Graded motor imagery for pathologic pain

A randomized controlled trial

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Abstract—*Background:* Phantom limb and complex regional pain syndrome type 1 (CRPS1) are characterized by changes in cortical processing and organization, perceptual disturbances, and poor response to conventional treatments. Graded motor imagery is effective for a small subset of patients with CRPS1. *Objective:* To investigate whether graded motor imagery would reduce pain and disability for a more general CRPS1 population and for people with phantom limb pain. *Methods:* Fifty-one patients with phantom limb pain or CRPS1 were randomly allocated to motor imagery, consisting of 2 weeks each of limb laterality recognition, imagined movements, and mirror movements, or to physical therapy and ongoing medical care. *Results:* There was a main statistical effect of treatment group, but not diagnostic group, on pain and function. The mean (95% CI) decrease in pain between pre- and post-treatment (100 mm visual analogue scale) was 23.4 mm (16.2 to 30.4 mm) for the motor imagery group and 10.5 mm (1.9 to 19.2 mm) for the control group. Improvement in function was similar and gains were maintained at 6-month follow-up. *Conclusion:* Motor imagery reduced pain and disability in these patients with complex regional pain syndrome type I or phantom limb pain, but the mechanism, or mechanisms, of the effect are not clear.

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Complex regional pain syndrome type 1 (CRPS) is considered a pathologic pain syndrome because the pain does not seem to reflect the underlying tissue pathology.[1] However, the pathophysiology of CRPS1 is not well understood: peripheral and central changes have been observed and altered central representation of perceptual, motor, and autonomic systems have been implicated.[1] If such cortical mechanisms underpin the disease, it would seem reasonable to target them in treatment—"train the brain." One such approach, graded motor imagery, reduced pain and disability in a relatively homogenous sample of patients with CRPS1 after wrist fracture, all of whom had motor dysfunction as part of their condition.[2,3] Although those clinical trials appear encouraging, about 50% of subjects were excluded, so whether the approach is effective for a wider CRPS1 population is not known. The first aim of the current study was to resolve this issue.

Graded motor imagery might also be effective in those with phantom limb pain, which is also considered a pathologic pain syndrome[4] and is also thought to be dominated by altered cortical mechanisms. The similarities between phantom limb pain and CRPS1, which have been noted elsewhere,[4-8] suggest that graded motor imagery may be effective for phantom limb pain as well as CRPS1. The second aim of the current study was to determine if this is the case.

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Methods. *Design.* A single blind randomized trial with 6-month follow-up was conducted (figure 1).

Eligible participants were drawn from three patient groups: patients with phantom limb pain after amputation of one limb, phantom limb pain (within deafferented zone, according to results of previous quantitative sensory testing, not verified here) after

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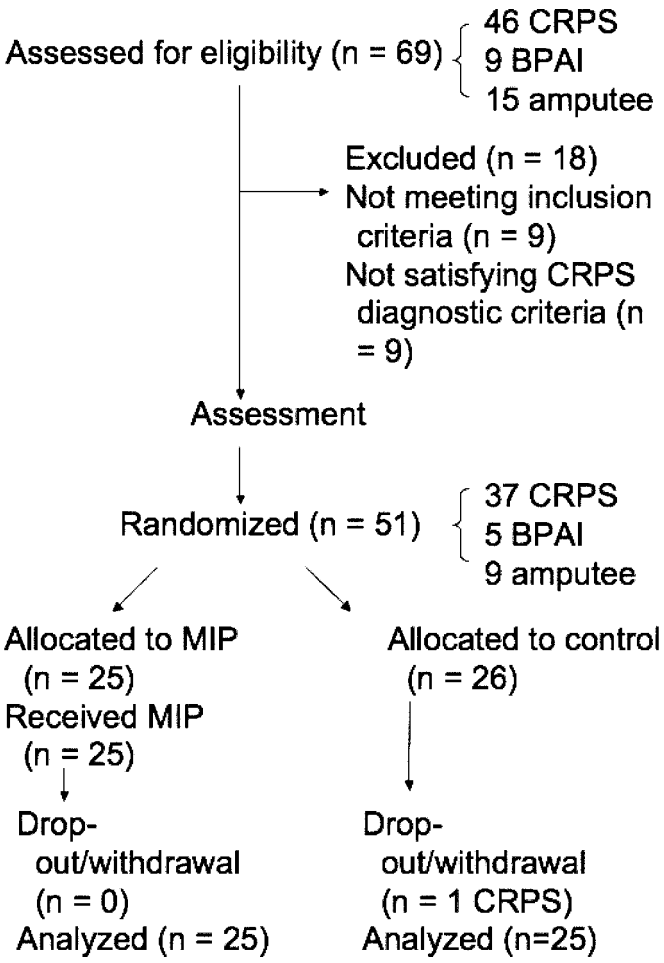

