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Using graded motor imagery for complex regional pain syndrome in clinical practice: Failure to improve pain

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Abstract

Background: There is good evidence from studies conducted in a single-centre research setting for the efficacy of graded motor imagery (GMI) treatment, a complex physiotherapy intervention, to reduce pain in long-standing complex regional pain syndrome (CRPS). However, whether GMI is effective in clinical practice is not established.
Aim: To establish whether GMI is effective in clinical practice.
Methods: We undertook a prospective audit of GMI treatment at two UK centres with a special interest in the management of patients with CRPS. All patients received GMI, in conjunction with a range of other 'best practice' physical and psychological interventions.
Results: The patients' average pain intensities did not improve with treatment [centre 1: $n = 20$, pre-post numeric rating scale (NRS) difference 0.6 [confidence interval (CI) −0.3 to 1.5]; centre 2: $n = 12$, pre-post NRS difference 0.2 (CI: −0.9 to 1.2)]. Patients at centre 1 reported significant functional improvement. Improved performance on left/right judgement replicated in both centres seen in the clinical trials.
Conclusions: The failure of our real-world implementation of GMI suggests that better understanding of both the GMI methodology and its interaction with other treatment methods is required to ensure that GMI research results can be translated into clinical practice. Our results highlight challenges with the translation of complex interventions for chronic pain conditions into clinical practice.

1. Introduction

Complex regional pain syndrome (CRPS) is a painful and debilitating disorder that usually occurs after limb injury or peripheral nerve lesion, or sometimes spontaneously. The condition involves numerous peripheral and central changes and the cause is unknown (Janig and Baron, 2003). Recently, several lines of evidence have suggested that communication between the cortex (both motor and sensory) and the affected limb is distorted (Maihofner et al., 2003); and further, that pain can be reduced by training the brain to better recognize, imagine and move the affected limb (Moseley, 2004a; McCabe et al., 2008).

One approach to rehabilitation of people with chronic CRPS is graded motor imagery (GMI), which aims to activate cortical networks involved in sensory-motor processing in three progressive stages: a left-right limb judgement task, imagined movements of the affected limb and mirror therapy (Parsons, 2001; Roux

et al., 2001; McCabe et al., 2003; Roux et al., 2003; Moseley, 2004a; Ramachandran and Altschuler, 2009). The outcomes from three assessor-blinded randomized controlled trials (RCTs) suggest that a 6-week programme of GMI offers better symptomatic and functional gains than General Practitioner (GP)-managed care (Moseley, 2004a, 2005, 2006b). The first of these trials involved only patients with CRPS triggered by a wrist fracture (Moseley, 2004a) and reported a number needed to treat of 2 to gain a >50% reduction in the neuropathic pain scale.[1] A subsequent RCT, conducted in a similar group, suggested that the above noted order of component treatments was important for the reduction in pain and disability – patients who undertook the same three stages but in a different order did not respond (Moseley, 2005). A third positive RCT ($n = 51$) included patients with long-standing CRPS ($n = 37$) regardless of the triggering incident. A recent systematic review of physical therapies for CRPS-1 concluded that there is good evidence that GMI is effective in adults with CRPS-1 and that GMI should be employed as part of good clinical practice (Daly and Bialocerkowski, 2009). Although results of GMI obtained within the context of clinical trials are encouraging, fundamental differences exist in clinical practice. For example, practical considerations of everyday clinical management of people in pain, such as patient access, selection and participation in rehabilitation, the training and expertise of therapists, staffing schedules, non-specific aspects of treatment, and non-treatment-related issues such as conflicting medical advice or intervention, may all affect outcome. We therefore wished to clarify the benefit of GMI within a hospital setting. Here, we present data from two tertiary care centres that diagnose and treat patient with CRPS. We predicted that GMI would result in improvements in both pain and disability.

2. Methods

2.1 General method

The participating centres were the Walton Centre National Health Service (NHS) Foundation Trust Hospital (Centre 1 – CR1), which is a neurocare specialist hospital providing a pain management service, and the Royal National Hospital for Rheumatic Diseases (Centre 2 – CR2), a NHS Foundation Trust Hospital that offers a national CRPS inpatient treatment service. The centres' CRPS services are described in more detail in the web appendix. Our groups initiated prospective audits[2] of GMI treatment. At CR1 this audit started 2 months after GMI had been introduced into the centre's routine clinical practice. The results from patients who initiated treatment with GMI during the following 12 months were analysed, in keeping with this hospital's normal audit practice. The last of these patients completed treatment in November 2009. Similarly, the CR2 audit data collection commenced a short-time period after GMI was introduced into routine clinical care, and data were analysed from patients treated with GMI between March 2008 and June 2009. Ethical approval was not sought following advice from local Research Managers and in accordance with NHS National Research Ethics Service guidance (http://www.nres.npsa.nhs.uk/applications/apply/is-your-project-research/).

