imagery, Graded functional exposure	Visit 1-7: Pain neuroscience education (pain metaphors were used to explain allodynia and central sensitivity) and GMI (laterality, explicit motor imagery and mirror therapy) Visit 8-20: Gradual weight bearing in walking, therapeutic exercise, manual therapy Visit 21-26: Motor performance exercises to improve strength and proprioception 9 month/ 26 visit L: NC MI: NC MT: NC	No	Foot and Ankle Ability Measure-Activities of Daily Living, Tampa Scale, Pain Catastrophizing Scale, patient's goals, Physical examination	Beneficial results have been demonstrated in functional and fear of movement outcomes.	Case Report	IX
16	Modified graded motor imagery (home exercise)	Phase 1: Hand laterality Phase 2: Imagined hand movements Phase 3: Mirror therapy with mobilization of the nonaffected hand Phase 4: Mirror therapy with mobilization of both hands Each phase 2 wk/6 days a wk/3 times a day/ 10 min	No	Short form of the McGill Pain Questionnaire, DASH, grip force, PGIC	No functionally (DASH) significant changes were observed, with significant changes in pain, grip strength, and PGIC.	Patient series	VIII
17	GMI, neural mobilization	Motor imagery: 5 days/wk for 1 week. Laterality recognition: 5 days/wk for 1 wk. Mirror therapy: 5 days/wk for 2 wk. Neural mobilization -Slump test in lateral decubitus (2 _ 20 at 0.5 Hz) – 2 days/wk for 4 weeks. Upper Limb Tension Test 1 – both arms (2 _ 20 at 0.5 Hz) – 2 days/wk for 4 wk.	No	VAS, pain thresholds, LANSS, catastrophizing survey	Improvement in pain threshold and pain perception was demonstrated.	Patient Series	VIII
18	GMI	GMI: Mental rotation, movement imagery, mirror movements 6 weeks L: 2 wk/ 5-10 min every waking hour MI: 2 wk/ 5-10 min every waking hour MT: 2 wk/5-10 min every waking hour	No intervention	Cerebral activation, VAS	There was a reduction in pain, changes in discriminative pain processing areas in the cortex, but no change in emotional pain processing areas.	Case report	IX

GMI: Graded motor imagery, L: Lateralization, MI: Motor imagery, MT: Mirror therapy, VAS: Visual Analog Scale, ROM: Range of motion, DASH: Disabilities of the Arm, Shoulder and Hand, MHQ: Michigan Hand Outcomes Questionnaire, MFT: Manual Function Test, tDCS: Transcranial Magnetic Stimulation, fMRI: Functional Magnetic Resonance Imaging, FMA: Fugl-Meyer Assessment, PCS: Pain catastrophizing scale, WMFT: Wolf Motor Function Test, RCT: Randomized Controlled Trials, WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index, SPADI: Shoulder Pain And Disability Index, G1: Group 1, G2: Group 2, G3: Group 3, NC: Not Clear, min: minute, wk: week, D: design, Q: quality

Table 3: Risk of bias assessment for randomized controlled trials.

	Dilek et al. 2017	**Limakatso et al. 2019**	**Moseley et al. 2004**	**Moseley et al. 2006**	**Gurudut et al. 2020**	**Moseley 2005**	**Ji et al. 2021**	**Birinci et al. 2022**	**Gurudut et al. 2022**	**Strauss et al. 2021**	**Lagueux et al. 2017**	**Strauss et al. 2021**
Risk of bias arising from the randomization process	Low	Low	Low	Low	Some concerns	Low	Some concerns	Low	Some concerns	Some concerns	Low	Some concerns
Risk of bias due to deviations from intended interventions	Some concerns	Some concerns	Some concerns	Some concerns	Some concerns	Some concerns	High	Some concerns	Some concerns	Some concerns	Some concerns	Some concerns
Risk of bias due to missing outcome data	High	Low	Low	Low	Low	Low	Low	Low	Low	High	Low	Low
Risk of bias in measurement of the outcome	Low	Low	High	Low	High	High	High	Low	Low	High	High	Low
Risk of bias in selection of the reported result	Some concerns	Some concerns	Some concerns	Some concerns	Some concerns	Some concerns	Some concerns	High	Some concerns	Some concerns	Some concerns	Some concerns
Overall risk of bias	High	Some concerns	High	Some concerns	High	High	High	High	Some concerns	High	High	Some concerns

Table 4: Risk of bias assessment for non-randomized studies.