Figure 1. Trial plan. CRPS = complex regional pain syndrome; BPAI = brachial plexus avulsion injury; NPS = neuropathic pain scale; MPQ = McGill Pain questionnaire; MIP = motor imagery program.

brachial plexus avulsion injury of one arm, and patients with complex regional pain syndrome, type 1 (CRPS1). Sixty-nine eligible patients (37 F) were contacted via hospital physiotherapy department, neurology, and pain clinic waiting lists. Patients were excluded if they had been diagnosed with any other neurologic, psychopathology, or motor disorder or dyslexia; had difficulty performing a rapid naming task; were visually impaired; had any other limb pathology or pain, or lived outside the immediate metropolitan area of the host department. Nine patients were excluded according to those criteria. Nine patients with CRPS1 who did not fulfill recognized diagnostic criteria[9] were also excluded, which left 51 patients (32 F). This sample size would detect an effect size of 0.80 (equivalent to a reduction in pain of 29 mm on a 100 mm visual analogue scale), with a probability of ≥80%, assuming $\alpha = 0.05$. There was no adjustment for multiple end points. Written informed consent was obtained and all procedures were approved by the institutional research ethics committee and conformed to the Declaration of Helsinki.

Protocol. Patients were randomized via random number generation by an independent investigator, to a graded motor imagery program (experimental group) or to standard medical and physiotherapy care (control group), using a random numbers table. Prior to randomization, an independent investigator obtained several assessments.

Assessments. Questionnaires. Patient-specific task-related numerical rating scale (NRS): patients were asked to select five activities or tasks that they regularly performed prior to their injury but now found difficult to perform because of pain. Using an 11-point numerical rating scale (NRS) anchored with "0, completely unable to perform" and "10, able to perform normally," they were asked "How well can you perform that task now?" This measure is based on similar measures validated in patients with neck pain[10] and knee pain.[11] It is sensitive to change in people with upper limb CRPS1 after wrist fracture.[3] In the current study, this measure estimated functional level and was a primary outcome variable. It is herein referred to as function NRS.

The McGill Pain Questionnaire (MPQ)[12]: patients completed the MPQ with regard to current pain, but the visual analogue scale (VAS) for pain intensity referred to the average level of pain over the previous 2 days. This measure of pain was a primary outcome variable and is herein referred to as pain VAS.

Successful response to treatment was estimated in three different ways: 1) pain VAS decreased by ≥50%, 2) function NRS increased ≥4 points, and 3) pain VAS decreased by ≥50% and function NRS increased ≥4 points. These criteria are consistent with recommendations made in the pain literature[13] and with special regard to patients with CRPS1.[14] The number needed treat (NNT) in order to get a successful response from the motor imagery program that would not be imparted by the control treatment was calculated for each criterion, for post program and for 6 month follow-up.

Clinical assessment. Diagnostic criteria for CRPS1[9] were assessed before and after the treatment period by independent investigators blinded to treatment group. The following clinical findings were also recorded for phantom limb pain patients: symptoms and signs of hyperalgesia and allodynia of the stump for amputees; symptoms of swelling and temperature changes in the phantom limb; and symptoms of motor disorders of the phantom limb (patients were asked whether the phantom felt as though it was cramping, cramped, or stuck in a particular position).

Assessments were undertaken and entered into a datasheet by an independent investigator who was blind to group and assessment occasion. All assessments were undertaken at prerandomization and at 6 weeks (completion of the treatment period). Pain VAS and function NRS were also undertaken at 6 months follow-up.

