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Impairment of the rubber hand illusion in focal hand dystonia

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Patients with dystonia display a number of disturbances in the cognitive processing of movements, such as movement simulation and prediction, but whether these deficits point to a deeper rooted disturbance of perceptual bodily representations remains unknown. A useful way to investigate the sense of body ownership is the rubber hand paradigm, in which an illusion of ownership is established by synchronous stroking of the participants' real unseen hand and a visible fake hand, whereas similar asynchronous stroking does not bring about the illusion. This paradigm allows testing of both the subjective experience of feeling ownership over the rubber hand and the proprioceptive relocation of the real unseen hand towards the viewed rubber hand. Previous studies have mapped these different aspects onto two anatomically distinct neuronal substrates, with the ventral premotor cortex processing the illusory feeling of ownership and the inferior parietal lobule and cerebellum processing proprioceptive drift. We applied the rubber hand illusion task to healthy subjects and to patients affected by two different types of focal dystonia—one specifically affecting the hand (focal hand dystonia) and one not affecting the hand (torticollis and blepharospasm). Results showed that in patients with focal hand dystonia, the proprioceptive drift was selectively disrupted on the dystonic hand while the subjective experience of the illusion was retained. In the non-dystonic hand and in the other two groups (non-hand dystonia and healthy subjects), the rubber hand illusion resembled the typical pattern with synchronous stroking eliciting the illusion. These findings provide support for the contention that the mechanisms underlying the presence of the illusory feeling of ownership and the proprioceptive drift are different. Selective impairment of the limb recalibration on the dystonic hand points to underlying deficits in integrating the visual-tactile input with the proprioceptive information in order to update the current body position and may support a model linking dystonia to dysfunctions in a network comprising the inferior parietal cortex and the cerebellum.

Keywords: focal dystonia; body ownership; rubber hand illusion; proprioception

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Introduction

The common definition of dystonia is that of a neurological syndrome characterized by continuous muscle contractions that cause abnormal movements and postures to the affected body parts (Bressman, 2004; Albanese and Lalli, 2009). Evidence suggests that difficulties occur even prior to movement execution, such as in movement planning, motor imagery, movement sequence learning and in mentally simulating movements (Ghilardi *et al*., 2003; Gilio *et al*., 2003; Quartarone *et al*., 2005; Fiorio *et al*., 2006, 2008*a*). Since movement representation and prediction rely on the presence of an internal dynamic model of the body (Wolpert *et al*., 1995), it could be hypothesized that impairments before movement execution in dystonic patients might be rooted in a deeper deficit, one that would possibly affect even the sense of the bodily self as an elementary feeling of self-consciousness.

A novel way to study the sense of body ownership is the so-called rubber hand illusion (Botvinick and Cohen, 1998). In this illusion, sensations of body ownership are referred to an alien limb. Subjects view an artificial hand, located next to their own hand, being continuously stroked by a paintbrush and simultaneously feel the touch of another paintbrush on their own unseen hand. After a few minutes of synchronous stroking, the subjects report to feel the touch not of the hidden brush, but of the viewed brush, as if the rubber hand had sensed the touch and belonged to their body (Botvinick and Cohen, 1998; Ehrsson *et al*., 2004, 2005; Tsakiris and Haggard, 2005; Longo *et al*., 2008). Both the subjective experience of feeling ownership over the rubber hand, evaluated through a questionnaire (Botvinick and Cohen, 1998), and the proprioceptive relocation of the unseen real hand towards the viewed rubber hand (Tsakiris and Haggard, 2005) can be investigated.

The phenomenon of the rubber hand illusion is associated with activity in a limited number of multisensory areas, which include the premotor cortex, the intraparietal cortex and the cerebellum (Ehrsson *et al*., 2004). However, there seems to be a behavioural and anatomical dissociation between the degree to which the rubber hand feels like part of one's body, and the perceived (re)location of one's body (Ehrsson *et al*., 2004; Longo *et al*., 2008; Kammers *et al*., 2009*a*, *b*). In this regard, a significant relationship has been demonstrated between bilateral ventral premotor activity and subjective ratings of ownership during the rubber hand illusion (Ehrsson *et al*., 2004). Additionally, activity in the inferior parietal lobule (Ehrsson *et al*., 2004; Kammers *et al*., 2009*a*) and cerebellum (Ehrsson *et al*., 2004) seems to be implicated in the recalibration of the perceived position of one's own limb. Hence, the rubber hand illusion may be a way to explore two distinct neuronal circuits involved in the subjective sense of body ownership and in limb recalibration. The mapping of two different behavioural variables to distinct anatomical regions makes the rubber hand illusion a unique behavioural tool for exploring cortical regions (Carbon and Eidelberg, 2009) possibly implicated in novel concepts regarding the pathophysiology of dystonia. While traditional models implicate cortico-striato-pallido-thalamocortical loops (Berardelli *et al*., 1998; Vitek, 2002), recent evidence emphasizes contributions from cerebello-cortical circuits (Argyelan *et al*., 2009).

