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Mirror visual feedback alleviates deafferentation pain, depending on qualitative aspects of the pain: a preliminary report

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Objectives. Following lesions in somatosensory pathways, deafferentation pain often occurs. Patients report that the pain is qualitatively complex, and its treatment can be difficult. Mirror visual feedback (MVF) treatment can improve deafferentation pain. We sought to classify the qualities of the pain in order to examine whether the potential analgesic effect of MVF depends on these qualities.
Methods. Twenty-two patients with phantom limb pain, or pain related to spinal cord or nerve injury, performed a single MVF procedure. Before and after the MVF procedure, we evaluated phantom limb awareness, movement representation of the phantom or affected/paralysed limb, pain intensity on an 11-point numerical rating scale (0–10) and the qualities of the pain [skin surface-mediated (superficial pain) *vs* deep tissue-mediated (deep pain)] using lists of pain descriptors for each of the two categories.
Results. Fifteen of the patients perceived the willed visuomotor imagery of the phantom or affected/paralysed limb after the MVF procedure. In most of the patients, a reduction in pain intensity and a decrease in the reporting of deep-pain descriptors were linked to the emergence of willed visuomotor imagery.
Conclusions. In this pilot study, we roughly classified the pain descriptor items into two types for evaluating the qualities of deafferentation pain. We found that visually induced motor imagery by MVF was more effective for reducing deep pain than superficial pain. This suggests that the analgesic effect of MVF treatment does depend on the qualities of the pain. Further research will be required to confirm that this effect is a specific consequence of MVF.

Key words: Deafferentation pain, Phantom limb pain, Mirror visual feedback, Neurorehabilitation, Visuomotor imagery, Pain description, Pain category, Superficial-mediated pain, Deep tissue-mediated pain, Origin of pathologic pain.

Introduction

Deafferentation pain is clinically defined as pathological pain that is associated with a partial or complete loss of sensory input from a portion of the body following lesions in somatosensory pathways (e.g. phantom limb pain, nerve injury-associated pain) [1]. Patients with deafferentation pain complain of a complex quality of the pain, and its treatment can be difficult [2, 3].

Using a mirror to allow amputees to view a superimposed mirror reflection of their normal limb on their phantom limb, Ramachandran *et al*. [4] found that phantom limb spasms and the associated pain were rapidly relieved when the patients subsequently exercised the normal limb. This visuomotor imagery training, called mirror visual feedback (MVF) has been reported to be useful for a variety of pathological pain conditions [5–7]. Currently, the leading theories about the underlying mechanism of pathological pain and the therapeutic mechanism of MVF are as follows [8–10]: (i) pathological pain results from incongruent sensorimotor information between the sensory feedback predicted by motor commands to move the limb and the sensory feedback corresponding to the executed limb movement; and (ii) visuomotor imagery training such as MVF can provide appropriate sensory feedback corresponding to the executed limb movement visually, thereby re-establishing congruent sensorimotor integration. However, unlike studies in which MVF and similar treatments were effective in improving pathological pain [4–7], Brodie *et al*. [11] reported that patients performing MVF experienced the willed visuomotor imagery of their phantom limb more frequently than those viewing the intact limb movements alone and further that the analgesic effects of performing MVF and viewing the intact limb movements alone were comparable. The patients' subjective pain descriptors in the Brodie *et al*.'s study [11] (e.g. unpleasant itching) were different from those used by Ramachandran *et al*. [4] (e.g. clenching pain), so this is a possible reason for the different effects of MVF. Therefore, in the present pilot study, we made detailed clinical observations, focusing on the emergence of willed visuomotor imagery following MVF and the variety of pain descriptors used by deafferentation pain patients, to gain insight into the analgesic mechanism of MVF.

Methods

Subjects

Subjects included 22 patients with deafferentation pain: 11 patients with single limb amputation as a consequence of either trauma ($n = 5$) or a surgical procedure for a malignant tumour ($n = 6$); two patients with partial spinal cord injury associated with cervical syringomyelia and ossification of the thoracic posterior longitudinal ligament; seven patients with a brachial plexus lesion as a consequence of either traumatic avulsion ($n = 6$) or a surgical procedure for a malignant tumour ($n = 1$); and two patients with traumatic peripheral nerve lesions. These patients were referred from the out-patient clinic at the Center for Pain Management (Anesthesiology), Osaka University Medical Hospital, where they were undergoing treatment. All participants had received daily MVF treatment described below in addition to some conventional interventions, and no attempt had been made to control

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medication intake and standard physiotherapy modalities. This study complied with the Declaration of Helsinki regarding investigations in humans and the local ethics committee approved the study as well as the procedure. Each subject gave informed consent to participate in this study.

