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Graded motor imagery is effective for long-standing complex regional pain syndrome: a randomised controlled trial

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Abstract

Complex regional pain syndrome type 1 (CRPS1) involves cortical abnormalities similar to those observed in phantom pain and after stroke. In those groups, treatment is aimed at activation of cortical networks that subserve the affected limb, for example mirror therapy. However, mirror therapy is not effective for chronic CRPS1, possibly because movement of the limb evokes intolerable pain. It was hypothesised that preceding mirror therapy with activation of cortical networks without limb movement would reduce pain and swelling in patients with chronic CRPS1. Thirteen chronic CRPS1 patients were randomly allocated to a motor imagery program (MIP) or to ongoing management. The MIP consisted of two weeks each of a hand laterality recognition task, imagined hand movements and mirror therapy. After 12 weeks, the control group was crossed-over to MIP. There was a main effect of treatment group ($F(1, 11) = 57$, $P < 0.01$) and an effect size of ~25 points on the Neuropathic pain scale. The number needed to treat for a 50% reduction in NPS score was ~2. The effect of treatment was replicated in the crossed-over control subjects. The results uphold the hypothesis that a MIP initially not involving limb movement is effective for CRPS1 and support the involvement of cortical abnormalities in the development of this disorder. Although the mechanisms of effect of the MIP are not clear, possible explanations are sequential activation of cortical pre-motor and motor networks, or sustained and focussed attention on the affected limb, or both.

Keywords: Reflex sympathetic dystrophy; Motor cortex; Physical therapy; Imagined movements

1. Introduction

Complex regional pain syndrome type 1 (CRPS1), also known as reflex sympathetic dystrophy (RSD), is a painful disabling disorder that occurs after stroke or limb trauma or occasionally without known incident and is difficult to both diagnose (van de Vusse et al. 2003) and treat (Forouzanfar et al., 2002). Numerous peripheral and central changes have been demonstrated in CRPS1 (see Janig and Baron, 2003 for review). Peripheral abnormalities include altered activity in sympathetic neurons and increased spontaneous pain with elevated sympathetic activity (Baron et al., 2002), enhanced neurogenic inflammatory response (Weber et al., 2001), skin hypoxia (Koban et al., 2003), reduced sympathetic vasoconstriction (Birklein et al., 1998) and reduction of proprioceptive reflexes (Schouten et al., 2003). Central abnormalities include disruption of sensory cortical processing (Juottonen et al., 2002; Rommel et al., 1999), disinhibition of the motor cortex (Schwenkreis et al., 2003) and disrupted body schema (Schwoebel et al., 2001). Taken together, the available data have led to proposals that CRPS1 is a disease of the central nervous system (Janig and Baron, 2002, 2003; Rommel et al., 2001).

Shrinkage of the cortical representation of the affected limb in the primary somatosensory cortex (Juottonen et al., 2002) and disrupted body schema (Schwoebel et al., 2001) have both been observed in CRPS1 patients, and also in amputees with phantom limb pain and post-stroke patients (Coslett, 1998; Flor et al., 1995; Grusser et al., 2001). In fact, common cortical mechanisms are thought to underlie post-stroke and post-trauma CRPS1 (Janig and Baron, 2003; Riedl et al., 2001). It is notable then that in both amputees with phantom pain and in stroke patients, a primary goal is to activate cortical areas that subserve the affected limb, which leads to symptomatic and functional improvements (Flor et al., 2001; Liepert et al., 2000) and which in turn

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correlate with cortical reorganisation (Flor et al., 2001; Kopp et al., 1999).

One strategy that aims to activate cortical networks and has been successful for acute CRPS1 (McCabe et al., 2003), phantom pain (Ramachandran et al. 1995) and stroke rehabilitation (Altschuler et al., 1999) is mirror therapy. Mirror therapy involves movement of the limb inside a mirror-box such that visual feedback of the affected hand is replaced with that of the (reflected) unaffected hand. Mirror therapy is thought to reconcile motor output and sensory feedback (Ramachandran et al. 1995) and activate pre-motor cortices (Seitz et al., 1998), which have intimate connections with visual processing areas (di Pellegrino et al., 1992). Although McCabe et al. (2003) reported reduced pain in acute CRPS1 patients during mirror therapy, there was no effect for chronic CRPS1 patients. Anecdotally, mirror therapy in chronic CRPS1 is associated with intolerable pain, and McCabe's group propose that trophic changes or enhanced efficacy of nociceptive mechanisms or cortical changes may prevent the analgesic response.