The aim of this study was to investigate whether or not the sense of body ownership is impaired in patients affected by dystonia and whether or not any impairment might be generally ascribed to the underlying dystonic pathology, independently from the localization of motor symptoms. We applied the rubber hand illusion paradigm to both hands in patients affected by writer's cramp, a focal dystonia in which motor symptoms are localized to one hand, in patients with torticollis and blepharospasm, in which the dystonia does not affect the hand, and in healthy subjects. We predicted that if the sense of body ownership is generally affected by the pathophysiology underlying the dystonic disease, it should be equally impaired in the two forms of dystonia, i.e. focal hand and non-hand dystonia. Conversely, if factors related to the dystonic phenotype are primarily important for the illusion to be established, then we should find impairment only in the affected hand of patients with focal hand dystonia, but not in patients with torticollis and blepharospasm.

Materials and methods

Subjects

We recruited a total of 30 consecutive outpatients affected by dystonia. Patients belonged to one of the following groups.

Focal hand dystonia

This group consisted of 15 patients (seven females and eight males, mean age 45.9 $\pm$ 5.6 years) affected by writer's cramp in the dominant hand (14 right handed and one left handed). Five patients were affected by simple writer's cramp and the remaining patients by dystonic cramp. Inclusion criteria were the absence of other neurological disease (apart from dystonia) and normal or corrected to normal sight. Disease duration ranged from 2 to 32 years (mean 11.7 $\pm$ 9.3 years). Severity of motor impairment was evaluated by using the Burke-Fahn–Marsden movement scale (Burke *et al*., 1985), ranging from 0 = no dystonia present to 4 = severe, no useful grasp. Mean severity score was 2.1 $\pm$ 0.6. Eight patients were untreated; the remaining patients had received treatment with botulinum toxin no later than 3 months before the study. Detailed demographic and clinical information is provided in Table 1.

Non-hand dystonia

This group consisted of 15 patients (10 females and five males, mean age 49.1 $\pm$ 6.1 years) affected by motor symptoms in body regions other than the hand. Thirteen patients were affected by torticollis, which is characterized by muscle contractions on the neck region, whereas two patients were affected by blepharospasm, in which symptoms are localized in the orbicularis oculi muscles. Inclusion criteria were the absence of other neurological disease (apart from dystonia) and normal or corrected to normal sight. Duration of disease ranged from 6 months to 25 years (mean 11.1 $\pm$ 8.5 years). In patients with torticollis, severity of motor impairment was evaluated with the Toronto Western Spasmodic Torticollis Rating Scale, ranging from 0 to 35 (Consky and Lang, 1994). Mean severity score of these patients was 14.5 $\pm$ 4.6. In the two patients with blepharospasm, severity of motor symptoms was evaluated with the

Table 1 Demographic and clinical information for patients with dystonia

Patient/gender	Age (years)	Type of dystonia	Disease duration (years)	Severity score[a]	Therapy
1/M	44	DWC	7	2	BTX
2/M	50	DWC	28	1.5	BTX
3/M	39	DWC	2	2	BTX
4/M	50	DWC	16	2.5	BTX
5/M	55	DWC	12	2.5	BTX
6/F	47	DWC	20	3	BTX
7/F	57	DWC	32	2.5	No
8/F	43	SWC	4	2	No
9/M	44	DWC	2	2.5	No
10/F	41	DWC	10	2	No
11/F	45	SWC	3	2	No
12/M	50	SWC	10	1	No
13/F	41	SWC	14	1	No
14/M	38	DWC	2	2	No
15/F	44	SWC	13	3	No
1/F	50	T	22	14	BTX
2/F	56	T	17	19	BTX
3/M	37	T	1	19	BTX
4/M	44	T	8	15	BTX
5/M	46	T	1	9	BTX
6/F	54	T	25	5	BTX
7/F	46	T	10	16	BTX
8/M	55	T	16	20	BTX
9/F	54	T	21	17	BTX
10/F	51	T	5	13	BTX
11/F	45	T	6	12	BTX
12/F	39	T	23	9	BTX
13/M	57	T	32	17	BTX
14/F	52	B	12	3	BTX
15/F	50	B	0.5	3	BTX

a Writer's cramp (Burke *et al*., 1985), torticollis (Consky and Lang, 1994), blepharospasm (Fahn, 1989). B = blepharospasm; BTX = botulinum toxin; DWC = dystonic writer's cramp; No = no treatment; SWC = simple writer's cramp; T = torticollis.