2.2 Referral to and inclusion into the GMI treatment pathway

At CR1 a consultant pain specialist saw new referrals of CRPS patients, and referred those with a confirmed diagnosis (Bruehl et al., 1999) and (patient-defined) insufficient pain relief from medical treatments (see section 'medical treatment') to the centre's team of physiotherapists and occupational therapists (PT/OT). Patients whose condition appeared to spontaneously resolve, who resided a large distance away from CR1 (making regular clinic attendances impractical), who were not interested to receive PT/OT treatment or who appeared to be in severe psychological distress were not referred; reasons for non-referral were recorded. All PT/OT staff were experienced in treating patients with chronic pain, and had been advised in the principles and approach to GMI by an experienced clinician researcher (GLM). A senior PT coordinated the GMI treatments by forwarding new referrals to the PT/OT with the soonest vacancy. The team aimed to limit the time from consultant referral to treatment to 4 weeks. The treating PT/OT then assessed each patient, and excluded patients if they were not suitable by the following criteria. Patients who had been referred for spinal cord stimulator (SCS) treatment, or who had an already implanted SCS, were excluded, because the interaction between the electrically

[1]The neuropathic pain scale uses 10 descriptors of pain quality and severity, each with a 0–10 scale of intensity to describe the qualities of neuropathic pain (Galer and Jensen, 1997).

[2]In the United Kingdom, clinical audit is a quality improvement process that seeks to enhance patient care and outcomes through systematic review of care against explicit criteria, and consequent implementation of change (Rawlins, 1999).

induced paraesthesias in the affected limb and GMI is unknown. Patients were also not offered treatment if they were or had been receiving components of GMI elsewhere, if surgery on the affected limb was planned or if they did not have computer access. These exclusions were in line with normal clinical practice at CR1. In general, the PT/OT who had assessed the patient also conducted the treatment.

At CR2 patients were selected to the GMI treatment from those newly referred to a 2-week CRPS inpatient rehabilitation programme. The selection of patients was dictated by the availability on the day of admission, of a single PT (JH), which in turn was determined by her other commitments on that day. Selected patients were considered eligible for GMI treatment if they had a confirmed clinical diagnosis of CRPS type I or II (Bruehl et al., 1999) and had not completed components of GMI elsewhere. Selected patients were only included if they passed a screening test in which their response to each stage of the programme was assessed. The screening was implemented because preliminary experience with GMI had indicated exacerbation of symptoms during and following GMI treatment in some patients. For those otherwise suitable patients who did not exhibit unacceptable symptom increase, GMI was commenced. The CR2 CRPS programme receives national referrals, and most patients live far from the hospital, so that regular attendance after discharge from the programme was not feasible. We therefore arranged an initial face-to-face training session during the patients' 2-week inpatient stay, and patients were then followed up by telephone consultation.

2.3 Treatment protocol

At each centre, patients were provided with verbal and written information about GMI treatment when they first met the treating therapist. The treatment protocol was based on published work well described elsewhere (Moseley, 2004a, 2006b). There were three stages: (1) left/right judgement of pictured hands or feet; (2) imagined arm or leg movements; and (3) mirror therapy. The protocol is described in detail in the supplementary methods. For pragmatic reasons there were variations between the two contributing centres and several deviations from the published GMI protocol (Supporting Information Table S0, web appendix).

2.4 Concomitant medical treatment

At CR1, prior to GMI referral, a consultant pain specialist reviewed all patients, and instigated pharmacological or interventional treatments. However, the consultant did not offer spinal cord stimulation (SCS) treatment. Although both GMI and SCS have been shown to be effective in reducing pain in CRPS (Kemler et al., 2000), since GMI is not invasive this method was considered more suitable to be commenced first. The consultant did not instigate new medical interventions while GMI treatment was ongoing, but if a patient requested medical review, medical management was altered in some cases. We consequently identified those patients with at least a 2-point or 30% numeric rating scale (NRS) pain reduction both following GMI, and after any of the GMI treatment stages, and reviewed their notes to document potential compounding effects from medical interventions.

Patients who commenced their treatment at the CR2 CRPS programme were initially reviewed by a consultant pain specialist and medications were optimized in some cases; however, no new treatments were initiated during the 2-week inpatient stage. After discharge, patients were advised that there were no restrictions to commencement of new medical treatments, although they were questioned on changes to their medication or therapy schedules during regular telephone consultations. Case notes of those patients with at least a 2-point or 30% NRS pain reduction at exit from the GMI programme were reviewed to examine potential compounding effects from concomitant interventions.

2.5 Assessments

CR1: At baseline, at the start of each treatment stage, and at the end of the programme, patients were asked to complete a Brief Pain Inventory (BPI) (Tan et al., 2004). Data were later entered into an anonymized audit database. CR2: Patients were asked to complete BPI at baseline and on exit from the programme; the latter was either posted or emailed back to the treating therapist, and later entered on an anonymized database.

2.6 Primary treatment endpoint

The primary measure of interest was the average post-treatment pain intensity compared with before treatment. This was recorded in the BPI on a 0–10 NRS where 0 = 'no pain' and 10 = 'pain as bad as you can imagine'. The number of patients with at least 2-point, 30% or 50% pain reduction was calculated: these thresholds have previously been defined as clinically important (Farrar et al., 2001; Dworkin et al., 2005; Dworkin et al., 2008). Early intervention has been

linked to better treatment outcome (Keefe et al., 2004), and we therefore investigated whether disease duration was correlated to the primary treatment outcome.