	Bias due to confounding	Bias in selection of participants into the study	Bias in classification of interventions	Bias due to deviations from intended interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported result(s)	Overall bias
Polli et al. 2017	Moderate	Low	Moderate	Low	Low	Low	Moderate	Moderate
Araya-Quintanilla et al. 2020	Moderate	Low	Moderate	Serious	Low	Low	Moderate	Serious

Table 5: Risk of bias assessment for case reports and case series.

Domain	Leading explanatory question	Study			
		Shepherd et al. 2018	Lagueux et al. 2012	García et al. 2015	Walz et al. 2013
Selection	1. Do patients represent the whole investigator (center) experience?	No	Yes	Yes	No
Ascertainment	2. Was the exposure adequately ascertained?	Yes	Yes	No	Yes
	3. Was the outcome adequately ascertained?	No	Yes	Yes	Yes
Causality	4. Were alternative causes explaining the observation ruled out?	NA	NA	NA	NA
	5. Was there a challenge/rechallenge phenomenon?	NA	NA	NA	NA
	6. Was there a dose response effect?	NA	NA	NA	NA
	7. Was follow-up long enough for outcomes to occur?	Yes	No	No	Yes
Reporting	8. Was there sufficient detail to replicate the research?	No	Yes	No	Yes
Overall score		2/8	4/8	2/8	4/8

There are some differences regarding the duration and frequency of application of the total and each stage of GMI. Total administration ranged from 2 to 8 weeks. Detailed information on the implementation of all phases of the GMI is shown in Table 2.

Outcomes

Pain was the outcome measure in 15 of the studies. Visual analog scale (VAS) [2,4,9,10,12,15,16,19,21,48] was used the most in pain assessment. In other studies, brief pain inventory (BPI) [11,14], the McGill Pain Questionnaire (MPQ) [8], the neuropathic pain scale (NPS) [6,7], and LANSS [16] were used. Other parameters related to pain were pain threshold [16] and the pain catastrophizing scale [3,11,15,16]. Other tools used include: range of motion (ROM) [2,15,17,21,48] and strength [2,8,21] were other outcome measures. In the evaluation of kinesiophobia and functional status, the Tampa Scale [3,11,15,21], Fear Avoidance Belief Questionnaire [48], Disabilities of the Arm, Shoulder and Hand (DASH) [2,8,21], Quick DASH [9], Michigan Hand Outcomes Questionnaire (MHQ) [2], WOMAC [17] and Functional Independence Measure (FIM) [19], Shoulder Pain and Disability Index [48], Foot and Ankle Ability Measure-Activities of Daily Living (FAAM-ADL) [3]. In addition, VAS of the EuroQol EQ-5D-5L [14], Modified Barthel Index [20], SF-12 [11], and Numerical Rating Scale (NRS) [4,6] were used for quality of life and activities of daily living. Reaction time [7,9] was also included as an outcome measure. Anxiety and depression were evaluated with the State-Trait Anxiety Inventory and Beck Depression Inventory [11]. In the sensory evaluation, skin sensory threshold (von Frey hair filaments) and spatial tactile resolution [9] were present. Evaluations of motor function were performed with the help of the Manual Function Test [20], Fugl-Meyer Assessment (FMA) [19,20], Wolf Motor Function Test (WMFT) [19], Roeder Manipulative Aptitude Test [9]. Only one study used the Tardeu Scale [19] for spasticity assessment. Three studies evaluated changes in the cortex [9,10,12]. Apart from these, right-left discrimination [21], finger circumference measurement [7], patient's global impression of change scale [8], Global Rating of Change [21], CRPS severity score [9], patient goals [3], Satisfaction questionnaire [19] were available. The outcomes of the studies are detailed in Table 2.