Fahn scale, ranging from 0 = no blepharospasm present, to 4 = severe, forceful contractions (Fahn, 1989). Mean severity score of these patients was 3 ± 0. All the patients of this group had received treatment with botulinum toxin no later than 3 months before the study. Detailed demographic and clinical information is provided in Table 1.

We applied the same task to 24 healthy subjects (12 females and 12 males, mean age 44 ± 9.5 years). All participants, apart from one healthy subject and one patient with writer's cramp, were right-handed (Edinburgh Handedness Inventory, Oldfield, 1971). Participants were recruited at the Department of Neurology, University of Wuerzburg. Patients were informed of the non-therapeutic nature of the test and local ethical committee approval was obtained.

Procedure

We administered a modified version of the rubber hand illusion task described originally by Botvinick and Cohen (1998). Participants were seated in front of a table, with one arm resting on the table, inside a black box (Fig. 1A) and in a pronated position, while the other arm rested on the thigh. The dominant (affected in focal hand dystonia) and the non-dominant (unaffected) hands have been tested in all subjects in a counterbalanced order. Hands and arms were out of sight and covered by a black cloth smock. A realistic, life-sized plastic model of a hand was placed inside another black box on the table, directly in front of the subject in an anatomically plausible position and at a fixed distance from the real hand (20 cm medial to the real hand—distance of the index fingers of the real and the rubber hand). Only the rubber hand was visible through a lock cut above the box (16×20 cm). The subject was asked to focus on the rubber hand. In the meantime, two small paintbrushes were used to stroke both the rubber hand and the subject's hidden hand either synchronously or asynchronously, in separated sessions. The illusion should occur only following synchronous stroking, whereas identical asynchronous stroking should have no effect (Botvinick and Cohen, 1998). The brushstrokes were small and brisk, and applied to the dorsal surface of the index, middle and ring fingers for a time period of 2 min. Before and immediately after the stimulation trial, participants had to refer the felt index finger position by reporting the corresponding number on a ruler variably positioned over the boxes (Fig. 1B). This point was used as quantitative measure of the displacement in the perception of the real hand position (Tsakiris and Haggard, 2005). The perceived position of the hand before and after the stroking was measured with respect to a landmark, which was the edge of the box. This allowed us to have a precise and identical starting point of the ruler in all the subjects. The ruler onset and offset numbers changed every time, in order to avoid response biases. During the proprioceptive judgement, the rubber hand and the subjects' hand were out of view.

After the proprioceptive judgement, subjects were asked to rate the degree of agreement or disagreement with nine sentences taken from the original paper by Botvinick and Cohen (1998) and assessing the subjective experience of feeling ownership over the rubber hand. The sentences were read aloud by the experimenter in a randomized order of presentation across subjects. For each statement, the subjects could rate their agreement on a visual analogue scale (from 0 = completely disagree, to 10 = completely agree). The first three statements (Statement 1: 'It seemed as if I were feeling the touch of the paintbrushes in the location where I saw the rubber hand touched'; Statement 2: 'It seemed as though the touch I felt was caused by the paintbrushes touching the rubber hand'; Statement 3: 'I felt as if the rubber hand was my own hand') are thought to be directly representative of the presence of the illusion (Botvinick and Cohen, 1998). Another six sentences are inserted as control (Statement 4: 'It felt as if my hand were drifting toward the rubber hand'; Statement 5: 'It seemed as if I might have more than one hand or arm'; Statement 6: 'It seemed as if the touch I was feeling came from somewhere between my own hand and the rubber hand'; Statement 7: 'It felt as if my hand were turning "rubbery"'; Statement 8: 'It appeared as if the rubber hand were drifting towards my hand'; Statement 9: 'The rubber hand began to resemble my own hand') (Botvinick and Cohen, 1998).

