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Title: A deranged body schema and susceptibility to experience anomalous somatosensory sensations in fibromyalgia syndrome.

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ABSTRACT

Objectives: Evidence suggests there to be an association between chronic pain and disruption of the body schema when we tested the hypothesis in fibromyalgia syndrome.

Methods: We investigated distinct perceptual aspects of the body schema both in a sample of patients with FMS and in healthy controls. Performances on the left/right judgment task were measured; tactile acuity was assessed by using the two-point discrimination test. Furthermore, we evaluated somatosensory sensations evoked by tactile stimulation with Von Frey filaments to body parts which were experiencing pain. Anomalous somatosensory sensations elicited by sensory-motor conflict also were investigated.

Results: Subjects with FMS showed inferior performance on the right/ left judgment task, both in terms of correct matches (75% *vs* 89%, respectively; $p<0.05$) and response time (2.58 s *vs* 1.91s, respectively; $p<0.05$). Effect sizes were large and very large, respectively.

Two-point discrimination thresholds were significantly higher ($p<0.05$) in participants from the FMS sample (mean of 49.71 mm, SEM 3.23 mm) relative to healthy controls (mean of 37.62 mm , SEM 2.23 mm).

Nine out of fourteen participants with FMS, but no control subjects, reported referred somatosensory sensations upon tactile stimulation, including tingling, pins and needles, weight, and chills. Referral sites included regions both adjacent and remote to stimulated sites. Subjects with FMS scored higher across all items within the administered questionnaire addressing anomalous sensations on the mirror set-up

(Cohen's *d* 1.02-2.42 across all items) and FMS subjects perceived pain during the sensory-motor conflict (the required statistical power for it to be statistically significant was 96% and for it to be recognized as a difference of means in pain item).

Conclusion: Our present findings suggest a disrupted body schema and propensity to experiencing anomalous somatosensory sensations during sensory-motor conflict in people suffering from FMS.

Keywords: Fibromyalgia, two-point discrimination test, somatosensory sensations, tactile stimulation, sensory-motor conflict.

INTRODUCTION

Fibromyalgia syndrome (FMS) is a highly prevalent, chronic musculoskeletal condition characterized by chronic widespread pain and evoked pain at specific tender points. Patients with FMS usually present with a myriad of concomitant conditions, including anxiety, depression, fatigue and non-restorative sleep, memory and cognitive impairment, muscle stiffness, and gastrointestinal disorders [1].

The pain experience is an embodied one, insofar as the body is one's way of experiencing the world, and the ability to localize and confine a sensation to the body depends on an intact neural body representation. Growing evidence suggests the association of chronic pain with disruption of mental representations of the body [2,3,4] Studies show that body schema, which is viewed as the dynamic, action-oriented implicit representation of position and movement of one's own body [5,6], is disrupted in chronic pain [7]. Although published data regarding FMS is scarce, there are indications of a distorted working body schema in people experiencing this condition. For example, studies have shown poor balance and higher frequency of falls [8,9] perception of enlarged body size and shrinkage of the surrounding space during exacerbations of pain 10, or deficits in tactile acuity or motor disturbance such as slight tremor [11,12,13,14].

Despite the available evidence, the underlying mechanisms of pain in FMS remains little understood. In a recent case-control study, we provided evidence supporting increased plasticity of the body schema in patients with FMS [15]. In the current study, we further investigated distinct sensory and perceptual aspects of the working body schema in a sample of patients suffering from FMS, by evaluating left/right judgment, two-point discrimination, and referred somatosensory sensations evoked by tactile stimulation. In addition, sensations elicited by sensory-motor incongruence, i.e. induced mismatch between sensory input and motor intent, were evaluated.

MATERIALS AND METHODS

Study participants

The study sample comprised of fourteen women (54.35 years, ETM 1.89) with a prior formal diagnosis of FMS, which were recruited from a local support group through advertisements and informative presentations, as well as thirteen healthy women (53.86 years, ETM 3.30) who served as controls. The study protocol was approved by the Ethical Review Board of the University of the Basque Country, and all participants provided written informed consent before participating.