Active treatment—motor imagery program. The first 2 weeks were the limb laterality recognition phase. Forty photographs of a right hand, matched to gender, and in various positions and alignments, were digitally mirrored to create a bank of 80 images. Twenty-four photographs of a right foot, matched to gender, and in various positions and alignments, were digitally mirrored to create a bank of 48 images. Thus, there were four banks of images: upper and lower limbs, male and female. Every image in the appropriate bank of images was classified by each subject into one of four categories, according to the level of pain that would be provoked if the subject were to adopt the position shown in the image. In a previous sample of patients with CRPS1, this categorization explained 45% of the variance in RT to recognize the laterality of the pictured limb [$F(1,54) = 46.6$; adjusted $R^2 = 0.45$; $p < 0.001$] and was used here as an estimate of task difficulty.[15] This estimate of task difficulty was used to increase the training load for the limb laterality recognition phase of the motor imagery program according to table 1. An in-house software program and

Table 1 *Protocol for training load during each phase of the motor imagery program*

Phase	Day 1–4	Day 5–8	Day 8–14
Limb laterality recognition	Categories 1–2 (80 trials)	Categories 1–3 (120 trials)	Categories 2–4 (120 trials)
Imagined movements	Category 1 (20 trials)	Categories 1–2 (40 trials)	Categories 1–3 (60 trials)
Mirror movements	Category 1 (20 trials)	Categories 1–2 (40 trials)	Categories 1–2 (80 trials)

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Table 2 *Mean (95% CI) for number needed to treat (NNT) to achieve a preset change in pain or function or both*

	NNT to get a 50% decrease in pain	NNT to get a 4-point increase in function	NNT for both criteria
Response at post-program	3 (2–6)	4 (2–11)	4 (2–17)
Response at 6-mo. follow-up	2 (1–5)	2 (1–5)	3 (2–4)

Pain = average pain intensity over previous 2 days; Function = ability to perform five patient-selected activities.

laptop computer were used to randomly present images from the appropriate image bank. Patients responded by pushing the left or right pressure-sensitive button, according to whether the picture showed a left or right limb. The software program recorded time of trial and response time (RT) and accuracy of each response. Correct responses were analyzed using the ratio between mean RT for the affected limb and mean RT for the unaffected limb.

The next 2 weeks were the imagined movements phase. Images of both limbs were randomly presented and subjects were advised to imagine twice adopting the posture shown with a smooth and pain-free movement. Subjects were advised not to imagine watching themselves perform the movement but to imagine actually performing the movement. Training load for imagined movements was increased according to table 1.

The next 2 weeks was the mirror movements phase, which used a purpose-built mirror box (single aperture 300 mm × 300 mm; cardboard with Perspex mirror on one external surface) (NOIgroup.com, Adelaide, Australia). Subjects were advised to twice adopt the posture shown with both hands, using smooth and pain-free movements. Training load for mirror movements was increased according to table 1. This clinical regimen is similar to one that has been discussed in detail previously.[2,3]

Throughout the motor imagery program, there were weekly consultations with the physiotherapist who supervised performance, monitored progress, and answered any questions raised by the patient. Because this study aimed to compare this treatment to standard care, patients were advised not to participate in other treatments during the study period. The software program recorded participation at home overtly during the first two phases and overtly by a training diary during the last phase.

Control treatment—medical/physiotherapy management. Subjects allocated to the control group undertook a 6-week physiotherapy treatment program and maintained usual medical care. Physiotherapists were instructed not to include treatments that were similar to those used in the experimental group, or that used mirrors or imagined movements. Physiotherapists were advised to include at least one treatment per week and a home program that involved a training load comparable to that in the motor imagery program (i.e., hourly training). Participation was recorded via a training diary.

Subjects in both groups were advised not to commence new treatments or medications, nor to reduce other treatments or medications, unless they were instructed by their treating clinician to do so. There were no instructions about management during the follow-up period, although at 6 months, subjects were asked what treatments they had received during that period.

Statistical analysis. All statistics were performed using SPSS 11.0.0 (SPSS, Chicago, IL). To compare mean response between treatment groups at 6 weeks or at 6 months, an analysis of covariance model (ANCOVA) was constructed, with covariates pretreatment score and diagnosis. The primary outcome was pain VAS or function NRS at 6 weeks or 6-month follow-up (ordinal data). Diagnosis was clinical group, dummy-coded as 0 for phantom limb pain (BPAI or amputee patients) and 1 for CRPS1.