The current study in patients with chronic CRPS1 evaluated the efficacy of activating cortical networks including pre-motor cortex in a manner that does not initially involve movement of the affected limb. Thus treatment involved motor imagery, which activates similar cortical networks to executed movements but does not involve movement (Decety et al., 1994; Jeannerod, 1995; Montoya et al., 1998; Stephan et al., 1995; Yue and Cole, 1992). It was hypothesised that in patients with chronic CRPS1, a standardised motor imagery program (MIP) is more effective than ongoing conventional management.

2. Methods

2.1. Design

Single blind randomised controlled trial with control group cross-over and repeated measures comparison of means.

2.2. Subjects

A convenience sample of 26 patients (16F) with upper limb CRPS1 was accessed through the hospital physiotherapy department. Those who had sustained a non-complicated wrist fracture more than 6 months previous and as a result had developed CRPS1, which was diagnosed according to Bruehl et al. (1999), were included. Subjects were excluded if they had previously obtained benefit from an intravenous regional sympathetic blockade, if they had any other upper limb pathology or pain, had any neurological or motor disorder including a diagnosis of dyslexia or difficulty performing a rapid naming task, were visually impaired or had a diagnosed psychopathology, had any invasive analgesic strategy (e.g. spinal cord stimulator), or who lived beyond the immediate metropolitan area of the host department. Thirteen patients (8F) were excluded according to these criteria. Written informed consent was obtained from the remaining 13 subjects (Table 1). All procedures were approved by the institutional research ethics committee and conformed to the Declaration of Helsinki.

2.3. Protocol

Patients were randomised by an independent investigator to the 6-week MIP treatment group or to ongoing medical management (control) using a random number table. Prior to randomisation, patients completed the Neuropathic pain scale (NPS) with responses regarding the 2 previous days. The properties of the NPS are maintained when used in other populations such as CRPS1 (Galer and Jensen, 1997). To provide an estimate of swelling, the circumference of the base of the second and third digits was measured using a hand measuring tape (Beiersdorf-Jobst, Hamburg, Germany) and an average measure was calculated. Assessments were repeated 2, 4, 6 and 12 weeks after the commencement of treatment of the 6-week program. All assessments were made by a separate investigator who was blind to experimental group and measurement occasion. If the hypothesis was supported at 12 weeks, the control group were crossed-over to MIP. Fig. 1 presents the experimental plan.

2.4. Motor imagery program

The MIP consisted of three stages, each of 2 weeks duration: (i) recognition of hand laterality, (ii) imagined hand movements and (iii) mirror therapy. Patients were requested not to participate in other treatments during the 12-week study period and not to change their medication type or dosage unless instructed to do so by their medical practitioner, who was informed about the study.

2.4.1. Recognition of hand laterality

Recognising a pictured hand to be a left or a right hand activates brain areas involved in higher-order aspects of motor output, the so-called pre-motor cortices (Parsons, 2001), whereas explicitly imagined movements also activate primary motor cortex (Decety, 1996). We aimed to initially avoid activation of primary motor cortex for two reasons. First, because modern theories of pain in populations similar to CRPS1 (e.g. phantom limb pain) emphasise an intimate relationship between pain and motor output such that movement execution commands may be sufficient to cause pain (Melzack, 1990). Second, extensive pilot work revealed no response or increased symptoms in response to imagined movements alone (Moseley, 2004).