Pain and clinical status

Pain and clinical status were assessed by using self-administered questionnaires. Subjects provided an overall measure of pain severity on a Visual Analogue Scale (VAS) [16,17], and the impact of ongoing pain on daily function was evaluated by means of the Spanish version of the short form of the Brief Pain Inventory (BPI-SF) [18]. The Spanish version of the Fibromyalgia Impact Questionnaire (FIQ) [19] was used to assess the spectrum of problems related to fibromyalgia and responses to therapy. Health-related quality of life was evaluated by using the SF-12 Health Survey validated in Spanish [20] a multipurpose questionnaire comprising 12 items selected from the SF-36 Health Survey [21], that provides scores in both mental and physical domains.

Left/right judgment test

A set of 30 different pictures depicting left- or right handed hands with different rotations and viewed from either the palmar or dorsal sides were presented on a computer screen by using a custom-programmed software application. Pictures were presented in a sequential and random manner for up to ten seconds each or until a response was provided, and the subjects were instructed to indicate hand side as quickly and accurately as possible by pressing an appropriate key on the computer keyboard, "Z" for the left and "M" for the right. Participants were shown an example image to familiarize themselves with the test and be shown to not move their hands during the test [22]. The reaction time (in seconds) and the correct hits (in terms of percentage) were recorded as result measurements.

Two-point discrimination test

The two-point discrimination (2PD) test is a standard technique for assessing tactile acuity during neurological examination [23]. Since 2PD threshold considerably varies across body regions, 2PD assessment in the current study was performed on the dorsal aspect of the neck in all participants, since it is one of the most predominant regions for pain in SFM sufferers for this geographic area [24]. TPD measurement in the neck region has adequate intra-rater and inter-rater reliability [25]. Briefly, a two-point aesthesiometer was placed under its own weight on the participant's skin overlying the spinous process of the 7th cervical vertebra (C7), with the patient's eyes closed, ensuring simultaneous contact of the two tips. The initial separation between the aesthesiometer's tips was 30 mm. In a series of ten stimulations, subjects were asked to report if contact with the tips was perceived at either one or two points. The distance between caliper tips was recorded as the TPD threshold if the subject reported to have perceived the stimulus as applied at two different points at least on 7 out of such 10 repetitions [26], and otherwise a new series of ten stimulations was performed by increasing tip separation by 2 mm.

Referral of evoked somatosensory sensations

We asked participants to describe perceived sensations upon mechanical stimulation at three sites reported by each participant as the most painful locations. In healthy control subjects, who were all free of pain, stimuli were applied to the predominant regions feeling pain for this pathology in this geographic area [24], in the anterior aspect of the right knee and to the mid-line of the low back and cervical regions. Stimulations were performed with the patient's eyes closed by applying a 300 g-force von Frey filament to the area. This ensured it produced pain for people suffering from FMS, since they have a greater sensitivity to pressure pain [27]. The stimulation on the surface of the skin was performed at a 90◦ angle until it bowed, and holding it in place for 1.5 seconds. Unlike healthy individuals, FMS subjects all reported mechanical stimulation with the filament as painful. Subjects were instructed to report when filament contact was felt, and to immediately draw the location of any perceived somatosensory sensation, other than that at the stimulated site, on a schematic diagram depicting anterior and posterior views of the body.

Feedback on the mirror test

We evaluated the occurrence of anomalous sensations triggered by incongruence of visual inputs and motor intent [28] by using the mirror set-up (Figure 1). Briefly, the subject placed her right upper limb in front of a vertical mirror orthogonal to the subject's body, while keeping her left limb hidden behind the mirror, in such a manner that she could see the reflected right hand when looking into the mirror. Participants were then asked to perform repetitive bilateral, synchronic movements for 5 min while looking into the mirror, including forearm flexions/ extensions and wrist pronation/ supination movements, and a series of hand grip and finger extension movements. Thereafter, discrepancy between reflected visual input and proprioceptive sensations from the hidden limb was induced by asking the participants to simultaneously and repeatedly displace both forearms first to the right and then to the left for 20 seconds. An ad hoc questionnaire used by different authors [13, 28, 29, 30, 1,32,33] was then immediately administered to record sensory sensations triggered by sensory-motor incongruence, which included 6 items addressing changes in shape and location, as well as additional 8 items addressing anomalous sensations such as pain, perceived temperature changes, pressure or fatigue. Responses to the questionnaire were all measured on 5-point Likert scales.