Because one proposed mechanism of effect of graded motor imagery involves normalization of cortical organization, which in turn is related to duration of symptoms,[16] a secondary analysis investigated the relationship between the duration of symptoms and the response to treatment, via two linear regressions between duration and change in pain VAS at post treatment and at follow-up.

For all analyses, significance was set at $\alpha = 0.05$.

Results. *Subjects.* All data were collected over 32 months. One female subject in the control group withdrew from the study because she sustained an unrelated injury. There were no other dropouts or withdrawals. Subject characteristics according to group are shown in table E-1 on the *Neurology* Web site at www.neurology.org. There was no difference between the groups by gender ($p = 0.56$ by χ^2 test), age, duration of disease, VAS pain score, or NRS score ($p > 0.50$ for all, by two-sample t-tests).

Pain and function at post-program. Statistical results are described here, NNTs in table 2 and results for specific diagnoses are presented in figure 2. The regressions showed effects for pain VAS [ANCOVA $F(3,46) = 6.77$, $p = 0.001$] and for function NRS [ANCOVA $F(3,46) = 8.95$, $p < 0.001$]. For pain intensity at post-program, there was a

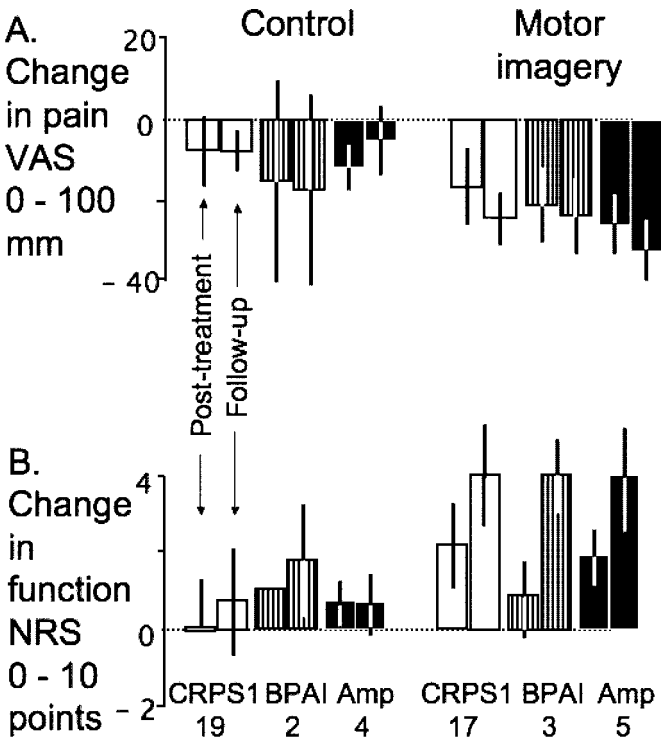

Figure 2. Mean (columns) and SD (error bars) change in (A) average pain level over the past 2 days, measured with a 100 mm visual analogue scale (VAS), and (B) average score for each of five patient-selected tasks, on an 11-point numerical rating scale (NRS), for patients in the control group and the motor imagery group. Data are shown for patients with complex regional pain syndrome (CRPS1, open columns), phantom limb pain after brachial plexus avulsion injury (BPAI, vertical stripes) or amputation (Amp, filled columns), and reflect the change between pre- and post-treatment (left column of each pair) and between pretreatment and 6-month follow-up (right column of each pair). No change is marked by the horizontal dashed line at zero.

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main effect of treatment group (unstandardized B = −1.298, $p = 0.002$). That is, the mean (95% CI) decrease in average pain over the last 2 days, as measured on the 100 mm VAS, was 23.4 mm (16.2 to 30.4 mm) for the MIP group and 10.5 mm (1.9 to 19.2 mm) for the control group.

For function NRS, there was a main effect of treatment group (unstandardized B = 1.532, $p = 0.001$). That is, the mean (95% CI) increase in average score for each patient-specific task, measured using a 0 to 10 NRS, was 2.2 points (1.3–3.0 points) for the MIP group and 0.6 points (0.2–1.0 points) for the control group.

