

Critical Review

The Effects of Graded Motor Imagery and Its Components on Chronic Pain: A Systematic Review and Meta-Analysis

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Abstract: Graded motor imagery (GMI) is becoming increasingly used in the treatment of chronic pain conditions. The objective of this systematic review was to synthesize all evidence concerning the effects of GMI and its constituent components on chronic pain. Systematic searches were conducted in 10 electronic databases. All randomized controlled trials (RCTs) of GMI, left/right judgment training, motor imagery, and mirror therapy used as a treatment for chronic pain were included. Methodological quality was assessed using the Cochrane risk of bias tool. Six RCTs met our inclusion criteria, and the methodological quality was generally low. No effect was seen for left/right judgment training, and conflicting results were found for motor imagery used as stand-alone techniques, but positive effects were observed for both mirror therapy and GMI. A meta-analysis of GMI versus usual physiotherapy care favored GMI in reducing pain (2 studies, $n = 63$; effect size, 1.06 [95% confidence interval, .41, 1.71]; heterogeneity, $I^2 = 15\%$). Our results suggest that GMI and mirror therapy alone may be effective, although this conclusion is based on limited evidence. Further rigorous studies are needed to investigate the effects of GMI and its components on a wider chronic pain population.

Perspective: This systematic review synthesizes the evidence for GMI and its constituent components on chronic pain. This review may assist clinicians in making evidence-based decisions on managing patients with chronic pain conditions.

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Key words: Graded motor imagery, GMI, mirror therapy, motor imagery, left/right judgments, chronic pain, systematic review.

Rapid advances in our understanding of the role of the brain in chronic pain have seen the development of treatments for chronic pain that directly target cortical reorganization.^{31,44} The first of these treatments was developed in response to remarkable

findings in amputees with phantom limb pain (PLP), which showed that pain was associated with reorganization of the primary sensory cortex contralateral to the amputated limb. The normal representation of the amputated hand had been invaded by the representation of the lip.¹² This cortical reorganization has also been demonstrated for chronic low back pain, in which representation of the painful side of the back was enlarged and shifted medially as compared with representation in healthy controls.¹¹ That primary sensory cortex receptive fields can be modified by tactile stimuli with a behavioral relevance (for example, eating or braille) is now well accepted.¹³ Flor et al aimed to exploit this plasticity in amputees with PLP by 2 weeks of sensory discrimination training, in which participants discriminated between stimuli of different frequencies and at different locations on their

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stump.^{10,14} Their randomized controlled trial (RCT) showed normalization of cortical organization and a clinically important reduction of pain. This process, from discovery of altered sensory cortex organization to targeted sensory discrimination training for clinical benefit, has been repeated in complex regional pain syndrome (CRPS).^{16,18,33,35}

As well as physiological evidence of disrupted somatotopic representation in chronic pain, there is also behavioral evidence of disrupted spatial representation—disrupted processing of stimuli delivered to healthy body parts held in the affected space,³² the abnormality of the perceived size of the painful body part,^{20,21,28,30} and poor voluntary movement and motor imagery performance.^{1,5,6,26,29,37-39} One treatment that was developed to directly target these cortical disruptions is graded motor imagery (GMI), a 3-stage treatment that aims to gradually engage cortical motor networks without triggering the protective response of pain. This treatment gets its theoretical framework from the principle established in the physical therapies, of graded increase in activity. This principle is adapted in GMI to cater to both the overly sensitive nociception system and the disrupted cortical mechanisms mentioned above. GMI was developed initially for an application to chronic limb pain or PLP but has been extended clinically to chronic back pain, where a component of GMI has been used for some time.⁴³

The first stage of the GMI program is left/right judgments of photographs that depict the affected area. For limb pain, this involves viewing an image of a limb and judging whether that image depicts a left or a right limb. Functional brain imaging studies in healthy subjects have shown that this task selectively activates the premotor cortex without activating primary motor areas.^{36,41,45} The second stage, motor imagery, requires imagined movement of the area. These imagined movements have been demonstrated to activate motor cortical areas similar to those activated in the actual execution of that movement.⁹ For the final stage, mirror therapy, patients place their affected limb inside a mirror box and watch movements of their nonaffected limb in the mirror, giving the illusion of a moving, but pain-free, affected limb. This task activates the motor cortex and also provides a strong visual input to the cortex that the movements are occurring normally and without impediment.¹⁹ While functional brain imaging studies have supported the proposed cortical activation for each stage of GMI in healthy subjects, no studies have investigated cortical activation of GMI stages in pain patients. These imaging studies nonetheless provide support for the possibility that similar sequential activation of cortical areas within each stage of the GMI program could occur in pain patients.