MVF treatment

In a quiet room, the patients were seated comfortably. A mirror board was positioned perpendicular to the patients' body midline, with the unaffected limb facing the mirror. The patients looked at the reflected image of their unaffected limb in the mirror now occupying the space of their phantom or affected limb. Subsequently, for 10 min, the patients were asked to exercise their unaffected limb at their discretion (e.g. flexion–extension cycles or rotation of the relevant body parts, wiggle the fingers) and simultaneously to perform similar exercise or imagined movements, of the paralysed/affected or phantom limb. The patients did this for 10 min once a day over a period that was agreed upon on an individual basis (mean 20.4 ± 23.8 s.d. weeks). None of the patients reported any complications concerning MVF treatment.

Evaluation of deafferentation pain

Before (pre-stage) and after (post-stage) a single 10-min MVF procedure, each patient was interviewed (by M.S.). The following assessments were made in the interviews: (i) a dichotomous measurement of the phantom limb awareness (presence or absence); (ii) motor imagery of the phantom or paralysed/affected limb (willed, involuntary movement, immobilized or absence); (iii) measurement of pain intensity on an 11-point numerical rating scale (NRS: 0 = no pain and 10 = pain as bad as it could be); and (iv) subjective descriptions of the qualities of deafferentation pain. The patients were asked to describe exhaustively the quality of every sensation they perceived subjectively in their phantom or paralysed/affected limb, but the patients were not specifically asked about the possible qualities of their pain, in order to avoid 'leading' and thus introducing a possible source of bias. Instead, when the qualities of the pain were described spontaneously by the patients, the interviewer noted the descriptive items. We categorized the pain descriptions into two main types: skin surface-mediated pain (superficial pain) and deep tissue-mediated pain (deep pain), because subjective somatic sensations mediated through sensory receptors in the skin surface can be distinguished from those mediated through deep tissue and because functional brain imaging has revealed that brain activation for noxious stimuli to the skin surface is quite different from that for noxious stimuli to deep tissue [12]. Descriptions of superficial pain consisted of nociceptive pain items (e.g. knife-like, tingling) and those related to temperature sensation (e.g. freezing, burning). Descriptions of deep pain consisted of pain items related to pressure sensation (e.g. taut, pressing) and the proprioceptive senses of movement and posture (e.g. clenching, twisting). Total counts of how many items in each description category (superficial pain or deep pain) were noted for all patients and then compared before and after the MVF procedure.

Statistical analyses

All results were expressed as mean ± s.d. We used the Wilcoxon signed-rank test to compare data (NRS, and descriptive item counts of superficial pain or deep pain) between the two stages. Decreases in NRS averages, and pain descriptor item counts of superficial pain and deep pain from pre-stage to post-stage were expressed in percentage terms. On the basis of the presence or absence of willed visuomotor imagery of the affected limb at post-stage, the patients were divided into two groups. Thereafter, we analysed demographic data and the decreases of NRS and respective pain-descriptor item counts between the two groups by the Mann–Whitney test.

Results

Demographic data of the patients

Table 1 contains the patients' demographic data, a summary of the findings from the interviews and the effect of the single MVF procedure. None of the patients reported any complications concerning the single MVF procedure in this study. All amputees were aware of a phantom limb, and three patients (Cases 14, 15 and 22), who were not amputees, perceived a supernumerary phantom limb. None of these patients could exercise their phantom limbs voluntarily at pre-stage. Two patients with pain arising from spinal cord injury (Cases 12 and 13) could actually exercise the affected limbs voluntarily and correspondingly perceive the experience of limb movements because of the partial nature of their injury. Two patients with a brachial plexus lesion (Cases 17 and 19) perceived involuntary movement experiences of the affected limb in spite of the paralysis, whereas other patients with a brachial plexus lesion or peripheral nerve injury (Cases 16, 18, 20 and 21) perceived their paralysed affected limb to be immobile. In 10 of the 14 patients who were aware of the phantom limb at pre-stage, a vivid sense of voluntary movement of the phantom limb emerged at post-stage. Likewise, five of eight patients could establish willed visuomotor imagery of their affected/paralysed limb. However, seven patients did not perceive any sense of voluntary movement of the phantom or affected/paralysed-limb throughout the study period. We then divided the 22 patients into two groups: those who reported willed visuomotor imagery of the affected limb (presence, $n = 15$) and those who did not (absence, $n = 7$). NRS data from the two patient groups at pre-stage (presence: 6.3 ± 1.5, absence: 7.3 ± 2.0; $P = 0.26$), disease durations (presence: 227.9 ± 296.9, absence: 349.3 ± 491.6; $P = 0.75$) and MVF treatment periods prior to this study (presence: 19.5 ± 21.0, absence: 21.0 ± 29.6; $P = 0.66$) were comparable.