Data analysis and statistics

The SPSS® v. 22 statistical package was used for all statistical analyses. Normality of distribution was checked using the Shapiro-Wilk test, and either the unpaired-sample two-tailed *t*-test or the Mann-Whitney-Wilcoxon *U*-test were used to investigate statistical significance of means differences between study groups.

Alpha values 0.05 and 0.01 were used as criteria of statistical significance (indicated where appropriate). Primary data are presented as means and standard errors, and Cohen's guidelines [34] were used to classify the magnitude of effects sizes (Cohen's d and 95% confidence intervals, where d = 0.2 represents small effect, d = 0.5 denotes a medium effect, and d equaling or in excess of 0.8 indicates a large effect). The power of the contrast has been analyzed through an online application Sample Size Calculator GRANMO [35], which gives us a value in terms of percentage.

RESULTS

Baseline clinical status of FMS patients

Subjects in the FMS sample scored an average of 88.38 (SEM 2.72) on the FIQ (data summarized in Table 1), which was slightly above the reported values of ca. 76 shown by studies conducted in the same geographic area (36.37). Ongoing pain intensity was 8.89 (SEM 0.98) on the VAS, and scores on the Brief Pain Inventory averaged 7.39 (SEM 0.37), which indicated severe clinical pain with high interference with daily function. Scores on the Physical and Mental Component Summaries of the 12-Item Short-Form Health Survey (SF-12) were both significantly lower in the FMS sample, thus reflecting inferior clinical health status (33.27, SEM 1.98 in the FMS sample, *vs* 54.08, SEM 2.09 in healthy controls).

Impairment of right/ left judgment

Measures recorded on the right/ left judgment task included correct side recognition scores (in percent terms) and average response time. Healthy subjects correctly discriminated right-side hands from left-side hands in an average 89 out of 100 hand pictures presented (SEM 2.0 %). In contrast, correct identification rate in the FMS sample was 75% (SEM 4.0 %), which was significantly lower than showed by healthy subjects ($p<0.05$ on the Student's *t*-test for independent samples). Effect size was large to very large (Cohen's *d* = -1.07; 95% confidence interval -0.20,-1.95). Mean response time recorded in the healthy control group was 1.91 s (SEM 0.14 s), which was significantly lower than the mean time of 2.58 s recorded in the FMS sample (SEM 0.26 s). Effect size of inter-group response time comparison was large (Cohen's *d* 0.88; 95% confidence interval 0.02, 1.74), and the difference between the two means was statistically significant ($p<0.05$ on the Student's *t*-test for independent measures).

Increased two-point discrimination thresholds

Two-point discrimination was assessed in the neck region at the level of the C7 vertebra. Healthy controls showed a mean two-point discrimination threshold of 37.62 mm (SEM 2.23 mm), whereas the recorded average value from the FMS sample was 49.71 mm (SEM 3.23 mm). Effect size was large to very large (Cohen's *d* 1.17; 95% CI 0.34, 2.01), and the difference between the two means was statistically significant ($p<0.01$ on the Student's *t*-test for independent measures).

Referred somatosensory sensations in FMS

Participants from the FMS sample received stimuli applied with a von Frey filament to three body sites that had been reported as the most painful. Nine out of fourteen such subjects reported referred somatosensory sensations (Table 2), i.e. sensations emanating from outside the stimulated site, including tingling, pins and needles, weight, and chills. Eleven out of twenty-one referral sites involved regions lying either adjacent to stimulus locations or within the same dermatome, whereas ten were located remotely, i.e.

separated from the stimulus site by a pain-free area, or referred to another limb (Table 2). No contralateral referrals were reported. However, none of participants in the healthy control group reported no referred somatosensory sensation.