To perform the hand laterality recognition task, 42 photographs of a right hand in a variety of postures were digitally mirrored to construct otherwise identical pictures of a left hand, to form a bank of 84 pictures. Using MATLAB 6.5 (release 13, Mathworks, Natic, MA, USA), 56 pictures

Table 1
Subject characteristics

Aff. limb	Prescribed medications (other medications)	Previous/current treatments	Age (years)	Sex	Dom.	Duration CRPS1 (weeks)	NPS intensity item	NPS total
l	Morphine, tramadol (paracetamol, codeine)	CBT, PT, hydro, OT	33	F	r	87	7	50
l	Tramadol, paracetamol, codeine	PT, hydro, massage	45	F	l	58	6	49
l	Gabapentin^ (paracetamol, codeine)	CBT, OT, hydro	36	F	r	49	7	49
r	Morphine, tramadol (act 3, aspirin)	PT, OT	20	M	r	34	6	40
l	Morphine, gabapentin (cannabis, paracetamol)	Counselling, PT, OT	28	M	l	33	7	49
r	Morphine, amytryptiline	PT	21	F	r	51	7	41
r	Gabapentin^, zoloft (cannabis)	PT, chiropractic, osteopathic	62	F	r	42	6	44
Experimental group mean (SD)			*35 (15)*			*51 (18)*	*6.6 (0.5)*	*46 (4.2)*
l	Morphine, amytryptiline	PT, chiropractic*, acupuncture*	37	F	r	60	6	46
l	Gabapentin, (paracetamol, codeine)	OT	39	M	r	75	5	46
l	Gabapentin, (paracetamol, codeine, cerebrex, aspirin)	CBT, hydro, massage	50	F	r	43	8	46
r	Morphine, gabapentin*, zoloft	PT	56	F	l	45	6	45
r	Morphine, amytryptiline, tramadol (paracetamol)	Counselling*, PT, OT, hydro	29	F	r	80	6	44
l	tramadol (paracetamol, neurofen)	CBT, PT	18	M	r	88	5	35
Control group mean (SD)			*38 (14)*			*65 (19)*	*6.0 (1.1)*	*44 (4.3)*

The mean (SD) for each group is shown in italics. PT, physical therapy; OT, occupational therapy; hydro, hydrotherapy; CBT, cognitive-behavioural pain management program; ^, reduced during MIP; *, commenced during study period. Affected limb (Aff. limb), dominant hand (Dom.) and the intensity item and total score on the NPS (Galer and Jensen, 1997)

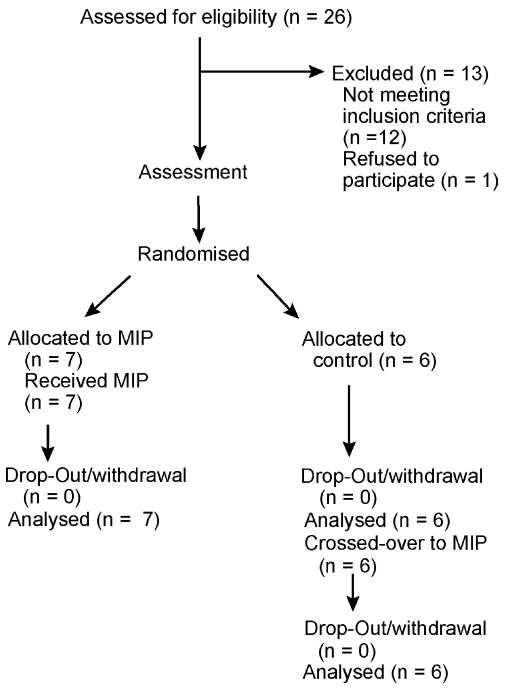

Fig. 1. Experimental plan.

were randomly selected and presented in random order on a monitor in front of the sitting subject. Patients responded by pressing a button as quickly as possible according to whether they recognised the pictured hand to be a left hand or a right hand. Emphasis was placed on speed and accuracy of performance. Patients borrowed a notebook computer and were advised to perform the task three times (~10 min) each waking hour. The time of each trial and speed and accuracy of performance was recorded by the software program for future analysis. Response time to recognise the affected hand was used as an outcome measure at subsequent assessments.

2.4.2. Imagined hand movements

To perform imagined hand movements, 28 pictures of the affected hand were randomly selected from the picture bank and presented in random order. Patients were advised to deliberately imagine moving their own hand to adopt the posture shown in the picture, three times. Patients were advised to perform the task three times every waking hour (~15 min). The emphasis was on accuracy not speed. The time at which each trial was performed was recorded by the software program for future analysis.