Both GMI and its components have been used in the clinical setting to treat chronic pain conditions such as CRPS, PLP, and back pain. However, an issue that remains to be addressed is whether the evidence supports or negates the use of GMI or its components in the treatment of a wider chronic pain population. A recent systematic review evaluating interventions for treating CRPS sup-

ported the use of GMI.⁷ However, a recent clinical audit of CRPS multimodal management including but not limited to GMI clearly showed no benefit of treatment.¹⁵ These conflicting findings, and that GMI has not, to our knowledge, been empirically evaluated in a wider chronic pain population, highlight the importance of systematic evaluation of the entire literature concerning GMI and its components. The aim of this review and meta-analysis was to synthesize all available literature regarding the efficacy of GMI programs, or any of the 3 constituent components, on chronic pain. The results of this systematic review will enable clinicians to make evidence-based decisions on the use of GMI with chronic pain patients.

Methods

Data Sources

For this review, several health-based databases were searched from their relative inception through January 2012. The electronic search was performed using the following databases: Medline (via OvidSP), Embase (via Ovid SP), Cumulative Index to Nursing and Allied Health Literature (CINAHL), Scopus, Academic Search Premier, Web of Science, Allied and Complementary Medicine, PubMed, the Cochrane Collaboration, and the Physiotherapy Evidence Database (PEDro). A sensitive search was completed using a combination of key words and relevant subject headings for GMI, its components, and chronic pain. The relevant subject headings were determined specific to each database. The complete Medline search strategy is provided in [Appendix A](#). Searches were limited to English language and humans only. To attempt to identify grey literature (specifically nonindexed published trials, conference abstracts, and book chapters), experts were contacted and asked to contribute any materials not identified by database search. The references of all relevant articles were also hand-searched for further articles. We did not search clinical trials registers for unpublished studies.

Study Selection

Four reviewers (K.J.B., A.T., M.J.C., and H.B.L.) were paired and each pair independently screened the titles and abstracts of half of the potential studies—thus, all papers were screened by 2 people. Results of the screening process were compared within pairs. In this process, studies were retained if they evaluated GMI or at least 1 component of GMI. Following initial screening, the full texts of potentially relevant studies were retrieved and reviewed independently by 2 reviewers (K.J.B. and A.T.). Studies were retained if they met the following criteria: human adult subjects (>18 years of age); clinically validated pain measure used; RCT; and subjects all had a chronic pain condition lasting longer than 3 months. No restrictions were placed on the comparison group used (ie, placebo, wait list control, or other active treatment). Any discrepancies were resolved through

discussion, or if necessary, through consultation with a third independent reviewer.

Outcome Measures

Pain intensity ratings were the primary outcome of interest for this review. This included self-reported measures such as the McGill Pain Questionnaire, a visual analog scale (VAS), a numerical rating scale (NRS), a neuropathic pain scale, or a categorical rating of pain (such as mild, moderate, severe). A rating of pain using 1 of these measures was required immediately preintervention and immediately postintervention. Follow-up pain ratings were a secondary outcome of interest for this review.

Risk of Bias Assessment and Data Extraction

Two reviewers (K.J.B. and A.T.) independently assessed the risk of bias of included studies using the Cochrane Collaboration's risk of bias tool. For the category of "other" sources of bias, the reviewers were particularly concerned with similarity of pain scores at baseline, as this is recommended by other quality assessment tools such as PEDro.⁸ In the "other" source of bias category we also included evaluation of sample sizes (ie, less than 50 participants per treatment arm considered a high risk of bias).²³ These items were added as we anticipated that studies identified were likely to be small and, as such, these factors were more likely to represent a significant source of bias.

For all eligible studies, data extraction was completed independently by 2 reviewers using a customized data extraction form. This data extraction form was piloted before use. Data extracted included participant characteristics such as age, gender, pain condition, and length of pain; the outcome measure used; the control and treatment intervention choices and their length (minutes per each session), frequency (sessions per day/week), and total duration (weeks of intervention); baseline and immediate postintervention pain scores; and follow-up pain scores if provided. Any disagreements regarding risk of bias or data extraction were resolved through discussion or, if necessary, through consultation with a third independent reviewer. If necessary, authors were contacted to provide further information.

Data Synthesis

We sought to pool data for pain relief from studies where adequate data were available. We planned a priori to pool data from studies comparing GMI programs with usual care or no treatment, and to perform separate meta-analyses for studies that investigated similar individual components of GMI.

Data were pooled using Review Manager 5 software⁴ using a random effects inverse-variance approach. A random effects model was chosen as it was anticipated and subsequently confirmed that there would be differences in the populations and interventions studied that would suggest that the effects might differ somewhat across studies. Using the postintervention means of each group

and the pooled postintervention standard deviations of pain scores, the standardized mean difference (Hedge's g) was calculated for each study to allow comparison between studies. Effect sizes were interpreted according to Cohen⁴⁰ ($\leq .2$ small, $.5$ moderate, $\geq .8$ large). We used the chi-square test to detect statistically significant heterogeneity and the I^2 statistic to estimate the amount of heterogeneity. When heterogeneity was high, we did not pool the outcomes. Further, we considered it inappropriate to pool data from studies that used full GMI programs with those that used individual components of GMI because it does not follow that the different types of interventions should be estimating the same effect size. We therefore planned separate meta-analyses for these types of studies considering both short-term (immediately postintervention or the closest measure presented to that point) and follow-up (>4 weeks postintervention) time points. We undertook a sensitivity analysis to investigate the influence of using a random effects model by reanalyzing the data using a fixed effects model.