Anomalous somatosensory sensations on the mirror test

FMS patients scored higher across all items of the administered questionnaire addressing anomalous somatosensory sensations during incongruent movements on the mirror set-up. Scores on individual items of the questionnaire are all shown in Table 3. Means comparisons between study groups all reached statistical significance ($p<0.01$ on the Mann-Whitney-Wilcoxon U-test), with effect sizes that ranged from large (Cohen's d 1.02 on item 8 – I felt that my hidden limb was hotter) to very large (e.g. Cohen's d 2.42 on item 10 – I felt pressure in my hidden limb). Accepting an alpha risk of 0.05 in a two-sided test with 14 subjects in the first group and 13 in the second, the statistical power was 96% to recognize it as statistically significant as a difference of means (pain item; 3.21 in FMS group 1 and 1.0 in control group (Table 3).

DISCUSSION

The present study comparatively addressed distinct perceptual aspects of the working body schema in a sample of patients suffering from FMS, relative to age-matched healthy controls. Performances on the left/right judgment task and two-point discrimination test, as well as referred somatosensory sensations evoked by tactile stimulation all concurred to suggest derangement of the body schema in the FMS population.

Disruption of the working body schema in FMS

We show that performance on the left/right judgment task was deficient in people with FMS, relative to healthy controls. The left/right judgment task is a surrogate evaluation of the working body schema and involves mental movement of one's own limb to the position and orientation of the one presented in the picture [38]. Deficient performance is commonly attributed to a disrupted body schema [7,39]. Previous studies have shown altered left/right orientation in chronic pain populations [2,5,7]. Here, we found that also people with FMS performed worse than healthy controls in the left/right judgment task, both in terms of response time and correctly discriminated pictures. These findings are in general agreement with the emerging notion of a disrupted body schema in chronic pain [40], and provides further support to our previous suggestion that the body schema is altered in people suffering from FMS [15].

Referral of evoked somatosensory sensations, i.e. perceiving sensations as emanating from a site other than the stimulated one, has been observed in several forms of chronic pain, including CRPS, limb amputation, or chronic low back pain [29, 41, 42]. Extending such observations, we found that participants from the FMS sample, but not healthy controls, reported referred sensory sensations following punctuate stimulation with von Frey filaments to painful sites. We interpret this outcome as further supporting the idea of reorganization of somatosensory pathways in chronic pain. Moreover, referral patterns recorded in the present study may offer additional insight into the nature and extent of this reorganization. Thus, perceived sensations reported in our current study were referred to contiguous regions in eleven out of twenty one cases, e.g. stimulation to the back of the neck evoked sensations in the occipital region (subjects #1 and #6).

This pattern of distribution was reminiscent of that observed in patients with phantom limb pain, in which sensations are thought to be referred to body regions whose representations on the primary somatosensory cortex lie close to that of the stimulated site, as a result of central sensory reorganization secondary to disruption of sensory pathways (Ramachandran and Rogers-Ramachandran, 1992). However, nearly a half of all reported referrals in the current study (10 out of 21) were rather remote from the site of stimulation, for example stimuli applied to the sacral region being perceived as pins and needles in the hypothenar eminence (subject #7), or stimulation to the low back evoking referred sensations to the left elbow (subject #9). These referral patterns can hardly be accounted for by cortical representational contiguity, but appear to be rather consistent with plasticity and reorganization of subcortical structures. In this regard, studies in laboratory animals have revealed somatotopic reorganization in at least the brainstem and thalamus following peripheral nerve injury [43, 44], and there is previous anatomical and electrophysiological evidence that may provide a neural basis for the observed referrals to remote regions of the body. In the macaque monkey, for example, thalamic ventrobasal complex neurons responding to hand or upper limb stimulation lie in close proximity to those activated from receptive fields as remote as the trunk, lower limb or tail [45]. In rat brainstem, neurons in the dorsal column nuclei receiving input from the wrist, for instance, are contiguous to those targeted by primary afferents arising from the footpads [46]. In addition, reorganization of receptive fields that ensues in the cat dorsal column nuclei after peripheral nerve injury includes expansion of receptive fields to the trunk, for example, in neurons usually responding to stimulation to the digits [47].