2.7 Secondary treatment endpoints

2.7.1 Worst pain

This parameter was recorded as part of the BPI data set. We thought it important to examine the GMI impact on worst pain, because worst pain may be a determinant of pain-related distress and avoidance behaviour (Hughes, 2006).

2.7.2 Response time and accuracy of left/right hand judgements

Response time (RT) is the average time required to correctly recognize a right or left limb image, and confirm the recognition by entering a computer key. This, and the overall accuracy of judgement, was automatically recorded by the Recognise© program used to deliver the first two stages of the GMI therapy (described in more detail in the web appendix). For the purpose of this audit, patients' response parameters at the beginning and end of the laterality stage were documented. At CR2 a mean of three tests was used to calculate recognition parameters. Previous studies have shown that, in people with CRPS of one hand, the time to make a left/right judgement is longer when the picture coincides with their affected hand than when it coincides with their unaffected hand, but the difference is reduced when pain decreases (Schwoebel et al., 2001a). In healthy controls, this judgement time depends on the complexity of the movement, which would be required to adopt the position shown in the image (Parsons, 2001), but in patients it also depends on the patient's prediction of pain that would be induced by performing the movement (Parsons, 2001). Therefore, we predicted that the left/right judgement times (= RTs) would relate to pain levels and that improvements would relate to decreased pain. Correlation analysis was used to test these predictions.

2.7.3 Function

The 'interference with general activity' subscale of the BPI (excluding the walking sub-question in patients affected by CRPS of the upper limb) was used to assess function (Tan et al., 2004). This subscale consists of seven items concerning different areas of life: for each, the respondent rates the degree of interference of pain with that aspect of life, from 0 = 'does not interfere' to 10 = 'completely interferes'. The score is the mean of the seven items. An average improvement of 1 point on the mean score of BPI interference has previously been determined as the smallest change which can be considered clinically important (Dworkin et al., 2008). We therefore recorded the number of patients with such change after treatment at both centres, and at CR1 in addition after each treatment stage. We also calculated whether changes in function and pain intensity were correlated.

2.8 Pain, interference and mood before enrolment

At both hospitals, a BPI and, in addition at CR1, the Hospital Anxiety and Depression Scale (HADS) (Zigmond and Snaith, 1983) are completed by all patients prior to their first appointment (independent of their enrolment to GMI). The HADS is a self-assessment scale that has been developed and found to be a reliable instrument for detecting extent of depression and anxiety in medical outpatients (Zigmond and Snaith, 1983). The BPI scores, and the HADS scores at CR1, were used to compare baseline characteristics of patients included into or excluded from the GMI pathway.

2.9 Statistical analysis

Demographics, pain, function and recognition data were tested for normal distribution using the Kolmogorov–Smirnoff test. Means or medians were used to describe summary statistics. To examine changes in the BPI data (pain intensity or pain interference), paired *t*-tests were used. Repeated measures analyses of variance (ANOVAs) were used where parametric distribution had been ensured, to investigate changes in recognition parameters (accuracy, time) in affected and unaffected limbs. Where the distribution was non-parametric, data were log transformed. Correlations between pain intensity, disease duration, recognition scores and function were calculated with Pearson's correlation coefficient for parametric data, and with Spearman's correlation coefficient for non-parametric data. Significance was set at 5%.

At CR1, Graphpad InStat and Prism (GraphPad Software, San Diego, CA, USA) was used to calculate summary statistics, and PASW Statistics (PASW Statistics 17.0; SPSS Inc., Chicago, IL, USA) for statistical analysis. At CR2, SPSS (PASW Statistics 18.0; SPSS Inc.) was used for statistical analysis.

3. Results

3.1 Patients

3.1.1 CR1

Between January 2008 and May 2009 [the months of the first consultant appointment of the first and last, subsequently (March 2008–June 2009) GMI-enrolled patients], the consultant saw 65 newly referred patients with CRPS (Figure 1). He referred 48 of these patients for GMI treatment. Reasons for non-referral are given in Table 1. Following initial assessment, the PT/OT excluded 22 of these patients from the GMI pathway (Table 1). Twenty-six patients commenced GMI treatment. Due to omissions by the treating clinicians, five of these did not provide a baseline BPI, and one patient provided a baseline, but no further BPI; these six patients were therefore not included into the analysis. To assess potential exclusion bias from PT/OT assessment, we compared demographic and baseline characteristics of excluded and included patients. Age, sex, pain intensity, pain interference with daily activities, and HADS depression and anxiety subscale scores did not differ between the two groups (not shown). Although we had planned to limit the consultant referral to treatment time to 4 weeks, the longest time had been 6 weeks (not shown).

3.1.2 CR2

Between February 2008 and May 2009 the CR2 admitted 69 patients for the CRPS rehabilitation programme (Figure 1). Twenty-seven patients were selected (selection had been determined by random scheduling factors: see Methods section), and 15 started the GMI intervention. Reasons for exclusion of selected patients are given in Table 1. Age, sex, pain intensity, and pain interference with daily activities did not differ between the 15 included and 12 excluded patients (not shown). Patients' demographics and CRPS details for both centres are shown in Table 2.