Pain and function at 6-month follow-up. The regressions showed effects for pain VAS [ANCOVA $F(3,46) = 8.701$, $p < 0.001$] and for function NRS [ANCOVA $F(3,46) = 7.327$, $p = 0.001$]. For pain VAS at follow-up, there was a main effect of treatment group (unstandardized B = −2.07, $p = 0.001$) (figure 2B). That is, the mean (95% CI) decrease in pain VAS between pretreatment and follow-up was 32.1 mm (23.8–40.3 mm) for the MIP group and 11.6 mm (2.4–20.7 mm) for the control group. The effect size at 6-month follow-up, but not at post-program, was consistent with the estimated effect size.

For function NRS, there was a main effect of treatment group (unstandardized B = 2.18, $p = 0.001$) (figure 2B). That is, the mean (95% CI) increase in task-specific NRS VAS between pretreatment and follow-up was 3.7 points (2.7–4.6 points) for the MIP group and 1.5 points (1–2.2 points) for the control group.

Outcome and response to treatment at follow-up: Pain VAS ≤ 3, function NRS ≥ 5, or both. NNT was calculated for pain VAS ≤ 3, function NRS ≥ 5, and for both, and are shown, with 95% CI, in table 2. The duration of symptoms did not relate to change in pain VAS at post-treatment ($p = 0.224$), nor to change in pain VAS at follow-up ($p = 0.071$).

Participation in home program. Participation with the home program was 75% throughout the treatment period. There was no difference between treatment groups in any phase ($p > 0.211$ for all).

Treatment during follow-up period. Only 11 patients in the treated group, but all patients in the control group, reported that they sought treatment for their pain during the follow-up period ($p < 0.001$ by χ^2 test). For the treated group, this constituted between 3 and 11 (median = 6) physiotherapy treatments, including motor imagery, tactile discrimination training, and functional exposure (9 patients), a multidisciplinary pain management program (1 patient), and between 2 and 4 general practitioner visits (3 patients). For the control group, treatments sought were physiotherapy treatment (motor imagery, desensitization, tactile discrimination, functional exposure) for 14 patients (median number of treatments = 12, range 1 to 18), multidisciplinary pain management program for 7 patients, general practitioner visits for 10 patients (median number of visits = 6, range 2 to 1), spinal cord stimulator for 1 patient.

Discussion. Graded motor imagery reduced pain and disability in a wider CRPS1 population and in those with phantom limb pain after amputation or brachial plexus avulsion injury. The following results support this position: 1) a significant effect of treatment group on both primary outcome measures (pain and function), such that pain decreased and function increased for the motor imagery group, relative to the control group; 2) NNTs for response to treatment at 6 months of about 3.

Graded motor imagery has been shown to reduce pain and disability in a relatively homogenous group of patients with chronic CRPS1[2,3] and mirror therapy alone has shown efficacy for those with acute CRPS1.[17] The current data corroborate those studies, although the mean magnitude of pain reduction was about 50% less in the current work than it was in the earlier studies using graded motor imagery. A likely contributor to the reduced mean effect is the relative heterogeneity of the current sample. First, phantom limb pain and CRPS1, although both categorized here and elsewhere[4,6,18] as pathologic pain disorders, and although changes in cortical organization and some clinical findings are common to both, are fundamentally different: whereas CRPS usually occurs after minor injury and involves no demonstrable nerve injury, phantom limb pain occurs after major trauma and undeniable nerve injury. Further to that, phantom pain after brachial plexus avulsion injury may involve different mechanisms to phantom pain after amputation. That is, the current design may conceal stronger effects in one group than another and that the effect occurred regardless of diagnostic group does not imply that the same mechanisms underpin that effect in each group. This study was underpowered to systematically evaluate different response profiles between the diagnostic groups.

Even the current sample of patients with CRPS1 was more heterogeneous than previous samples: previous studies limited inclusion to CRPS1 initiated by wrist fracture, limited disease duration to more than 6 months, and excluded those without motor signs and symptoms. The final issue is particularly important because diagnosis of CRPS1 is based on presenting signs and symptoms, not on mechanisms, and many contributing mechanisms exist.[1] Perhaps subclasses of CRPS1 exist and some are better suited to motor imagery training than others.

The control group here was intended to reflect current practice, which is dominated by drug and physical therapies, implemented according to a cognitive-behavioral model.[19-21] That the medical component of the control group treatment constituted ongoing medical care and therefore was not new probably reduced its effect because most treatment is effective to some extent when it is first started.[22] Importantly, however, the commencement of conventional physiotherapy in addition to ongoing medical care had no discernible effect on pain or function. This seems discouraging, although the current study limited the duration and frequency of physical therapy, which suggests that firm conclusions are probably premature.