Discussion

This systematic review included 18 articles applying the stages of the GMI in order and a total of 513 participants. The results of this systematic review, which examined different types of research in the literature, showed that GMI was used in many neurological and orthopedic conditions. In studies, application durations varied between 2 and 8 weeks and treatment protocols with different frequencies. In addition, the GMI reduced pain in 14 of the 15 studies whose outcome was pain.

While the studies on GMI are increasing, it is seen that there are different protocols in the studies. Moseley's [7] study has been used as a guide in many studies. Moseley et al. [1] have made significant contributions to the development of GMI. Moseley [7] applied each stage of the GMI for 2 weeks in the study. In 55.5% (n=10) of the studies included in this systematic review, the GMI application period was 6 weeks. In eight of these studies (including Moseley's study), each stage of the GMI was applied for 2 weeks [4,6,7,9-12,14]. Apart from this, the duration of application in the included studies ranged from 2 to 8 weeks.

Another difference in the studies on GMI is how many times a day they are applied. In Moseley's study [7], lateralization (<10 min) and motor imagery (<15 min) phases were applied three times per waking hour, and mirror therapy was applied as ten repetitions of 20 movements at each waking hour. In other words, each component was applied at every waking hour. In seven of the studies included in this review, each phase was performed at each waking hour [2,6,7,9,10,12,14]. Although beneficial effects of administration at each waking hour have been demonstrated, its feasibility is low [49]. Therefore, there are different forms of application. Lageux et al. [8] applied each step three times per day for 10 min. The result

of this study was significant improvements in pain, grip strength, and overall patient change. A study protocol planned for patients with distal radius fractures in 2018 was based on the work of Lageux et al. [49]. In another study included in this review, GMI was administered three times per day [11]. In other included studies, there are applications such as 20 min [17], 30 min [20], and 1 h [19] per day. In one study, the laterality phase was applied in short sessions for 1 h per day, the motor imagery phase was applied three times per day, and the mirror therapy was applied for 30 min per day [15]. In five studies, the mode of administration is unclear [3,4,16,21,48].

This systematic review has applied GMI in different conditions and for various purposes. It is known that GMI has effects on pain and movement [3]. It has been stated that mechanisms such as the development of cortical activation and reorganization are the basis of recovery in patients with CRPS1, phantom limb pain, and stroke. Therefore, it is thought that graded motor imagery will provide beneficial effects in these situations [50]. In a study, the effects of GMI and routine physiotherapy applied to patients with phantom limb pain after upper or lower extremity amputation were compared, and it was shown that GMI was more effective than routine physiotherapy [14]. In his study, Moseley [7] showed reductions in pain, edema, and reaction time, in which he compared the effects of routine medical treatment and GMI in individuals with chronic CRPS.

In another study, Moseley investigated the effect of changing the order of the 3 stages of GMI in patients with CRPS. As a result of this study, a significant difference was observed when three stages were applied consecutively (laterality, motor imagery and mirror therapy, respectively). This study has led to significant results. The sequential application of the three phases is more effective as it activates the premotor and, subsequently, the motor networks, resulting in a sequential exposure [6]. Strauss et al. [9] investigated the effects of 6 weeks of GMI therapy and 6 weeks of the waiting protocol in individuals with upper extremity chronic stage CRPS. GMI applied without waiting has been shown to cause improvements in functional parameters with a slight reduction in movement pain. In another study with a waiting protocol, 6 weeks of GMI treatment without waiting was shown to improve motion pain and hand laterality task performance [10]. In another study, it was thought that applying GMI and tDCS would increase the therapeutic effects. It did not appear to provide additional benefits when administered together [11].