Pain intensity

At post-stage, the subjective pain intensity averaged across all patients was significantly ameliorated (NRS: Pre 6.6 ± 1.7; Post 4.2 ± 2.8; $P < 0.002$). The patients with the willed visuomotor imagery, on average, reported significantly lower pain intensity at post-stage (NRS: Pre 6.3 ± 1.5, Post 3.2 ± 2.4; $P < 0.001$), whereas the patients without the visuomotor imagery did not (NRS: Pre 7.3 ± 2.0, Post 6.4 ± 2.4; $P = 0.50$). The decrease in pain rating (NRS) of the patients with the willed visuomotor imagery ($51.4 \pm 31.8\%$) was more than that of the patients without the visuomotor imagery ($12.5 \pm 21.7\%$; $P < 0.004$) (Fig. 1).

Qualities of deafferentation pain

The total count of entered pain descriptive items at pre-stage was 86 (superficial pain = 44; deep pain = 42), whereas at post-stage it was 53 (superficial pain = 37; deep pain = 16) ($P < 0.005$) (Table 2). The decrease in item counts of deep pain between the two stages was significant ($P < 0.0004$), whereas that of superficial pain was not ($P = 0.34$). The patients who experienced the willed visuomotor imagery showed a significant decrease in descriptive item counts for deep pain (Pre 31, Post 7; $P < 0.0001$), but not for superficial pain (Pre 28, Post 22; $P = 0.43$). The patients without the visuomotor imagery did not show a significant decrease in descriptive item counts of superficial pain (Pre 16, Post 15; $P = 0.72$) or deep pain (Pre 11, Post 9; $P = 0.64$). Between the two patient-groups, the decrease of descriptive item counts of superficial pain was not significant (patients with the willed visuomotor imagery $18.2 \pm 26.3\%$, patients without the visuomotor imagery $4.8 \pm 12.6\%$; $P = 0.17$) but that of deep pain was significant (patients with the willed visuomotor imagery $78.6 \pm 26.5\%$, patients without the visuomotor imagery $22.2 \pm 40.4\%$; $P < 0.02$) (Fig. 1).