3.2 Sequence of treatments

A summary of treatment sequences for both centres is given in Table 3. Three patients were discharged following laterality training: at CR1, patient W19 had improved significantly; at CR2, patients B4 and B13

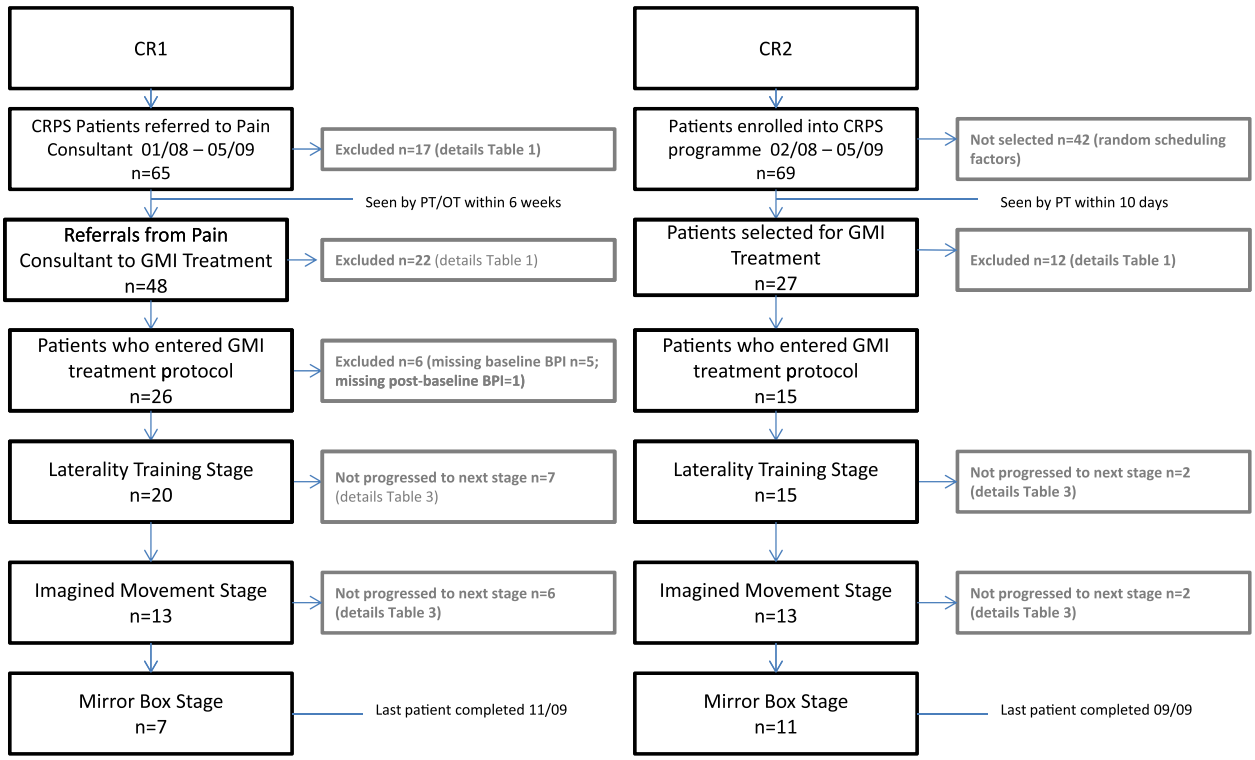

Figure 1 Audit flow diagram. Flow of patients between referral and last procedure. CR1/CR2, Centres 1/2; CRPS, complex regional pain syndrome; *n*, number of patients; GMI, graded motor imagery; PT/OT, physiotherapist/occupational therapist; BPI, Brief Pain Inventory.

Table 1 Patients who did not enter the GMI protocol.

Reasons for non-referral to PT/OT by pain consultant	CR1	CR2
Condition mild or resolving	8	NA
Patient from out of area, and/or unable/unwilling to attend for regular GMI visits	6	NA
Patient in severe psychological distress, pain management referral arranged	3	NA
Reasons for not entering GMI protocol after PT/OT assessment		
Declined treatment	2	0
Already receiving/ed treatment incompatible with GMI (GMI elements, spinal cord stimulation, surgery, PMP)	8	2
Symptoms resolved	1	1
Failed to attend a first appointment: no response to reminders	7	NA
Failed to attend after first appointment: no response to reminders	2	2
Lack of consistent computer access	2	0
Unacceptable symptom increase at assessment with GMI	NA	3
Interference with functional restoration programme	NA	3
Cognitively unable to work with laterality programme	0	1
Total PT/OT excluded	22	12

CR1/CR2, centres 1/2; GMI, graded motor imagery; NA, not applicable; PMP, pain management programme; PT/OT, physiotherapist and occupational therapist.

had sustained increases in pain. Two patients from the CR2 (patients B2 and B9) were discharged following the imagined movement stage as their pain had increased. Seven CR1 patients were referred to the pain management programme (PMP), which interrupted the treatment sequence. There had been little pain reduction with GMI upon referral to PMP (Supporting Information Table S1, web appendix). CR1 patient W9 was discharged after tactile discrimination training (TDT) due to failure to attend further appointments. Seven CR1 patients progressed through all three GMI stages in the previously published component order (without TDT). Eleven CR2 patients progressed through all three GMI stages (Table 3).