Decreased tactile acuity has been reported to occur in several chronic pain populations, at least including arthritis, complex regional pain syndrome and chronic low back pain [48]. We assessed tactile acuity by using the TPD test, a well-established procedure to evaluate peripheral and central somatosensory function [49]. We found significantly higher discrimination thresholds in our FMS sample, relative to healthy controls. These findings may be interpreted as further indication of disruption of higher-level body maps in the brain, since discriminative ability is dependent on the integrity of primary somatosensory cortex [50]. Because in the present study, TPD has been evaluated in the neck region, previously established as a zone of high pain prevalence for this pathology in this geographic area 24, whether or not changes in tactile acuity may be more pronounced in areas affected by ongoing pain could not be established. There is previous evidence, however, that TPD thresholds are indeed decreased in the affected region in people suffering from low back pain, such decreases correlate with ongoing pain [51].

May a disrupted body schema lead to SMC?

Sensory-motor conflict (SMC), which arises when motor intention is inconsistent with the expected sensory feedback [52], and is known to generate anomalous sensations including dysaesthesia, paraesthesia and referred sensations 13,[41,53]. SMC has previously been proposed as a potential mechanism leading to pain [13,54], and clinical studies have shown that induced SMC gives rise to or exacerbates pain in amputees, whiplash-associated disorder, or FMS[28,30, 34, 55]. In the current study, we relied on the mirror set-up to elicit discordance between motor intention and visual input. We found that anomalous sensory sensations elicited by the procedure, which included perceived alterations in size, shape and location of the hidden limb, as well as changes in thermal and tactile sensations, were more likely to occur in the FMS sample.

As in a previous study [30], the sensation of pain was reported here by six subjects of the group of FMS (43%). The subjects #1#, #6, #9, #10, #11, #14 reported pain sensations during the test with values equal or greater than a 4, measured on 5-point Likert scale. Moreover, SMC induced by the mirror set-up, reveal significant response differences between the two study groups, suggesting that patients with FMS may be prone to experience anomalous sensations secondary to SMC. If, as posited previously, SMC of sufficient magnitude can give rise to pain [13, 54], then identification of factors leading to or maintaining this conflict is a matter of pivotal clinical importance. In this regard, a distorted body schema harboring inaccurate spatial information may be seen as a potential source of mismatch with actual visual input, and hence a factor potentially contributing to SMC. In phantom limb pain, reorganization of somatosensory pathways is thought to be triggered by disruption to the sensory pathways. However, pathophysiological paths in other chronic pain states such as FMS remain to be established. We have previously reported on distortion of the body image in FMS, viewed as a cognitive and interpretative representation that integrates the conscious perceptual corporeal experiences and contributes to beliefs and attitudes towards the body [15]. Further investigation is warranted to determine whether altered body image may be a contributing factor to a distortion of the working body schema and ultimately to chronic pain.

In summary, our current study provides evidence supporting the notion of a disrupted body schema in patients suffering from FMS. In addition, we show that subjects with

FMS are prone to experience anomalous sensations caused by SMC. A link between a deranged body schema and SMC may be seen as potentially contributing to chronic pain in FMS.

AUTHOR CONTRIBUTIONS

All authors contributed equally to this paper and all authors discussed the results and commented on the manuscript.