TABLE 1. Clinical details of patients with deafferentation pain

Case	Disease	Gender	Age	Limb	Laterality	Disease duration prior to this study (week)	MVF follow-up period (week)	NRS (pre)	Effect of MVF	Phantom limb awareness		Motor imagery of the phantom or paralysed/affected-limb		Treatment
										Pre	Post	Pre	Post	
1	Amputation	Male	32	Lower	Left	6	3	7	Good	+	+	Involuntary	Willed	Amytriptyline, Clonazepam, Carbamazepine, Oxycodone
2	Amputation	Male	62	Upper	Right	2	7	6	Good	+	+	Immobilized	Willed	Imipramine, Clonazepam
3	Amputation	Male	43	Lower	Left	4	3	6	Good	+	+	Involuntary	Willed	Amytriptyline, Clonazepam, Neurotropine
4	Amputation	Male	56	Upper	Right	20	4	6	Good	+	+	Involuntary	Willed	Gabapentin
5	Amputation	Female	74	Lower	Right	100	4	7	Fair	+	+	Involuntary	Willed	Gabapentin, Amytriptyline, Carbamazepine, Clonazepam
6	Amputation	Male	57	Lower	Left	110	6	9	Fair	+	+	Involuntary	Willed	Mexiletine, Neurotropine, prosthesis
7	Amputation	Male	47	Upper	Right	900	78	8	Poor	+	+	Willed	Willed	
8	Amputation	Male	67	Upper	Left	2	27	8	Fair	+	+	Involuntary	Involuntary	Morphine, Amytriptyline, Clonazepam
9	Amputation	Female	33	Lower	Right	850	4	10	Poor	+	+	Involuntary	Involuntary	
10	Amputation	Male	65	Upper	Left	3	11	5	Poor	+	+	Immobilized	Immobilized	Clomipramine, Baclofen
11	Amputation	Male	64	Upper	Right	3	20	5	Poor	+	+	Immobilized	Immobilized	Nortriptyline, Imipramine, Fentanyl
12	Partial spinal cord injury	Female	62	Upper	Right	250	4	5	Good	–	–	Willed	Willed	Gabapentin
13	Partial spinal cord injury	Male	42	Lower	Right (>left)	32	24	8	Poor	–	–	Willed	Willed	
14	Brachial plexus injury	Female	75	Upper	Left	4	36	5	Good	+	–	Immobilized	Willed	Amytriptyline, Imipramine, Clonazepam
15	Brachial plexus avulsion	Male	44	Upper	Left	550	7	4	Good	+	+	Involuntary	Willed	Gabapentin
16	Brachial plexus avulsion	Male	39	Upper	Right	1110	8	5	Good	–	–	Immobilized	Willed	Nortriptyline
17	Brachial plexus avulsion	Male	22	Upper	Left	4	24	5	Fair	–	–	Involuntary	Willed	Imipramine, Clonazepam
18	Brachial plexus avulsion	Male	44	Upper	Left	56	16	6	Good	–	–	Immobilized	Immobilized	Clonazepam, Baclofen, Morphine, Neurotropine
19	Brachial plexus avulsion	Male	40	Upper	Left	1158	90	8	Poor	–	–	Involuntary	Involuntary	
20	Brachial plexus avulsion	Female	17	Upper	Left	6	8	9	Poor	–	–	Immobilized	Immobilized	Nortriptyline, Carbamazepine, Clonazepam
21	Peripheral nerve injury	Female	29	Lower	Left	128	48	8	Fair	–	–	Immobilized	Willed	Splint-plaster-cast
22	Peripheral nerve injury	Male	50	Lower	Right	200	16	5	Good	+	+	Involuntary	Willed	Amytriptyline
	Mean ± S.D.	–	48.4 ± 16.3	–	–	249.9 ± 389.1	20.4 ± 23.8	6.6 ± 1.7	–	–	–	–	–	–

Effect of mirror visual feedback is categorized into three subjective criteria: pain relief of >50% = 'good'; 30–50% = 'fair'; and <30% = 'poor'. NRS with 0 = no pain and 10 = pain as bad as it can be. Concerning the motor imagery, patients with a phantom limb were asked to imagine moving the phantom limb, whereas patients without a phantom limb were asked to have a kinesthetic experience of the paralysed/affected limb.

The patients with the willed visuomotor imagery introspected that they could stretch the affected limb, push back and sustain a feeling of oppression or relieve spasms in internal movement representation of the affected limb, although they could not actually exercise the phantom or paralyzed limb, and thus they could voluntarily prevent unpleasant painful motor imagery of the affected limb with looking at the mirror. The patients (Cases 7 and 13) with willed visuomotor imagery suffered from superficial pain primarily and deep pain secondarily. Their deep pain could be improved by using the willed visuomotor imagery but their superficial pain remained severe and hence they reported poor relief of their overall pain intensity.

Discussion

Our results empirically confirm the short-term usefulness of MVF treatment in alleviating deafferentation pain, as previous controlled studies have already shown [5–7]. Further, we found qualitatively that our patients described >50% relief of deep-pain descriptors but <30% relief of superficial pain descriptors following the MVF procedure. Comparing the patients with and without willed visuomotor imagery of the phantom or affected/paralysed limb following MVF, we found that the patients with willed visuomotor imagery decreased their reported pain intensity in parallel with the number of reported deep-pain descriptors more than the patients without visuomotor imagery. Decreases of superficial-pain descriptors of the two patient groups were comparably small. Based on our clinical observations, we preliminarily conclude that the pain-alleviating effect of MVF promisingly corresponds with the emergence of willed visuomotor imagery of the phantom or affected/paralysed limb. This is in close agreement with Ramachandran *et al.*'s finding [4]. Further, we conclude that the pain-alleviating effect of MVF would depend on the qualitative aspects of the deafferentation pain. In addition, although Brodie *et al.* [11] suggested the possibility of different analgesic effects of MVF in upper *vs* lower limbs, we did not find any difference between upper-limb and lower-limb patients with regard to decreases of NRS and descriptive item counts of superficial pain and deep pain following MVF (data not shown).