3.3 Treatment duration

At both centres the average duration of treatment exceeded the maximal 6 weeks stipulated by the published protocol, and at CR1 it also exceeded the 4 weeks per stage set by the CR1 protocol (Supporting Information Table S2, web appendix). Causes included that patients were unable to attend scheduled appointments (either in person or via the telephone), or had relatively poor compliance, such as temporary lapses in practicing, but which did not qualify for discharge. In some cases, treatment was prolonged as the therapist felt that progress may result from further practice.

3.4 Primary outcome

The primary outcome, the average pain intensity after treatment, was not decreased from baseline pain at either centre [CR1: $n = 20$, median[3] average pain before 7.0 (range 2–9), after 6.5 (range 1–10), mean of paired pre-post differences 0.6 [confidence interval (CI) –0.3 to 1.5][4]; CR2: $n = 12$[5], mean average pain before 5.7 [standard deviation (SD) 1.6], after 5.5 (SD 1.8), mean of paired pre-post differences 0.2 (CI –0.9 to 1.2)]. Overall, seven patients had at least a 2-point or 30% pain reduction (CR1: $n = 4$, W3 and W15: 7–5, W19: 8–1, W20: 3–1; CR2: $n = 3$, B8: 6–4, B10: 7–5, B11: 6–2). Raw data for both centres are available in the web appendix, Supporting Information Table S3. Pain reduction was not correlated to the patients' disease duration at either centre (Supporting Information Table S4).

At CR1 (where these data had been recorded) pain was reduced after the laterality stage, but not after either of the other stages (for details, see Supporting Information Table S5). Five patients had at least a

[3]Average and worst pain intensities at CR1 were not normally distributed.

[4]For four CR1 patients the final BPI questionnaire had erroneously not been completed on the day of completion (W1/W4 following imagined movements, W8/W14 after TDT training). Patients W1, W4 and W8 were approached over the phone 2 days later and their average and worst pain intensities were recorded at that time. These patients felt that there had been no change during the preceding 2 days and these values were therefore used in the overall analysis; the average and worst pain for patient W14 had been documented in the patient's clinical notes on the day of her final outpatient visit, and these values were used; final BPI interference data are not available for these four patients.

[5]At CR2 three patients (B5–B7) had not returned their BPI data set; however, response time data were available for B5 and B7.

Table 2 Subject characteristics at baseline.

Patient No.	Age	Sex	Onset of pain	Upper limb/lower limb	Duration (years)	Pain worst 0–10	Pain average 0–10
CR1							
W1	39	M	Fall	U	2	9	6
W2	47	F	Bunion removal	L	2	10	5
W3	27	F	No trigger	L	3	8	7
W4	54	F	Internal fixation of tibia and fibula	L	0.9	7	6
W5	24	M	Scaphoid fracture	U	1	10	9
W6	35	F	Knock	L	1.6	10	9
W7	33	F	No trigger	L	8	9	7
W8	57	M	Sprain	U	1.5	10	8
W9	48	F	Distal tibia fracture	L	1.5	9	7
W10	49	F	Subacromial decompression	U	5	7	6
W11	49	F	Distal radius fracture	U	1.5	8	7
W12	60	F	No trigger	U	0.3	3	2
W13	40	F	Hallux surgery	L	4	10	7
W14	57	F	Osteophyte removal	L	4.5	7	7
W15	55	F	Bunion surgery	L	0.5	5	7
W16	44	F	Distal radius fracture	U	0.5	9	7
W17	36	M	Hamate fracture	U	3	10	6
W18	33	M	Sprain	L	2	9	9
W19	19	F	Tibia stress fracture	L	1	8	8
W20	43	F	Distal radius fracture	U	5	8	3
Mean	42.5 (11.7)	M = 5 F = 15		U: 45%	1.8 (MD)	9 (MD)	7 (MD)
CR2							
B1	34	F	Scaphoid fracture	U	2.3	9	8
B2	41	F	Sprain	L	7	7	3
B3	42	F	Wrist fracture	U	1.6	5	4
B4	56	F	Head injury	U + L	9	8	5
B5	37	F	Venflon insertion	U	1.4	6	5
B6	47	F	Tibial plateau fracture	L	5	9	7
B7	53	F	Ulna fracture	U	0.6	5	3
B8	39	M	Shin haematoma	L	0.8	9	6
B9	40	F	Radial head fracture	U	2	8	7
B10	20	F	Sprain	L	5	7	6
B11	44	F	Fall	U	4	10	6
B12	23	F	Metatarsal fracture	L	2.5	6	5
B13	22	F	No trigger	L	1.5	8	6
B14	55	F	Shoulder arthroscopy	U	1.8	6	4
B15	34	F	Ankle fracture	L	0.8	9	8
Mean	39.1 (11.4)	M = 1 F = 14		U: 47%	2 (MD)	7.4 (1.6)	5.3 (1.6)

Values in brackets denote standard deviation. For non-parametric data the MD is given. CR1/CR2, centres 1/2; MD, median.