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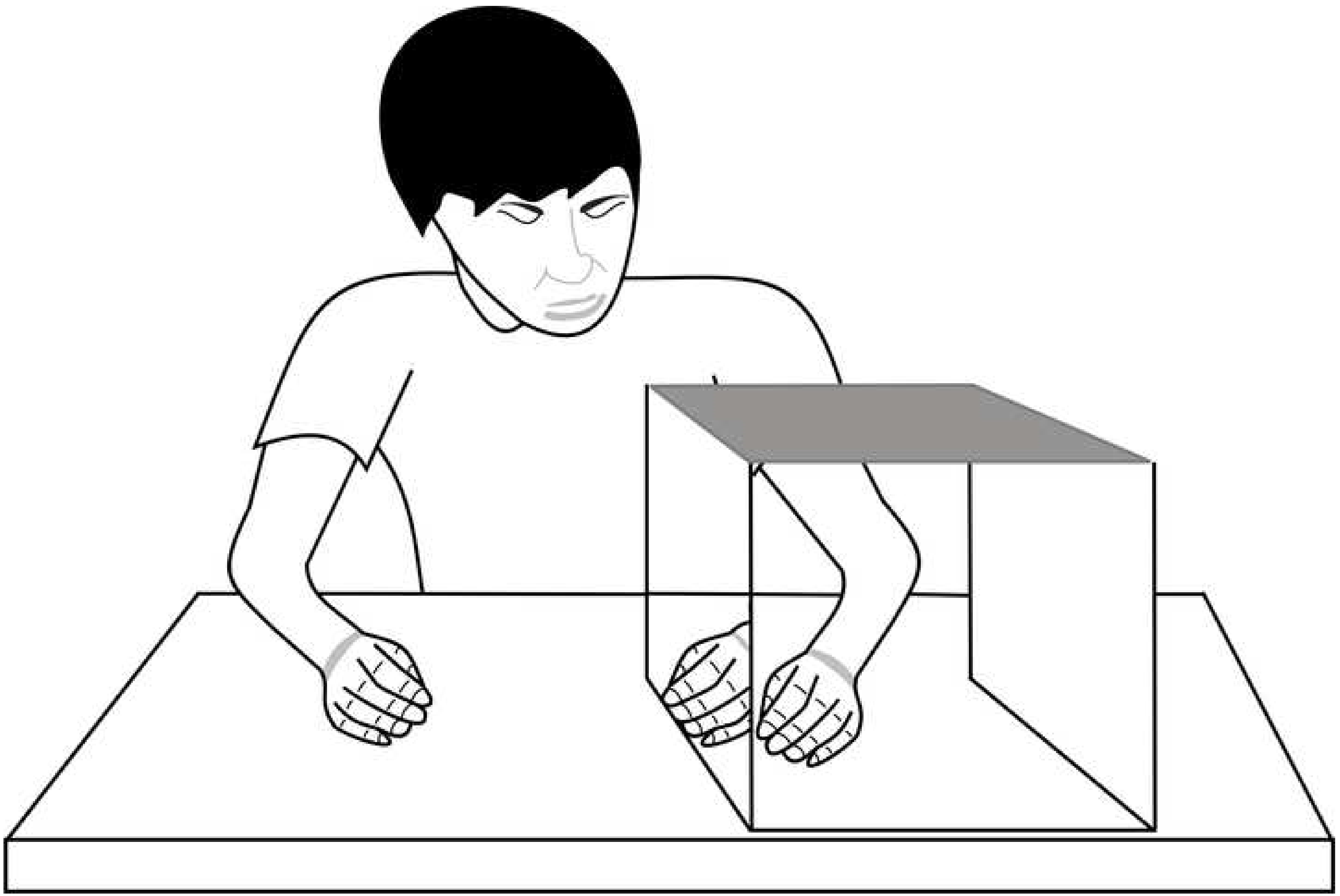
FIGURE LEGENDS

Figure 1. *Illustrative diagram of the procedure of the mirror illusion*. The left hand of the subject is hidden from view within the opaque box so that the subject sees only the reflected image of his right hand which he then interprets as his left hand.



Table

Table 1. Clinical status in the two study groups.

	Healthy Controls	**FMS**
Fibromyalgia Impact Questionnaire (FIQ)	–	88.38 (2.72)
Brief Pain Inventory – Short Form	0.16 (0.09)	7.39 (0.37) **
Pain intensity (Visual Analogue Scale)	0.15 (0.12)	8.89 (0.28) **
SF12 – Physical Component Summary	53.68 (1.23)	23.10 (0.82) **
SF12 – Mental Component Summary	54.08 (2.09)	33.27 (1.98) **

Subjects in the FMS sample had lower health indicators in terms of physical and mental summary scales of the 12-Item Short-Form Health Survey (SF-12), and exhibited significantly higher levels of clinical pain intensity on the VAS. The Fibromyalgia Impact Questionnaire (FIQ) was administered only to FMS subjects. Data are presented as mean (SEM).
** $p<0.01$ on the Student's *t*-test for independent samples.

Table

Table 2. Details on the locations of referred somatosensory sensations upon mechanical stimulation to those body sites reported by each subject as most painful.