In studies that evaluated a comprehensive GMI program, the effect sizes for the first component (ie, left/right judgments stage) were also calculated using postintervention scores when individual participant data were present. It was decided, a priori, that effect sizes would not be calculated for the second or third GMI treatment components (motor imagery and mirror therapy, respectively) because in these latter components, the methodological tenets of the RCT study design do not hold. Specifically, participants are not re-randomized following each component stage, so there are preintervention pain differences between groups in the latter stages. That the responses of the latter components were due to carryover effects or continuing improvement from the previous treatment could therefore not be ruled out. We did not establish any a priori sensitivity or subgroup analyses because we anticipated identifying inadequate data to support this process.

Results

Study Description

The initial literature search yielded 6,160 records following the removal of duplicates. Six thousand fifteen studies were excluded in the initial screening of title and abstracts. One hundred thirty-nine studies were then excluded following review of the full text. The most prevalent reason for exclusion was that articles did not include primary research data; primarily, these were reviews, conference abstracts, and book chapters, all presented in a narrative form. Other reasons for exclusion were studies that recruited sample populations without chronic pain or did not evaluate pain outcome measures, were not of RCT design, were non-English studies, and that recruited children. The screening and review process is shown in a PRISMA flow-diagram in Fig 1. Key data of the remaining 6 RCTs included are summarized in Table 1.

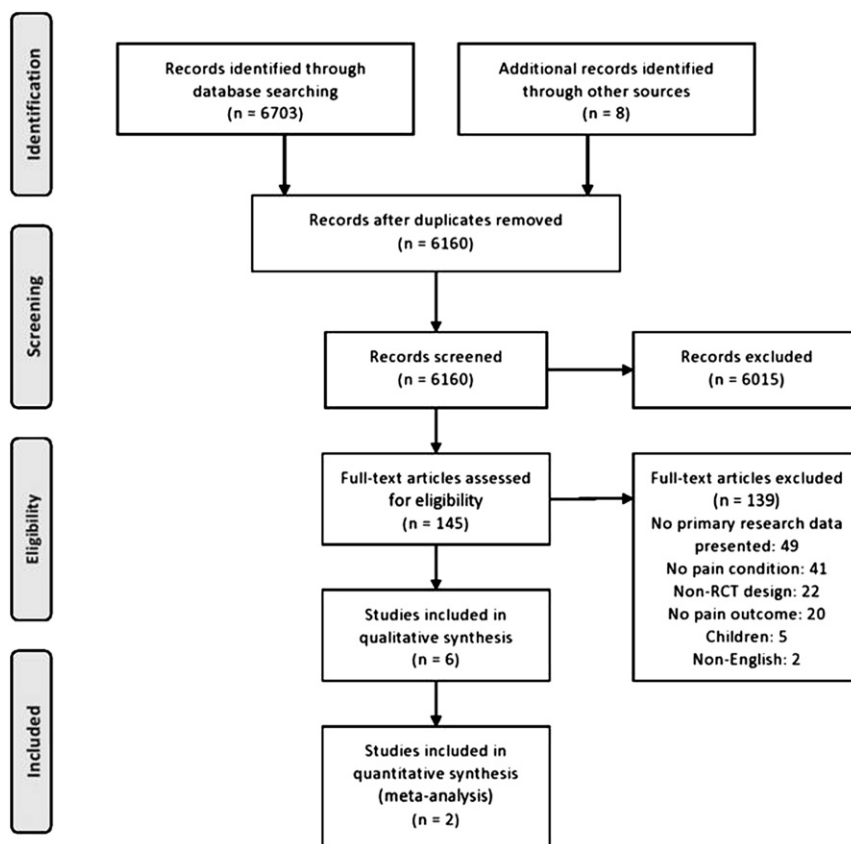


Figure 1. The PRISMA flow-diagram describing the screening and review process.

Characteristics of Included Studies

Three studies evaluated the effects of GMI on chronic pain.^{24,25,27} Two of these studies compared a 6-week program of GMI to usual physiotherapy care.^{24,25} The third study compared an ordered program of GMI to an unordered program of GMI.²⁷ Participants were instructed to spend 10 minutes of each waking hour on the intervention. All studies collected follow-up data: 1 study at 6 weeks postintervention,²⁵ 1 study at 12 weeks postintervention,²⁷ and 1 study at 6 months postintervention.²⁴ These studies used varying methods of collecting participant pain scores. The author of each study was contacted, and NRS data for each participant's pain level was provided. These NRS data were used in the analyses. Only 1 study²⁴ provided data on adherence to the treatment program. This study found that both GMI and usual care groups had adherence rates of 75%.