In this systematic review, examining studies of lower methodological quality on GMI in CRPS also provides important contributions. We think that using different methods in these studies is important in examining the literature on GMI. For the patient with psychosocial problems, pain neuroscience training was added beforehand to make the GMI more solid and to provide an environment in which the patient would feel more confident. Improvements in functional and fear-related outcomes have been demonstrated [3]. In the case series of patients with upper extremity CRPS, the GMI was modified and applied. The motor imagery phase was applied by imagining the unaffected extremity while watching its reflection in the mirror. In addition, the third stage, mirror therapy, was applied in two different ways.

First, the mirror therapy was applied with the movement of the unaffected hand, and then, the fourth stage was added to be performed with the movement of both hands. There was a significant reduction in pain intensity and significant increases in grip strength but no significant changes in the functional capacity of the extremity. The results of this research are important in that mirror therapy is included in the motor imagery phase and that the mirror therapy phase is divided into two and applied in a total of four phases [8]. The case report by Walz et al. [12] evaluated the effects of GMI in a patient with CRPS by functional magnetic resonance imaging (fMRI) and compared the time effects with a healthy control participant. A reduction in pain has been demonstrated after GMI intervention. In addition, fMRI showed significant changes in discriminative pain processing areas during movement execution but not in affective pain processing areas. After the mental rotation phase, a change was observed in the processing area of the posterior parietal cortex. A comparison of results in this study with a healthy control group indicates that the effects are due to treatment. Dilek et al. [2] included GMI in the early phase of rehabilitation after distal radius fracture in their study. There were significant improvements in pain intensity, ROM, and upper extremity functional status in the group that included GMI in conventional rehabilitation. In addition, GMI has been tried in cases of osteoarthritis, elbow stiffness, shoulder pathologies, and cancer-related neuropathic pain [15-17,21,48]. In addition to traditional rehabilitation, GMI and progressive muscle relaxation exercises were applied in patients with osteoarthritis. It was reported that the GMI group was significantly better than the PMR group in terms of knee flexion range of motion and WOMAC scores [17]. In elbow stiffness, the GMI group caused significant improvements in function, ROM, pain, fear of movement-related pain, and muscle strength compared to the control group [21]. Significant improvements in the affective components of pain and range of motion have been demonstrated after GMI intervention in individuals with chronic shoulder pain due to tendinopathy or partial rotator cuff tear [15]. In frozen shoulder patients, the GMI was also better than conventional therapy alone in pain, functional disability, fear of movement, and ROM outcomes [48]. Casanova-García et al. [16] applied GMI as a non-invasive option for neuropathic pain in a group of children with cancer. Improvements were seen in pain perception and threshold, although the sample size was small.

GMI was applied in two studies after stroke, a neurological condition [19,20]. CRPS is also used to regulate GMI cortical disinhibition. Cortical disinhibition is a condition that causes motor problems in stroke. Therefore, GMI targeting cortical disinhibition was applied to improve motor function in stroke patients. GMI improved pain and function compared to normal rehabilitation [19]. As a result of another study investigating the effects of a home-based GMI program on upper extremity function after stroke, it was reported that applying for the GMI program with traditional rehabilitation would be beneficial [20].

This review has some limitations. First, the results were difficult to interpret due to the heterogeneous studies. GMI was

used alone or in addition to another treatment. This leads to contradictory results about whether the results can be attributed to GMI. In addition, the included studies used very different outcome measures, making it difficult to interpret the results.

Despite some limitations, this systematic review is important in that it summarizes the methods of the articles expanding in the field of GMI by examining and evaluating the risk of bias. In addition, although it is not known which of the stages of the GMI is effective, it is known that the order of the stages is necessary for cortical organization [2]. In this systematic review, it is important to understand GMI that the articles that are not applied sequentially are excluded.

Conclusion

Although some articles in this review have small sample sizes, the application protocols of GMI in neurological and orthopedic disorders have been examined in detail. Although heterogeneous, it has been observed that a 6-week application is common. Primarily effect of GMI on pain outcomes has been investigated in the literature. GMI is a safe and effective therapeutic tool that can be incorporated into a rehabilitation program to treat painful conditions. However, this literature summary suggests that more work is needed to uncover the role of GMI.

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