2.4.3. Mirror movements

The cardboard mirror box consisted of two compartments (300 × 300 × 300 mm) separated by a vertical mirror. Paper copies of 20 pictures of the unaffected hand that involved less complex movements were selected from the picture bank. The patient was advised to, each waking hour, slowly and smoothly adopt the posture shown in each picture with both hands, 10 times. The affected hand was concealed and emphasis was on watching the reflection of their unaffected hand in the mirror. They were advised to stop if they had an increase in pain either during or directly after mirror therapy, and to keep a diary of training.

2.5. Control group—ongoing management

During the 12-week treatment and follow-up period, the control group were required to visit the department for assessments. No limitations were placed on treatment. However, patients were requested not to change medication type or dosage and to record any new treatments they received. In light of the chronic nature of CRPS1 in the present study and that treatment is not quickly progressed, the ongoing management group were in some ways analogous to a waiting-list control.

2.6. Statistical analysis

All statistics were performed using SPSS 11.0.0 (SPSS, Chicago, IL, USA). Pre-treatment differences were assessed with a series of *t*-tests. A two-way repeated measures MANOVA compared NPS, finger circumference and response time to recognise the affected hand (dependent variables) between groups and assessment occasions (independent variables). Scheffé tests were selected for post hoc analyses. The number needed to treat (NNT) to obtain a successful outcome at 6 and 12 weeks was based on a 50% reduction in pain according to the NPS score (Forouzanfar et al., 2003). Significance was set at $\alpha = 0.05$.

3. Results

There were no pre-treatment differences between groups ($P > 0.24$ for all) (Table 1). Between 8.00 am and 8.00 pm, mean ± SD participation rate between was 80 ± 13% and training occupied 17 ± 9% of the time. At 6 weeks, two patients in the MIP no longer fulfilled the criteria for CRPS1 (Bruehl et al., 1999). This number had increased to four at 12 weeks. Two of the control group no longer fulfilled the diagnostic criteria for CRPS1 12 weeks after they had crossed over to MIP.

The NPS, finger circumference and response time to recognise the affected hand data are shown in Fig. 2. There was a main effect of treatment group ($F(1, 11) = 57$, $P < 0.01$) and measurement occasion ($F(6, 11) = 21$, $P < 0.01$) and a group × occasion interaction ($F(4, 11) = 11$, $P < 0.01$). Post hoc analyses showed no differences between the groups on initial assessment but a significant reduction in all three variables during the MIP with the effect maintained for at least 6 weeks after the completion of treatment ($P < 0.01$ for both). The NNT (95% confidence interval) to obtain a 50% reduction in the NPS total score was 3 (1.4–10.1). Table 2 presents the effect size for NPS and finger circumference at 6 and 12 weeks.