Subject ID	Stimulation site	Referral
FMS 1	Right hip	Right groin
	Posterior cervical region	Occipital region
	Left shoulder blade	Not referred
FMS 2	Right hip	Right thigh
	Left thigh	Not referred
	Left deltoid region	Not referred
FMS 3	Right elbow	Not referred
	Low back	Not referred
	Left knee	Not referred
FMS 4	Right shoulder blade	Not referred
	Right gluteal region	Not referred
	Left knee	Not referred
FMS 5	Low back	Gluteal region
	Left groin	Not referred
	Right groin	Not referred
FMS 6	Posterior cervical region	Occipital region
		Left deltoid region
	Posterior aspect of left thigh	Left sural region
	Right elbow	Right antebrachial region
FMS 7	Posterior aspect of left arm	Left thenar eminence
		Left elbow
	Left half of sacrum	Left hypothenar eminence
	Posterior neck	Not referred
FMS 8	Anterior aspect of right thigh	Not referred
	Anterior aspect of left thigh	Not referred
	Posterior aspect of left thigh	Not referred
FMS 9	Low back	Left elbow
	Right deltoid region	Right palmar region
	Posterior cervical region	Not referred
FMS 10	Low back	Infrascapular region
		Posterior cervical region
		Left brachial region
	Posterior aspect of right thigh	Lumbar region
	Posterior cervical region	Not referred
FMS 11	Posterior cervical region	Not referred
	Posterior aspect of left thigh	Not referred
	Low back	Not referred
FMS 12	Low back	Posterior cervical region
	Left scapular region	Not referred
	Posterior cervical region	Not referred
FMS 13	Right scapular region	Posterior cervical region

	Left elbow	Left antebrachial region
	Right lateral cervical region	Not referred
FMS 14	Left deltoid region	Not referred
	Posterior cervical region	Not referred
	Right gluteal region	Not referred

Table

Table 3. Anomalous sensations triggered by visuo-proprioceptive incongruence in the FMS sample.

Feedback items	Healthy Controls	FMS	Effect size Cohen's *d* (95% CI)
Anomalous sensation in shape and location domain			
1. *I felt that my hidden limb has changed in shape.*	1.07 (0.07)	2.57 (0.34) **	1.62 (0.73, 2.51)
2. *I felt that my hidden limb was larger.*	1.07 (0.07)	2.57 (0.34) **	1.62 (0.73, 2.51)
3. *I felt that my hidden limb was smaller.*	1.07 (0.07)	2.35 (0.28) **	1.62 (0.74, 2.51)
4. *I felt that my hidden limb was swollen.*	1.15 (0.15)	3.35 (0.34) **	2.25 (1.36, 3.23)
5. *I felt that my hidden limb was distorted.*	1.23 (0.23)	2.92 (0.33) **	1.58 (0.70, 2.46)
6. *I felt that my hidden limb was in a different location*	1.76 (0.34)	3.35 (0.30) **	1.33 (0.48, 2.18)
Anomalous sensation in thermal, paraesthesia and pain domain			
7. *I felt that my hidden limb was colder*	1.07 (0.07)	1.78 (0.15) **	1.59 (0.70, 2.47)
8. *I felt that my hidden limb was hotter*	1.30 (0.23)	2.28 (0.28) **	1.02 (0.20, 1.84)
9. *I felt that my hidden limb has changed in weight*	1.76 (0.36)	3.50 (0.29) **	1.45 (0.58, 2.31)
10. *I felt pressure in my hidden limb*	1.07 (0.07)	3.28 (0.33) **	2.42 (1.41, 3.44)
11. *I felt fatigue in my hidden limb*	1.69 (0.32)	3.07 (0.30) **	1.19 (0.35, 2.02)
12. *I felt tingles in my hidden limb*	1.30 (0.23)	2.64 (0.28) **	1.38 (0.52, 2.23)
13. *I felt cramps/jabs in my hidden limb*	1.00 (0.00)	1.85 (0.14) **	2.27 (1.28, 3.25)
14. *I felt pain in my hidden limb*	1.00 (0.00)	3.21 (0.40) **	2.05 (1.10, 3.00)

Feedback items are assessed by using 5-point Likert scale (1 – *totally disagree*, 5 – *totally agree*). Data are presented as means (SEM), and effect size is provided as Cohen's *d* (95% CI); ** p<0.01 on the Mann-Whitney-Wilcoxon *U*-test.