Subsequently, we discuss the relationship between the pain-alleviating mechanism of MVF and sensorimotor re-integration of the deafferentated limb, and then we discuss the origin of deafferentation pain in the central nervous system (CNS), on the basis of our preliminary clinical observations.

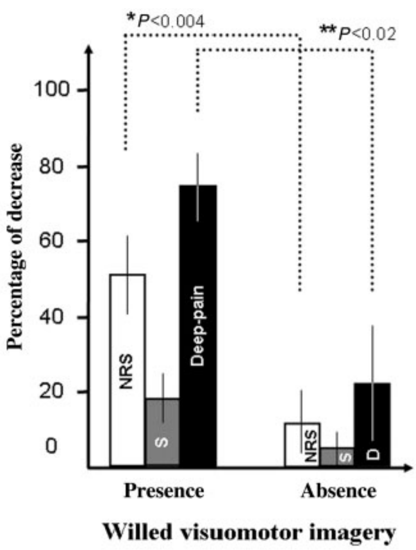

Fig. 1. Percentage decreases of pain data and emergence of the willed visuomotor imagery of phantom or affected/paralysed limb following MVF. Bar graphs (mean ± 1 s.e.) show percentage decrease in pain intensity (NRS, white bars) and descriptor item counts of superficial pain (S, grey bars) and deep pain (D, black bars), in deafferentation pain patients with (presence, $n = 15$) or without (absence, $n = 7$) willed visuomotor imagery of their phantom or affected/paralysed limb following the MVF procedure. Between the two patient-groups, the decreases of pain intensity and descriptor item counts of deep pain were statistically significant (*$P < 0.004$, **$P < 0.02$, Mann–Whitney test).

How can MVF alleviate deafferentation pain? And why do the qualities of deep pain improve more by MVF?

Much of the complexity of human movement arises as a simple coupling of one transformation from motor commands to their sensory consequences and the other transformation from sensory feedback to motor commands. This sensorimotor loop is represented as an internal model of movements in the CNS. Subsequent to a partial or complete loss of somatosensory feedback, such as deafferentation by nerve injury or amputation, the sensorimotor loop becomes incongruent. It is proposed that the sensorimotor incongruity then provokes deafferentation pain (e.g. phantom limb pain, post-spinal cord injury pain and post-brachial plexus avulsion pain) [9, 10]. Multimodal sensory information, especially visual and somatosensory information, contributes to the integration of the sensorimotor loop and consequently the internal representation of movements [13]. Somatosensory information is mediated through nerve endings innervating skin and deep tissue (e.g. muscle spindles). An electrophysiological study revealed that cutaneous exteroceptors can provide the CNS with kinesthetic information; however, they often lack detailed signalling of the direction or state of joint movement [14]. Another electrophysiological study revealed that afferent information from deep tissue plays a specific role in one's proprioceptive sense of limb movement and position [15]. Considering these studies, the afferent information from deep tissue contributes much more to congruent sensorimotor integration and movement representation than does information from the skin surface. Furthermore, the afferent information from deep

Table 2. Qualitative descriptor items of deafferentation pain in two stages

Superficial pain (44/37)		Deep pain (42/16)	
Nociceptive pain	Pain associated with temperature sensation	Pain associated with pressure sensation	Pain associated with sense of movement and posture
Knife-like (2/1)	Freezing (1/0)	Crushing (5/2)	Twisting (3/0)
Sawing (3/3)	Burning (8/4)	Pressing (6/2)	Clenching (4/1)
Electric shock-like (3/3)		Throbbing (3/2)	Cramp-like (5/0)
Tingling (11/11)		Dull (4/3)	Tearing (2/2)
Pricking (4/3)		Taut (10/4)	
Shooting (1/1)			
Sticking/piercing (3/3)			
Lancinating/stabbing (5/5)			
Stinging (3/3)			

In the parentheses, total counts of the respective descriptive items are given for before and after the MVF procedure (i.e. pre-MVF/post-MVF).