2-point or 30% pain reduction after laterality practice (patient W3: NRS 7–5, W6: NRS 9–6, W15: NRS 7–3, W19: NRS 8–1, W20: NRS 3–2), but there were no demographic or disease characteristics common to these five patients (not shown). One patient each reported significant improvement after imagined movement training (W20: NRS 2–1) and mirror box training (W12: NRS 3–2). Pain relief was not associated with concomitant medical interventions (not shown).

3.5 Secondary outcomes

3.5.1 Worst pain

At CR1, but not CR2, patients reported significantly reduced worst pain intensity after GMI treatment [CR1: $n = 20$, median worst pain before 9 (range 3–10), after 8 (range 0–10), mean of paired pre-post differences 1.2 (CI 0.2–2.2, $p < 0.02$); CR2: $n = 12$, mean 7.7 (SD 1.5) before versus 6.9 (SD 2.3) after treatment].

Table 3 Summary of treatment sequences.

Treatment sequence				CR1		CR2	
				n	Patient	*n*	Patient
Laterality	Discharged			1	W19	2	B4, B13
Laterality	PMP	Discharged		1	W3	0	NA
Laterality	Imagined	Discharged		0	NA	2	B2, B9
Laterality	Imagined	PMP	Discharged	3	W1, W4, W5	0	NA
Laterality	Imagined	Mirror	Discharged	7	W2, W6, W7, W10, W11, W12, W20	11	B1, B3, B5, B6, B7, B8, B10, B11, B12, B14, B15
Laterality	Imagined	TDT	PMP	3	W8, W13, W14	NA	NA
Laterality	TDT	Imagined	Discharged	4	W14, W15, W16, W17, W18	NA	NA
Laterality	TDT	Discharged		1	W9	NA	NA
Total				20		15	

n = number of patients. CR1/CR2, centres 1/2; NA, not applicable; W/B, enrolment number (CR1/CR2) as per Table 2; PMP, pain management programme; TDT, tactile discrimination training.

3.5.2 RT and accuracy of left/right hand judgements before and after laterality training

Average RT and accuracy [recognition accuracy (RA)] for the left/right judgement task are shown in Table 4. For two patients at CR1, the final values had not been recorded and four patients at CR2 had not returned their training files from the laterality tests. CR1: The RT results were not normally distributed and were therefore log transformed (see Methods). There was a limb-independent main effect of treatment on both RT and accuracy ($F = 47$, $p = 0.0005$ for RT; $F = 14.9$, $p = 0.0001$ for RA, ANOVA), and there was a significance between limbs effect for RA ($F = 4.16$, $p < 0.05$). The interaction between treatment and either RTs or RAs for both limbs was not significant. CR2: Treatment had no effect on either RT or RA (RT $F = 2.1$; RA $F = 1.2$). There was a significant between limbs effect on RT with increased RT for the affected limb ($F = 7.6$, $p = 0.02$). The patients' baseline pain intensities did not correlate to their RTs, nor did the change values of these two parameters correlate (Supporting Information Table S4).

3.5.3 Function

Patients at both centres reported moderate or high levels of pain interference at baseline [CR1[6]: $n = 15$, 7.3/10 (2.1); CR2: $n = 12$, 6.4/10 (2)] (Turk et al., 2008). At CR1, patients documented significant improvement with GMI treatment [interference post-treatment: 5.3/10 (3.01), mean of paired pre-post differences 2 (CI 0.8–3.1, $p = 0.003$)]. Inclusion of the four CR1 patients, for whom results at GMI exit were not available (see footnote[4]), by using for these patients the last available BPI interference score, i.e., that score *before* the start of the last completed GMI stage, still resulted in significant functional improvement [$n = 19$, 7.4/10 (1.9) before, 5.7/10 (2.8) after, mean of paired pre-post differences 1.7 (CI 0.7–2.6, $p < 0.003$)]. There was no significant improvement of BPI values at CR2 [interference post-treatment: 5.5 (2.4), $n = 12$]. At CR1, 8/15 patients (53%) reported an average > 1 point improvement overall (W2, W9, W11, W12, W13, W17, W19 and W20), 3/12 patients (25%) had at least a 1-point improvement at CR2 (B8, B10, B11). Further details are given in the web appendix, Supporting Information Table S6. Changes in pain interference were correlated with changes in the patient's average pain intensities ($p < 0.02$ at both centres, Supporting Information Table S4).

[6]For one CR1 patient (W3) the initial BPI interference score had erroneously not been recorded, and four patients had not completed final BPI interference questionnaires (see footnote[4]), so that changes to interference scores were assessed in 15 patients.

3.6 Pain increase with GMI treatment

At both centres, some patients experienced an increase in pain intensity with treatment, 6/20 patients (30%) at CR1 (W1: 6–7, W7: 7–9, W9: 7–9, W14: 7–8, W17: 6–7, W18: 9–10), and 6/12 patients (50%) at CR2 (B2: 3–4, B3: 4–5, B4: 5–6, B9: 6–7, B13: 6–7, B14: 4–6).

3.7 Patients who completed the original GMI sequence

At CR1, seven patients progressed through all three stages of GMI in the order delineated in the original

Table 4 Response times and accuracy pre and post laterality training (mean and SD).