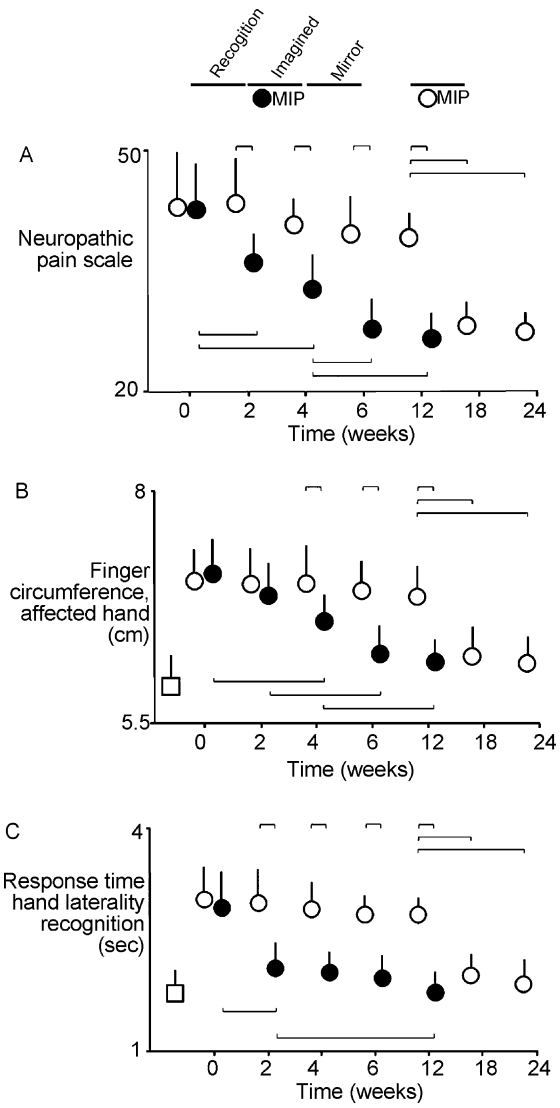

Fig. 2. Mean (circles) and standard error of the mean (vertical bars) for NPS scores (A), mean second and third digit finger circumference (B) and response time to recognise the laterality of the affected hand (C) for the MIP group (filled circles) and control group (open circles) during the experimental period (weeks 0–12) and after cross-over of the control group (weeks 12–24). MIP consisted of two weeks each of recognition of hand laterality (recognition), imagined hand movements (imagined) and mirror movements (mirror). Horizontal bars indicate significance ($P < 0.05$) on post hoc Scheffé tests. Finger circumference data for the unaffected hand (B, open square) and response time to recognise the laterality of the unaffected hand (C, open square) are shown.

Table 2
Effect size (95% confidence interval) for NPS, the intensity item of the NPS, and mean circumference of the base of the second and third digit as an estimate of swelling, at the completion of the MIP and at 6-week follow-up

	6 weeks	12 weeks
NPS points	20(10.1–29.9)	22(13.4–30.6)
NPS intensity item	3(2.6–5.4)	3(2.8–5.6)
Finger circumference (mm)	9(2.3–15.7)	10(2.6–17.3)

The reduction in response time to recognise hand laterality occurred predominantly during the first stage of the MIP.

There was no change in any measure for the control subjects, however, when they crossed over to MIP, there was a significant reduction in all three variables, which was maintained for at least 6 weeks after the completion of MIP ($P < 0.01$ for both).

During the 12-week study period, the control group predominantly received 2–3 sessions of physical therapy per week, which consisted of active and passive mobilisation of the limb, systematic desensitisation and hydrotherapy. Of the control group, one patient had been receiving chiropractic manipulations and acupuncture treatment, which was voluntarily discontinued at week 2 of the MIP (i.e. after the cross-over), and another patient had been receiving psychological counselling, which was also discontinued voluntarily at week 4 of the MIP. Of the MIP group, two patients decreased their medication intake (gabapentin) by 25 and 50%, respectively, during the 12-week study period because they felt their analgesic requirements had reduced. In the control group, one patient began new medication (gabapentin) at 3 weeks, which did not affect his NPS score.

4. Discussion

This study evaluated the efficacy of a new treatment for long-standing CRPS1. The MIP is based on sequential activation of cortical pre-motor and motor networks via a hand laterality recognition task, imagined movements and mirror therapy. Several main findings offer strong support for the hypothesis that the MIP is more effective than ongoing medical management. First, there was a strong effect of treatment group on pain and swelling. The effect size of the treatment was ~20 points on the NPS and this was maintained for at least 6 weeks. Second, when the control group crossed-over to the MIP, they demonstrated similar reductions in pain and swelling. Third, 6 weeks after completing the MIP, ~50% of patients no longer fulfilled the diagnostic criteria for CRPS1 and the NNT to gain a >50% reduction in pain was 3.

The use of hand laterality recognition to investigate mechanisms underlying CRPS1 was instigated by Schwoebel et al. (2001). They found CRPS1 patients took longer to recognise the hand that corresponded to their affected hand and concluded that on-line nociceptive input disrupts the internal body schema. There is a strong relationship between duration of CRPS1 and average response time (Moseley, 2003), which, based on other work in chronic low back pain (Flor et al., 1997) and phantom pain (Flor et al., 1995), supports the disrupted body schema theory. However, there is also a strong relationship between the posture of each pictured hand and the response time for that picture, a relationship that is dependent on the predicted intensity of pain that would occur if the patient adopted the posture shown

(Moseley, 2003). This latter finding raises the possibility of a guarding type mechanism that impacts higher order motor processes such as motor intent or motor planning.