Three other studies evaluated individual components of GMI.^{2,3,22} No studies primarily evaluated left/right judgments; however, 2 studies^{24,25} evaluating GMI provided sufficient data to enable calculation of effect sizes for the 2 weeks of left/right judgment training. Two studies^{2,3} evaluated the effects of motor imagery. Three studies^{2,3,22} evaluated the effects of mirror therapy on chronic pain. The time spent on the intervention differed between studies. In 1 study, participants completed 5 1-hour sessions of mirror therapy a week.²² In the second study, participants spent 30 minutes per day doing either mirror therapy or motor

imagery, depending on their group allocation.² In the third study, participants spent 15 minutes per day doing either mirror therapy or motor imagery, depending on their group allocation.³ Follow-up data from these studies were collected at either 4 weeks^{2,3} or 6 months.²² All 3 studies used 100-mm VAS data to report participants' pain levels.

Characteristics of Included Populations

The participants in each study had experienced pain for greater than 3 months. The chronic pain conditions included CRPS,^{2,24,25,27} PLP,^{3,24} and pain following stroke.²² Studies including children were excluded from this review. The mean age in each study ranged from 32 to 57 years. Overall, there were more females (n = 90) than males (n = 81) in the included studies.

Risk of Bias of Included Studies

The results of the risk of bias assessment are shown in Table 2 (see also the Supplementary graph for a representation of risk of bias results). The study appraised to be at lowest risk of bias was that by Moseley,²⁴ which met every criterion except the blinding of therapists and participants and the "other" category, for its small sample size. None of the 6 included RCTs met the blinding of therapists and participants criterion. In therapy trials such as these, direct participant-therapist involvement means that blinding is not feasible; hence, all 6 RCTs had nonblinded therapists and participants. While

Table 1. Study Characteristics Data for Randomized Controlled Trials of Graded Motor Imagery or Its Components for Chronic Pain

STUDY	PARTICIPANTS	CONDITION	INTERVENTION	OUTCOME MEASURES
Studies evaluating the components of GMI				
Michielsen et al ²²	n = 40 Mean age = 57* Gender = 50% male	Chronic pain following stroke (mean time since stroke 3.9 years)	Exp: 6-week bilateral hand movement with mirror therapy program. Practiced 5x/week, 1 hour per session. Con: 6-week bilateral hand movements. Practiced 5x/week, 1 hour per session.	100-mm VAS† Follow-up: 6 months
Cacchio et al ²	n = 24 Median age = 62 (53 to 71)‡ Gender = 46% male	CRPS	Exp: 4-week mirror therapy program, 30 min daily. Con: 4-week covered mirror program, 30 min daily. Exp2: 4 weeks of motor imagery, 30 min daily.	100-mm VAS Follow-up: 4 weeks
Chan et al ³	n = 22 Mean age = 29 ± 8.8§ Gender = 100% male	PLP	Exp: 4-week mirror therapy program, 15 min daily. Con: 4-week covered mirror program, 15 min daily. Exp2: 4 weeks of motor imagery, 15 min daily.	100-mm VAS† Follow-up: 4 weeks
Studies evaluating GMI				
Moseley ²⁴ ¶	n = 50 Mean age = 41 ± 16§ Gender = 36% male	CRPS, PLP following amputation or brachial plexus avulsion	Exp: laterality retraining, motor imagery, mirror therapy. 2 weeks each component, 10 min for each waking hour. Con: usual physiotherapy/other treatment.	MPQ, NRS† Follow-up: 6 months
Moseley ²⁷	n = 20 Mean age = 32 ± 11§ Gender = 30% male	CRPS type 1	Exp: sequential GMI. 2 weeks each component, 10 min for each waking hour. Con: nonsequential GMI: MI, left/right, MI. 2 weeks each component, 10 min for each waking hour. Con2: nonsequential GMI: left/right, mirror, left/right. 2 weeks each component, 10 min for each waking hour.	NPS, NRS† Follow-up: 12 weeks
Moseley ²⁵ ¶	n = 13 Mean age = 57 ± 19§ Gender = 30% male	CRPS type 1	Exp: sequential GMI. 2 weeks each component, 10 to 15 min for each waking hour. Con: usual physiotherapy/other treatment.	NPS, NRS† Follow-up: 6 weeks

Abbreviations: Exp, experimental group; Exp2, secondary control group; Con, control group; Con2, secondary control group; n, number recruited (prior to drop-out or loss to follow-up); MPQ, McGill Pain Questionnaire; NPS, neuropathic pain scale; MI, motor imagery; left/right, left/right judgments; mirror, mirror therapy.

*Range or standard deviation not provided.

†Data used to calculate effect sizes.

‡Range.

§Standard deviation.

¶Due to the presence of individual participant postintervention data, the left/right judgments component of treatment was also examined.

blinding in these trials is not feasible, it is still an inherent source of bias that must be highlighted for every study. No study was free of additional bias, as all studies had sample sizes less than 50. Michielsen et al²² presented additional bias in that they failed to report any baseline similarities or differences between groups on pain scores. Two other studies also failed to report whether groups had similar baseline pain levels.^{2,3} The lack of this information has implications for the validity of the observed effect sizes as it is uncertain whether differences found between groups may have been influenced by baseline group differences. These same studies also failed to provide information regarding whether the person who determined participant eligibility was blinded to treatment allocation. Given the lack of participant/therapist blinding due to nature of the interventions within the

studies, all studies were considered to have some inherent bias.