	CR1 ($n = 18$)		CR2 ($n = 11$)	
Response times and accuracy	Pre	Post	Pre	Post
Response time affected (s)	3.9 (1.9)	2.3 (2.1)	2.7 (1.9)	1.9 (0.8)
Response time unaffected (s)	3.4 (1.6)	2.2 (1.4)	1.9 (1.3)	1.6 (0.7)
Response accuracy affected (%)	66.3 (22.9)	82.6 (14.2)	75 (12.6)	78 (16.7)
Response accuracy unaffected (%)	77.6 (15.5)	88.8 (12.4)	80.9 (17)	84.6 (20.8)

n = number of complete data sets. CR1/CR2, centres 1/2; SD, standard deviation.

GMI protocol (patients W2, W6, W7, W10, W11, W12 and W20). We expected that these patients might do better than other patients because they may have had less initial clinical distress and functional interference than those who entered the TDT/PMP pathways. Baseline pain intensities between both groups did not differ (not shown). HADS scores (these had been taken before the first contact with the consultant rather than during the audit) were available from three patients in the original sequence group and five in the other group; there were no significant differences between these groups (not shown). Baseline interference of pain with function (BPI interference score) was unexpectedly higher for the original sequence group ($n = 7$, 7.9, SD 0.8) compared with the others ($n = 12$, 5.7, SD 1.9, $p < 0.02$). This group of patients did not differ in their lack of reported pain reduction from the other patients [0.4 points (SD 1.3) average NRS improvement in this original sequence group versus 0.7 points (SD 2.3) for the other patients $n = 13$].

4. Discussion

We predicted that in our prospective clinical audits GMI treatment would be associated with a decrease in pain in people with CRPS. This prediction is consistent with systematic review evidence derived from three research trials (Daly and Bialocerkowski, 2009). Disappointingly, our patients' average pain intensities did not change, and only 3/32 patients reported that their pain had at least halved. The secondary outcome of pain interference with activities of daily life was significantly improved at one centre. Our results are in stark contrast to those of the research trials (Moseley, 2004a, 2005, 2006b). Clearly, more work is needed to untangle the reasons for this contrast and to determine whether and how the excellent research outcome can be replicated in public hospitals such as ours.

The important strengths of this study include the proximity to clinical practice: we have treated patients in a clinical context, with as close adherence to the research protocol as both service provision and patient preferences would allow. The clear similarity between the two centres' results enhances confidence in their validity. A further important strength is that the treatment teams were experienced, senior allied health professionals who work predominantly with patients suffering from chronic pain conditions in centres with an established interest in CRPS. It would seem unlikely that our poor results could reflect a lack of clinical experience.

There are some possible explanations for the poor effect observed here. Most obviously, our rehabilitation protocols varied somewhat from that used in the published clinical trials. This was in part a consequence of our intent to implement GMI in 'the real world': First, there was less contact with therapists, and likely a lower frequency of practice (although this was not measured), than there had been in the published RCTs (Moseley, 2004a, 2005, 2006b). In the RCTs, patients were seen daily and advised to practise three times every waking hour [actual practice was about nine times per day (Moseley, 2006a)]. In our audits, therapists only saw patients every 2–4 weeks, or contact was by phone and email every 2 weeks. In addition, many audit patients reported that complying with training every waking hour was not feasible for them. On the other hand, in the audits patients were seen over a longer time period. It would be interesting to investigate whether outcomes might improve with daily therapist contact and monitored hourly training, but this would require significant adjustments to the service structure and substantial financial implications. In addition, novel methods of encouragement, facilitating and monitoring hourly adherence in clinical practice would be needed. A second point of variation was the multimodal and multidisciplinary nature of treatment in these audits. Therapists were allowed to utilize basic physiotherapeutic methods in parallel to the GMI treatment, and at CR1 therapists also used TDT where treatment with GMI stages was

unsuccessful (Moseley et al., 2008). In addition, for CR1 patients who demonstrated prominent distress or depressive symptoms at any time, we offered a PMP. Our sample was underpowered to detect specific effects from using these multimodal methods (Supporting Information Table S7). We observed just as poor effects in those patients who completed the full GMI sequence in the published order, without TDT or early discharge. For this group of 14/32 CR1 and CR2 patients, the only multimodal variation was the addition of basic physiotherapeutic methods in some patients. Whether offering additional treatments, as we did, could indeed minimize the efficacy of GMI (e.g., by disrupting perceived credibility of GMI) is currently unknown.

Perhaps the difference between our results and those of the RCTs stems from as yet unidentified treatment effects captured in the RCTs. Reducing pain-related fear in CRPS may actually reduce pain (de Jong et al., 2005), and perhaps the clinicians in the RCTs better captured this particular effect, although this would seem unlikely as our clinicians were familiar with fear as a component of chronic pain-related disability. Given that patients and therapists in the GMI research studies were not blinded in at least two of the trials, a further potential treatment effect that would be present in the RCTs but not in our situation is the very fact that patients are participating in research studies, where they receive a great deal of attention, and where their treatment outcome is being regarded with the utmost priority. These issues are very difficult to control for in physical or psychological interventions and, although the GMI RCTs were considered to be of a high methodological quality (Daly and Bialocerkowski, 2009), the possibility that such unspecific effects contributed to the good results cannot be ruled out. All RCTs were conducted by a single research group, which is likely to increase the risk for bias from unspecific treatment effects. Finally, the poor outcomes of the current audit may also be due to baseline differences between the patient groups involved; although age and gender distribution, pain duration and baseline pain intensity were broadly similar across the research studies and the current work, other unknown baseline factors may have a role.