It is not clear however, how the MIP might address either of these processes. Similar approaches for phantom pain and acute CRPS1 are thought to reconcile motor output and sensory input (McCabe et al., 2003; Ramachandran et al. 1995), which implies that a mismatch between motor intent and sensory feedback is causative of pain. McCabe's group concluded that chronic CRPS1 does not respond to mirror therapy because of enhanced synaptic efficacy of nociceptive networks and cortical changes, or because of trophic changes in the affected limb. Our data are not corroborative: the initial stages of the MIP, during which significant reductions in pain and swelling occurred, did not involve explicit movement commands, nor visual feedback about movement. However, our data are consistent with an effect mediated by activation of pre-motor networks has been proposed for mirror therapy in stroke rehabilitation (Altschuler et al., 1999).

Imaging studies have demonstrated activity in the pre-motor cortex but not primary motor cortex during recognition of the laterality of drawn hands at different orientations (Parsons, 2001). The current work used photographed hands in various postures rather than line drawings presented in different orientations, but initial imaging data using our pictures corroborate Parson's work (Moseley et al., 2003). In contrast, imagined hand movements, which comprised the second stage of the MIP, activate primary motor cortex in addition to pre-motor cortex (Decety, 1996). We have observed little or a negative response when chronic CRPS1 patients perform imagined movements alone (Moseley, 2004), which raises the possibility that success is dependent on sequential activation of pre-motor and then motor networks.

The nature and effect of MIP for chronic CRPS1 is consistent with recent proposals that some patients with CRPS1 have an involuntary neurological neglect-like condition and may have to focus mental and visual attention in order to move the limb (Galer and Jensen, 1999). Although the survey conducted by Galer and Jensen was compromised by a very low response rate, the available data were supportive; 84% of patients reported neglect-like symptoms and 56% agreed with the statement "I need to focus all of my attention on my painful limb to make it move the way I want it to". Thus, perhaps the MIP requires the patient to attend, initially at an involuntary level, to the affected limb for a substantial proportion of their waking day (~20%). In which case, the MIP may simply serve to reverse a learned disuse of the limb. Activation of motor networks via forced attention to the affected limb is a rationale that underpins the use of constraint-induced movement therapy, which can be effective for acute stroke (Taub et al., 1998). It is notable in this regard that post-stroke CRPS1 and post-trauma CRPS1 are thought to share common mechanisms (Riedl et al., 2001).

Finally, it is worth noting three main limitations of the current work. First, the generalisability of findings to the wider CRPS1 population may be limited. Only those for whom CRPS1 was initiated by a non-complicated wrist fracture were included in the current study and the exclusion criteria were extensive. These criteria were set in order to maximise the possibility of detecting a true difference with a limited sample size by using a relatively homogenous group. Nonetheless, the current findings need to be verified in a less homogenous population. Second, it was not possible to blind patients to treatment group and there may have been a systematic effect introduced by simply participating in a research experiment, particularly considering the novel nature of the treatment and the volume of training involved. This issue presents a paradox to any randomised trial in which an interactive treatment is compared to an ongoing management group and is a potential source of bias in the current work. Finally, the follow-up period, although comparable to previous work (e.g. Gobelet et al., 1992; Zuurmond et al., 1996) may not have been sufficient to determine the long-term effect of the treatment and did not permit evaluation of the MIP on work status or long-term quality of life.

In summary, the current study supports a motor imagery approach to chronic CRPS1. The MIP, involved 2 weeks each of hand laterality recognition, imagined hand movements and mirror therapy and reduced pain by ~20 points on the NPS. The mechanism of effect, although not clear, may involve sequential activation of cortical pre-motor and motor networks, or sustained and focussed attention to the affected limb, or both. The results need to be verified in a wider chronic CRPS1 population but offer a promising treatment direction for what is a difficult condition to treat.

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