Outcomes

Four authors were contacted to gain additional information required to calculate the effect size of their intervention.^{2,3,22,24,25,27} One author could not be contacted, so the effect size for this study could not be calculated.² The effect sizes for the remaining studies are presented in Table 3.

GMI Program

Three studies evaluated the effects of a 6-week GMI program on chronic pain, with all finding that GMI reduced pain when compared to usual physiotherapy care^{24,25} and unordered GMI.²⁷ The 2 studies comparing GMI to

Table 2. Risk of Bias Assessment of Included Randomized Controlled Trials

	RANDOM ALLOCATION	CONCEALED ALLOCATION	BLINDING OF PARTICIPANTS/ THERAPISTS	OUTCOME ASSESSORS	INCOMPLETE DATA	NO SELECTIVE OUTCOME REPORTING	FREE OF ADDITIONAL BIAS
Michielsen et al ²²	Y	Y	N	Y	Y	Y	N
Cacchio et al ²	U	U	N	N	U	Y	N
Chan et al ³	U	U	N	N	U	Y	N
Moseley ²⁴	Y	Y	N	Y	Y	Y	N
Moseley ²⁷	Y	U	N	Y	Y	Y	N
Moseley ²⁵	Y	U	N	Y	Y	N	N

Abbreviations: Y, yes, low risk of bias; N, no, high risk of bias; U, unclear, uncertain risk of bias.

usual physiotherapy care both found large effect sizes (1.70 [95% confidence interval (CI), .36, 3.04]²⁵ and .89 [95% CI, .31, 1.47]²⁴). In the study that compared a course of GMI to an unordered course of GMI,²⁷ moderate-to-large effects in favor of the ordered GMI were found (.73 [95% CI, -.41, 1.87] and .99 [95% CI, -.19, 2.17]).

The immediate postintervention results of the 2 studies comparing GMI with usual care were pooled.^{24,25} The results of the study evaluating GMI versus unordered GMI²⁷ were not included in the meta-analysis because the control group intervention had pronounced differences; this heterogeneity meant that pooling of these data was not appropriate. The heterogeneity of the pooled studies was low ($I^2 = 15\%$) and produced a large pooled effect size (1.06 [95% CI, .41, 1.71]; Fig 2). While the statistical heterogeneity of the studies was low, it must be noted that the chronic pain population in each study differed slightly; 1 included only CRPS participants²⁵

and the other a mix of CRPS, PLP, and pain after brachial plexus avulsion.²⁴ Sensitivity analysis using fixed effects, rather than random effects, meta-analysis had no substantive impact on our findings ($I^2 = 0\%$; effect size, .97 [95% CI, .52, 1.42]; test for overall effect, $P < .0001$).

Follow-up data also suggest an effect of GMI further reducing pain, with large effect sizes reported at 6 months for GMI when compared to usual physiotherapy care (1.59 [95% CI, .28, 2.90]²⁵ and 1.68 [95% CI, 1.02, 2.33]),²⁴ and also at 12 weeks for GMI when compared to an unordered GMI program (1.35 [95% CI, .09, 2.60] and 1.31 [95% CI, .06, 2.55]).²⁷ Pooling of these effect estimates was not considered appropriate as the follow-up in each study was conducted at a markedly different time point.

Left/Right Judgments

No studies were found that evaluated left/right judgments as the primary intervention, although 2 studies

Table 3. Effect Sizes (95% CI) for GMI and Its Components on Chronic Pain When Compared to Control Groups

STUDY	CONTROL	NUMBER OF PARTICIPANTS		POSTINTERVENTION PAIN (MEAN \pm SD)		EFFECT SIZE (95% CI)
		CONTROL	INTERVENTION	CONTROL	INTERVENTION	
Laterality judgment task						
Moseley ²⁴	Usual care	25	25	54 \pm 13	48 \pm 14	.44 (-.12, 1.00)
Moseley ²⁵	Usual care	6	7	61 \pm 10	57 \pm 15	.29 (-.81, 1.39)
MI						
Cacchio et al ²	Covered mirror therapy	8	8	—	—	—*
Chan et al ³	Covered mirror therapy	6	6	34 \pm 22	58 \pm 20	-1.05 (-2.30, .19)
Mirror therapy						
Michielsen et al ²²	Bilateral hand movements	19	17	9.2 \pm 14	8.8 \pm 10.8	.03 (-.62, .69)
Cacchio et al ²	Covered mirror therapy	8	8	—	—	—*
	MI	8	8	—	—	—*
Chan et al ³	Covered mirror therapy	6	6	34 \pm 22	17 \pm 21	.73 (-.46, 1.92)
	MI	6	6	58 \pm 20	17 \pm 21	1.85 (.40, 3.29)†
GMI						
Moseley ²⁴	Usual care	25	25	47 \pm 16	33 \pm 15	.89 (.31 to 1.47)†
Moseley ²⁷	MI, left/right, MI	6	7	40 \pm 10	33 \pm 8	.73 (-.41, 1.87)
	Left/right, mirror, left/right	6	7	42 \pm 9	33 \pm 8	.99 (-.19 to 2.17)
Moseley ²⁵	Usual care	6	7	58 \pm 12	38 \pm 10	1.70 (.36, 3.04)†

Abbreviations: MI, motor imagery; left/right, left/right judgments; mirror, mirror therapy.