tissue and vision are known to be interdependently involved in congruent sensorimotor integration, and many experimental results stress a predominant role of vision over other senses in congruent sensorimotor integration [16]. For example, if visual information signals correct spatial position and movement of a hand, humans ascribe the hand to themselves [17]. Thus, the visual image of limb movements has great potential to compensate for an insufficiency of somatosensory information. In almost all of our patients who reported >30% relief of deafferentation pain, viewing images of limb movements could reawaken and increase vivid willed visuomotor imagery of the phantom or affected/paralysed limb. Using this newly emerged willed visuomotor imagery, the patients became able to voluntarily rival and restrain the painful involuntary motor images of their affected limb, and thereby they could decrease their pain intensity and descriptive item counts of deep pain to some extent. Such visually induced willed movement representation may be related to a feedforward model of motor control-utilizing internal representations of limb position, in which the position of a limb is assumed to be experienced on the basis of a desired state derived from motor commands in conjunction with visual and deep tissue-mediated afferent feedback [18], and thereby MVF would act with the motor commands to update the kinesthetic experiences of the phantom or affected/paralyzed limb without deep tissue-mediated afferent feedback. Therefore, it seems inevitable that deep pain improved exclusively, corresponding to the emergence of the willed visuomotor imagery following MVF. As mentioned earlier, cutaneous afferent information does not play an important roll in congruent sensorimotor integration and hence superficial pain is not expected to improve by MVF. However, our patients' superficial-pain descriptors improved slightly. Because various types of sensory stimuli and a task were used to distract attention from the pain and subsequently decrease the pain [19], the improvement of superficial pain as well as deep pain might result from such non-specific consequence of MVF. As McCabe *et al.* [5] pointed out, however, the patients who had been treated with MVF were aware that any procedures other than MVF were for control conditions, and therefore the attempts no longer worked as a fair control. Our patients in fact did not report any changes of their answers in the interviews when viewing the limb in the mirror immediately before the limb movements. Thus, we did not use any control conditions. Further controlled experiments will be required to confirm whether the observed reduction of deafferentation pain is a specific consequence of MVF.

Pain-alleviating effect of MVF depends on the qualities of deafferentation pain

Concerning the origin of pain, it has been speculated that the variability of patients' descriptions of pain suggests different underlying pain mechanisms. However, the multitude of pain measurement instruments used in clinical settings, both quantitative and qualitative, such as the McGill Pain Questionnaire [20], have not shed much light on the underlying mechanisms of pain. To aid our understanding of how MVF can alleviate deafferentation pain more specifically, we categorized our pain descriptors so as to incorporate the possible implications of evaluating the qualitative aspects of deafferentation pain in this study. This way, we were able to relate the pain-alleviating effects of the MVF procedure to the different pain descriptors reported by our patients, and our results suggest that different pain qualities arise from different underlying mechanisms. Using the classification of pain qualities proposed here, deep pain (e.g. cramp-like, taut, twisting) would be derived from a relatively higher-order cognitive process of sensorimotor integration and movement representation in the CNS, whereas superficial pain (e.g. pricking, shooting, sticking) might be derived from other underlying mechanisms such as abnormal hyperexcitability and firing patterns of neurons in the pain pathways [21]. Among superficial-pain descriptors, temperature sensation-associated pain items improved markedly after MVF. We speculate that these painful temperature sensations may be derived from incongruent sensorimotor integration, although they were categorized as superficial pain in this study. This kind of pain is common to complex regional pain syndrome (CRPS) or other neuropathic pain, and our idea is in agreement with the assumption that CRPS results from incongruent sensorimotor integration [5, 9, 22].

Alternatively, differences in descriptor items between deep pain and superficial pain may simply reflect the different peripheral anatomical origin (i.e. nociceptive endings supplying deep or superficial tissues) of the abnormal neural activity induced by deafferentation. Noxious stimuli to deep tissue and those to superficial tissue are processed in different neural substrates [12], suggesting that neural substrates for the top-down pain-alleviating mechanism provoking the willed visuomotor imagery by the MVF procedure may overlap with or selectively work on the neural substrates for noxious stimuli to deep tissue.

This classification might thus, at least in part, implicate possible underlying mechanisms of deafferentation pain in human subjects. However, future studies across a wider variety of patient groups with diffuse types of pain are needed to insure the validity of this classification.

Rheumatology key messages

- Different pain-alleviating effects are observed for different qualities of deafferentation pain, suggesting a different origin of the pain.
- Treatment strategies should consider the qualities of deafferentation pain.
- MVF treatment is a promising therapeutic approach to certain types of deafferentation pain.

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