There were some important effects of GMI in the current study. Although average pain intensities did not change, we observed a statistically significant decrease in worst pain intensity at CR1. Patients with chronic pain often report exacerbations of pain ('flare-ups') as being distressing and debilitating (Hughes, 2006), thus this result may be clinically useful, with a potential for reducing pain anxiety and related avoidance of particular activities. Some patients documented over 50% pain relief, which is traditionally considered a meaningful pain reduction (Farrar et al., 2001). Importantly, at CR1 we observed a 2-point average reduction in pain-related interference with daily activities, an effect which is likely to be clinically meaningful (Dworkin et al., 2008), and which was statistically significant in our group. In keeping with previous findings, we saw that patients took longer to recognize images of limbs corresponding to their affected limb, and RTs were improved with training (Schwoebel et al., 2001b; Moseley, 2004b). We had theorized that improvements in both pain intensity and RT might be correlated, but following laterality training no such correlation was observed. The observation indicates that the effect of laterality training on response parameters is independent from its analgetic effects, although what was missing in our setting to achieve analgesia is unknown. Pain increased in some patients, suggesting that the GMI technology might be harmful in some cases as long as its methodology is not fully understood and its interaction mechanisms with other clinical treatment methods are not identified.

We took great care to implement best GMI practice within a multidisciplinary management approach, yet the patient's pain, on the whole, did not improve. The factors that have led to poor treatment results in the audits remain unknown. Further investigation with larger samples and analytical tools developed for complex interventions (Paterson et al., 2009; Bennett and Closs, 2010) are required to elucidate the elements of GMI treatment that determine success, and investigate possible interactions between GMI treatment and multidisciplinary management. We suggest that our experience is directly relevant to clinicians treating CRPS, and that more clinically based research will be required to translate the RCT-related results into real-world outcomes. As GMI is now recommended practice, it is important to understand that treatment failure is not necessarily a patient's or a therapist's fault, but may reflect that we do not yet fully understand what the active ingredients of this complex intervention are, and how it integrates and interacts with other therapeutic strategies.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Supporting Information Table S0. Deviations of the audit protocols from the published protocol.

Supporting Information Table S1. Treatment sequences and outcomes of CR1 patients who underwent multidisciplinary, cognitive behavioural therapy treatment. Lat = laterality training, PMP = pain management programme, Imag = imagined movement training; TDT = tactile discrimination training, NRS = numeric rating scale, W = patient enrolment number as per Table 2.

Supporting Information Table S2. Treatment duration for each stage in weeks.

Supporting Information Table S3. Average pain intensities before and after GMI treatment recorded on an 11-point numeric rating scale; + these patients followed the original treatment sequence (laterality – imagined – mirror), without tactile discrimination or pain management treatment, or early discharge; * score taken over the phone 2 days after completion of the pathway as BPI questionnaire was not completed on the day of the last outpatient visit; ** score copied from clinical notes, as BPI was not completed on that day; *** BPI not returned, therefore no post-GMI score available.

Supporting Information Table S4. Correlations between pain intensity, recognition parameters and laterality change values. AP = baseline average pain, RT = baseline recognition time (affected limb), RA= baseline recognition accuracy (affected limb), 'change %' relates to the percent change post versus pre-laterality (affected limb), 'difference change' refers to the absolute difference in values between unaffected and affected limbs. PRI = pain-related interference score as documented in the Brief Pain Inventory. All tests are with Pearson's, except disease duration versus AP (Spearman's).

Supporting Information Table S5. Average pain intensities before and after treatment with stages of GMI at Centre 1. n = number of complete data sets; NRS = brief pain inventory average pain intensity numerical rating score; numbers in brackets denote the standard deviation; MD = median; * $p < 0.03$ (paired t-test).

Supporting Information Table S6. Pre- and post-test BPI interference scores following treatment with GMI stages at Centre 1. n = number of completed scores available, the total number of patients in each stage is given in Table 3; * $p < 0.05$.

Supporting Information Table S7. Summary of NRS score changes following each treatment phase for each treating therapist at CR1. At the CR1, patients were treated by either of four therapists. One therapist (No. 1) provided advice on pacing and gentle passive movements in conjunction with GMI. The other three therapists utilized additional basic methods of physiotherapy which they judged to be appropriate; these included large amplitude limb movements, strengthening exercises, desensitization, progressive weight bearing and proprioceptive work. Individual therapists' results were recorded to explore outcome differences which may be related to these differences in adjunctive treatments. Positive change scores denote worsening of an outcome at the end of a treatment phase as compared with on entering that phase. NRS = average pain intensity numerical rating scale score; n = number of patients; changes were not significant. The treatment results did not significantly differ between therapists (ANOVA).