NOTE. The effect sizes are standardized mean differences, calculated using Hedge's g (ie, the difference in postintervention pain scores between control and intervention groups divided by the pooled standard deviation of the 2 groups, each weighted for sample size). Effect sizes are grouped according to intervention type. Positive effect sizes indicate a lower pain score in the intervention group, favoring the intervention group. Negative effect sizes indicate a lower pain score in the control group, favoring the control group.

*Did not provide postintervention pain data for control or intervention groups.

† $P < .05$; For all Moseley studies, pain scores and effect estimates are for NRS results.

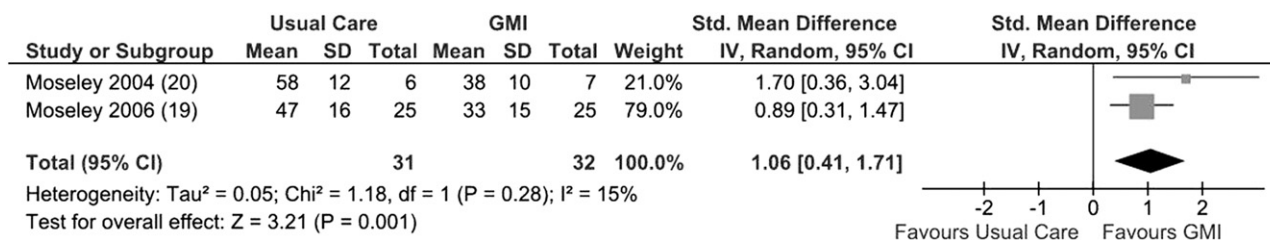


Figure 2. The pooled effect estimate for GMI versus usual care. Abbreviations: SD, standard deviation; CI, confidence interval.

investigated the effects of left/right judgments as part of a GMI program on chronic pain.^{24,25} Neither study found statistically significant effect estimates for left/right judgments reducing pain when compared to usual care. However, the effect estimates produced were positive, albeit small (.29 [95% CI, -.81, 1.39]²⁵ and .44 [95% CI, -.12, 1.00]²⁴). The heterogeneity of the pooled studies was low (I² = 0%) and produced a similarly small effect estimate (.41 [95% CI, -.09, .91]; Fig 3). Sensitivity analysis using fixed effects, rather than random effects, meta-analysis again had no substantive impact on our findings (I² = 0%; effect size, .41 [95% CI, -.09, .91]; test for overall effect, P = .11).

Motor Imagery

None of the included studies had a primary aim of evaluating the effects of motor imagery on chronic pain. However, in 2 studies, motor imagery was used as a secondary control group^{2,3} and was compared to covered mirror therapy (in which the participant is instructed to look at a mirror that is covered with a cloth so as to offer no reflection; controlling for attention). These studies found contrasting results. Chan et al³ found covered mirror therapy to be much more effective at reducing pain when compared to motor imagery, with a large effect size found (-1.05 [95% CI, -2.30, .19]). Interestingly, participants receiving motor imagery treatment had increased pain levels (compared to baseline pain). Similar findings were reported by Cacchio et al,² in which 6 out of 8 participants experienced increased pain levels following 4 weeks of motor imagery. However, Cacchio et al² found no difference between motor imagery and covered mirror therapy (5 of 8 participants had increased pain in covered mirror therapy group). All pain assessments were immediately postintervention; no short- or long-term follow-up data were available. Both studies had small sample sizes and had a high risk of bias.

Mirror Therapy

A total of 3 studies evaluated mirror therapy as a stand-alone treatment in chronic pain; in each study, mirror ther-

apy was the primary treatment evaluated.^{2,3,22} All 3 studies found positive effects of mirror therapy in reducing pain, despite using different control groups. The effect sizes ranged from trivial (.03 [95% CI, -.62, .69],²² bilateral hand movement control group) to moderate (.73 [95% CI, -.46, 1.92],³ covered mirror control group) to large (1.85 [95% CI, .40, 3.29],³ motor imagery control group). Notably, this final effect size was the only statistically significant finding in the mirror therapy analyses. This finding was further supported by Cacchio et al,² who reported 7 of 8 participants in the mirror therapy group experiencing decreased pain levels (compared to only 1 of 8 participants in the covered mirror group and only 2 of 8 participants in the motor imagery group having decreased pain levels).