Although the patients used here were broadly similar to those involved in other studies[19,23-27] including therapeutic trials,[17] it is not possible to di-

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rectly compare the current results to established data from CRPS1 or phantom limb pain because robust trials of other therapies are lacking. This lack of data probably explains why tricyclic antidepressants, antiepileptics, and opioids remain the mainstay of treatment, particularly with phantom limb pain—these drugs have demonstrated some efficacy in other types of neuropathic pain.[28] That said, the demonstrated effect of such drugs in those groups is not better than the current results. For example, a systematic review of drug therapies for peripheral neuropathic pain reported NNTs of between 2.2 and 5.0 for tricyclics, antiepileptics, and opioids, and between 2.9 and 7.7 for selective serotonin reuptake inhibitors.[29] The present study found NNTs of about 3 for similar outcome parameters.

How progressive motor imagery reduced pain and disability is not known. This study was based on the idea of applying established principles of rehabilitation to training the brain. That limb laterality recognition activates premotor cortices but not primary motor cortex, whereas imagined movements activate both,[30] and that the order of hand laterality recognition, imagined movements, and mirror movements seems to be important in the effect motor imagery,[3] seem consistent with this possibility. Perhaps practicing laterality recognition is to limb movement[31] as practicing knee movement is to walking. This seems sensible in principle, but the neural mechanisms by which it might occur are unknown.

An alternative possible explanation for the effect of motor imagery is that it promotes sustained attention to the affected limb. That probably does not explain the effect in patients with CRPS1 post-wrist fracture, because undertaking the treatment components in a different order does not work,[3] but it may explain the effect observed here. Such an explanation would seem consistent with several findings in the literature. For example, patients with CRPS1[15,32] and with phantom limb pain[33] take longer to recognize the laterality of a pictured limb if it corresponds to their own affected limb. Acute experimental pain,[34] and the expectation of acute experimental pain,[35] delays recognition of the laterality of the opposite limb, which implies an information processing bias toward the body part in pain, yet patients with CRPS1 and phantom limb pain show the opposite effect, which implies an opposite information processing bias—away from the body part in pain. If so, progressive motor imagery may simply serve to reverse that tendency. That speculation remains to be verified, but other signs and symptoms in CRPS1 and after amputation or brachial plexus avulsion are consistent with some sort of neglect: symptoms of foreignness and neglect[25,36]; the perception that their affected limb is bigger than it is,[37] which also occurs after anesthesia.[38]

The question, then, is why would a neglect-like disorder cause pain? Pain is not characteristic of the usual parietal neglect syndromes. The cortical model of pathologic pain[4] is relevant here because it proposes that the changes in cortical proprioceptive representation, themselves related to the neglect-like phenomena outlined above, underpin the pain because they evoke an incongruence between motor commands and sensory feedback. It is established that 1) cortical proprioceptive representation is altered in CRPS1 and in phantom limb pain,[39-41] 2) that the extent of reorganization relates to the duration of symptoms[42] (it is notable that although the current study did not find a relationship between duration of symptoms and response to motor imagery, it was probably underpowered [$p = 0.071$] to do so), and 3) that resolution of symptoms is associated with normalization of cortical reorganization.[43]

There is a large amount of literature on sensory-motor incongruence, typified by the reafference principle, whereby an exact copy of the command for movement is subtracted from sensory input about the actual movement to yield an error signal.[44] However, only recently has sensory-motor incongruence been empirically investigated with regard to pain[45,46] and there are insufficient data to conclude whether motor imagery might remove sensory-motor incongruence. If it does, this mechanism may also mediate the effect of sensory discrimination training in phantom limb pain[24] and of sensory-motor retuning in CRPS1, for which there is preliminary evidence.[43] Alternatively, perhaps the neglect-like phenomena and the pain are not causally related but both result from, for example, altered central representations of somatic input in the thalamus or cortex,[1] in which case motor imagery might primarily serve to normalize these central representations. Thus, although evidence is emerging that treatments such as graded motor imagery and sensory discrimination training can be effective for pathologic pain, further studies are needed to replicate the current data and elucidate the mechanisms involved.

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