The pooling of studies of mirror therapy demonstrated high levels of heterogeneity (I² = 63%) but no effect (P = .07). Visual inspection of the forest plot showed that the 1 study that utilized a different comparison condition³ (motor imagery as opposed to covered mirror therapy) was the most likely source of this variance. Post hoc sensitivity analysis removing this study from the analysis reduced this heterogeneity substantially (I² = 2%) and continued to demonstrate no effect (P = .51). Sensitivity analysis using fixed effects, rather than random effects, meta-analysis again had no substantive impact on our findings (I² = 63%; effect size, .42 [95% CI, -.011, .95]; test for overall effect, P = .12).

Only 1 study presented follow-up data,²² reporting a small, nonsignificant effect size (.34 [95% CI, -.29, .96]) of mirror therapy compared to bilateral hand movements in patients with pain following stroke at 6 months follow-up. All 3 studies were considered to have a high risk of bias.

Discussion

This is the first review to systematically evaluate the effect of GMI or its components on pain outcomes in people with chronic pain. The limited number of small RCTs available have found mixed results for the effects of GMI or its components on chronic pain. Of the six RCTs

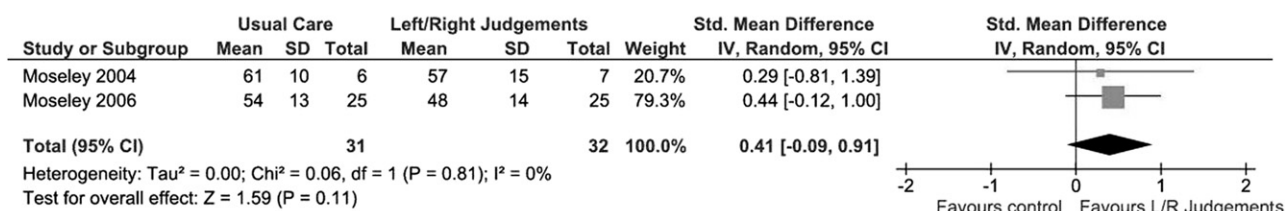


Figure 3. The pooled effect estimate for left/right judgments versus usual care. Abbreviation: L/R, left/right.

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identified, all contained some inherent bias. A key finding of this review was that the majority of studies evaluated the effect of GMI or its components in CRPS or PLP, so it is unclear how GMI might relate to other chronic pain conditions. We will first consider our findings with respect to individual components of GMI and then consider our findings with respect to full GMI programs.

Effect of Individual GMI Components on Pain

Left/Right Judgments

Left/right judgments as a sole treatment appear to have no effect on chronic pain.^{24,25} That all effect sizes were positive raises the possibility that even the pooled data were underpowered to detect an effect, but one might conclude that such a small effect is of little clinical consequence.

Because left/right judgments have never been used as a stand-alone treatment for chronic pain, there have been no studies that evaluate only left/right judgments as a treatment for chronic pain. Because only data from the first stage of a GMI program can currently be used to evaluate the effect of left/right judgments, there are no data available on the long-term effect of this treatment. While left/right judgments alone may not produce statistically significant effects, they are an integral part of the sequential GMI program that our results suggest may be effective. Nonetheless, the clinical importance for left/right judgments per se remains to be shown.

Motor Imagery

Motor imagery appears less effective at treating chronic pain than covered mirror therapy.^{2,3} Covered mirror therapy was utilized in these studies as an inactive control condition. That 2 studies found an increase in pain relative to baseline following motor imagery and 1 observed greater improvements in an inactive control group suggests that motor imagery might have the potential to increase pain intensity. These findings are consistent with those of a separate pre-/posttreatment trial not included in this review, in which motor imagery increased pain and swelling in those with chronic arm pain³⁴ and speaks against the use of motor imagery alone as a treatment for chronic pain.

Mirror Therapy

Mirror therapy is arguably the most studied component of GMI in terms of its effects on pain; however, much of the available literature concerns case studies, which were excluded from this review. The results of the included studies were consistently positive in favor of mirror therapy reducing pain^{2,3,22} although there is wide variance in the reported effect sizes.

This variance may reflect differences between studies in the patient group and the choice of control treatment. For example, Michielsen et al²² recruited chronic pain patients with very low baseline pain scores, which are atypical of chronic pain populations and provide minimal room for improvement, creating the possibility of a floor

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effect. In contrast, the baseline pain scores for participants in the Chan et al³ study were high, providing the opportunity for greater pain reductions and therefore a larger effect size. Both the Chan et al³ and Cacchio et al² studies suggest that mirror therapy is substantially more effective than motor imagery. However, motor imagery appeared to increase participants' pain levels, so the difference might reflect both the worsening in the control motor imagery group and the improvement in the mirror therapy group.

One important consideration when interpreting the effect of mirror therapy relative to a covered mirror control condition is the possible impact of variable placebo effects. That is, covering the mirror might imply to the patient that the mirror is the powerful component of treatment and, as such, the covered mirror condition might not be perceived as credible by the patient. As stated, blinding of therapists and participants in therapy interventions such as mirror therapy is nearly impossible. Through matching the frequency and duration of therapy sessions for both the covered and active mirror groups, all studies achieved structural equivalence, which is particularly important in situations where indistinguishable placebo controls are not possible.¹⁷ While covered mirror therapy as a control may not be ideal, it is a pragmatic control.

Effect of Full GMI Programs on Pain

Our results suggest that a GMI program likely has moderate effects when compared to unordered GMI²⁷ and large effects when compared to usual physiotherapy care.^{24,25} Both of the 2 identified studies evaluating GMI versus usual physiotherapy found a large effect size^{24,25} and clearly support the efficacy of GMI, at least as delivered within 1 clinical center.

Recently published clinical audit data appear to contradict the GMI findings of this review. Prospective audit data from 32 patients treated at 2 interdisciplinary centers showed no reduction in pain after a multimodal approach that included GMI¹⁵; indeed, some patients (30% in 1 center and 50% in the other) actually reported an increase in their pain intensity following treatment. The authors proposed that variations in GMI protocol from other studies and logistic constraints may have led to the poor result. Nonetheless, this study, while less robust than an RCT, highlights that independent replication of the results of Moseley²⁵ and Moseley²⁴ in controlled trials remains a research priority.

That GMI produced moderate effects when compared to an unordered program of GMI²⁷ is interesting. The order of GMI components seems to be important, which is consistent with its proposed mechanism.⁴² Moreover, that there is such an effect relative to an unordered treatment control group^{24,25} suggests against the possibility that the effects of GMI are largely due to a placebo response. That is, unordered GMI might be a more appropriate placebo control treatment in future studies because it would capture much of the novelty of GMI, but it appears to have little effect. That this finding arises from a single small trial indicates that it also requires independent replication.

Given the limited data available, it is difficult to draw firm conclusions, but these data and those relating to the ordering of GMI components suggest that the gradual and progressive nature of GMI may be clinically important. Motor imagery particularly demands attention. Not only was no significant benefit observed with motor imagery, but unlike with left/right judgments, there was no suggestion in the data of a trend toward pain relief with this intervention and some evidence to suggest a worsening of pain. This leads to the inevitable question of whether GMI might be more effective without a motor imagery stage. To our knowledge, no study has currently investigated this.

The majority of the evidence pertains to patients with CRPS, and we identified little evidence pertaining to the efficacy of GMI for other chronic pain conditions. Caution is advised when extrapolating these findings to the broader chronic pain population.

Limitations

Non-English studies were not included due to lack of translation resources, and we did not search clinical trials registers for unpublished studies. However, experts in the area of GMI/chronic pain were consulted regarding any missing relevant publications or active research groups and did not identify any relevant contributions, so we would suggest that the chance of missing a study would seem low. The number of RCTs included was small, and the majority had a high risk of bias. The limited number of studies published in this area also raises the possibility of publication bias.

In terms of the evidence of the effectiveness of full GMI programs for reducing chronic pain, perhaps the strongest

limitation is that all of the included trials were completed by 1 research group with which we ourselves are affiliated.^{24,25,27} To increase confidence in our findings, the need for further trials of GMI by independent research groups cannot be overstated. There was significant heterogeneity between the included study populations; the type and duration of chronic pain varied, and studies used a range of methods for sourcing and recruiting participants. Lastly, there were very few long-term follow-ups (ie, all follow-ups were 6 months or earlier), which suggests that the effectiveness of these treatments in the longer term remains unknown.

In conclusion, while the results of this systematic review suggest that the effectiveness of GMI and its components is encouraging in CRPS and PLP, no evidence exists for these treatments in a wider chronic pain population. It is critical to acknowledge that more work is required—the theoretical framework underlying these treatments suggests the value of additional trials in a wider chronic pain population. It is difficult to be certain of the findings because there are very few studies of mixed risk of bias available. Differing methodologies and samples within each study significantly limits the generalizability of these findings to people with CRPS or PLP, although there seems to be good reason to extend this line of investigation into different chronic pain populations.

Supplementary Material

Supplementary data related to this article can be found at <http://dx.doi.org/10.1016/j.jpain.2012.09.007>.

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Appendix A

Full Medline search strategy (23/3/11)

1. exp "Imagery (Psychotherapy)"/
2. graded motor imagery.mp.
3. exp Physical Therapy Modalities/
4. physiotherapy.mp.
5. physical therapy.mp.
6. device therapy.mp.
7. Occupational Therapy/
8. Rehabilitation/
9. Functional Laterality/
10. laterality.mp.
11. left right judg\$.mp.
12. exp Pattern Recognition, Visual/
13. visual pattern recognition.mp.
14. Discrimination (Psychology)"/
15. discrimination.mp.
16. Imagination/
17. imagined movement.mp.
18. mental imagery.mp.
19. mental movement.mp.
20. visual imagery.mp.
21. exp Kinesthesia/
22. kinaesthetic imagery.mp.
23. kinesthetic imagery.mp.
24. mirror therapy.mp.
25. Feedback, Sensory/
26. mirror visual feedback.mp.
27. user-computer interface/
28. Therapy, Computer-Assisted/
29. virtual reality therapy.mp.
30. user computer interface.mp.
31. mirror box therapy.mp.
32. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or
12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or
21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or
30 or 31
33. Pain/
34. 32 and 33
35. limit 34 to human