The whole procedure was performed for the dominant (and affected in focal hand dystonia) and the non-dominant (and non-affected in focal hand dystonia) hands and with synchronous and asynchronous stroking, for a total of four conditions (dominant synchronous stroking; dominant asynchronous stroking; non-dominant synchronous stroking; non-dominant asynchronous stroking). The order of presentation of the four conditions was pseudo-randomized by balancing the order of the stimulated hand (right or left) and the order of stimulation (synchronous or asynchronous) separately across subjects. For each

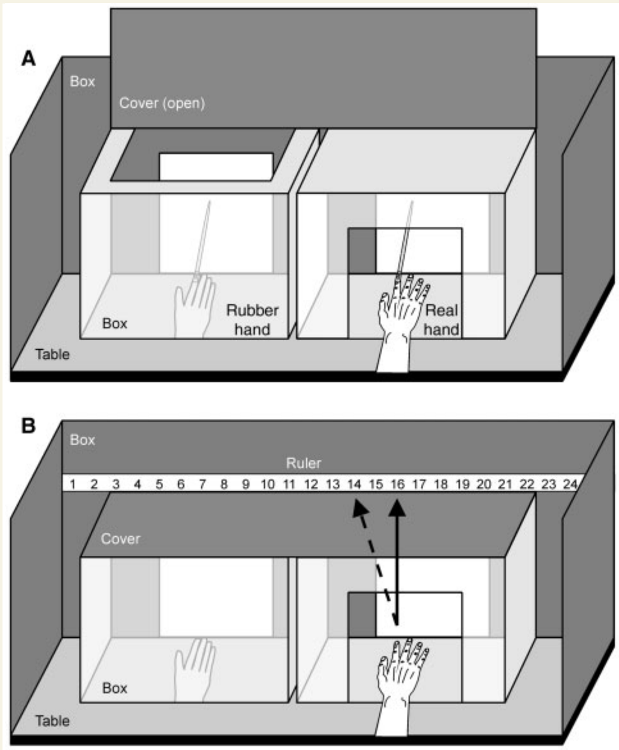

Figure 1 Schematic representation of the experimental set-up. Two black boxes (20 × 33 × 15 cm) were placed on a table. The box containing the rubber hand was open on the top and at the back, while the box in which subjects put their real hand was open in the front and at the back. Subjects' real hands and arms were out of sight. A paperboard was used to cover the boxes. During the stimulation phase (**A**), the cover was lifted and subjects could see the rubber hand from the top of the box and the stroking with the paintbrushes through the back lock. The experimenter was not visible. After the stimulation phase (**B**), the cover was drawn down and a ruler was introduced. Subjects had to report the number on the ruler corresponding to the felt position of their index finger. A drift in the felt position of the real hand towards the rubber hand is to be expected after synchronous stroking (dashed arrow) compared to the measure collected before the stimulation (continuous arrow).

condition there was one stimulation trial lasting 2 min. The proprioceptive judgement was required before and soon after each condition (for a total of eight measurements). The questionnaire was applied only after each stroking condition (for a total of four measurements), once the subjects gave the proprioceptive judgement.

Statistics

In each of the four experimental conditions, we measured the proprioceptive judgement regarding the hand position prior to stroking (baseline) and after stroking (final). The difference between the final and baseline judgements gave a measure of the so-called 'proprioceptive drift', that is the proprioceptive displacement of the real hand towards the rubber hand and was considered as an implicit indicator of the presence of the illusion (Tsakiris and Haggard, 2005). A drift in the perception of the real hand towards the rubber hand was expected only after synchronous stroking (Botvinick and Cohen, 1998). To compare the proprioceptive drift between groups, drifts of each subject were normalized as percentage change from baseline [(final-baseline)/baseline]. This procedure allowed inter-subject variability to be reduced. Normalized data were analysed for each hand separately by means of repeated measures ANOVA with 'Group' (focal hand dystonia, non-hand dystonia, healthy subjects) as between-subjects factor and 'Stroking' (synchronous versus asynchronous) as within-subjects factor. *Post hoc* comparisons were made by means of *t*-tests applying the Bonferroni correction for multiple comparisons where necessary.

In addition to the proprioceptive drift, we also analysed the ratings to the questionnaire (adapted by Botvinick and Cohen, 1998) after synchronous and asynchronous stroking of the dominant and the non-dominant hands. Judgements given to the three sentences strictly related to the feeling of ownership (Statements 1–3) and to the other six control statements (Statements 4–9), were analysed for each hand separately by means of repeated measure ANOVAs with 'Group' as between-subjects factor and 'Stroking' as within-subjects factor.

Finally, the Spearman's correlation coefficient was applied in order to assess any correlation between severity of disease in the two groups of dystonic patients and the proprioceptive drift after the synchronous and the asynchronous stroking. In all the analyses, $P < 0.05$ was considered significant.

Results

Preliminary analyses showed that before stroking the three groups of participants were accurate in reporting their real hand position, both of the dominant and non-dominant hand. No significant difference has been found between the felt hand position reported by the subjects on the ruler and the actual hand position measured by the experimenter (paired samples *t*-test, focal hand dystonia: $P > 0.080$ for both hands; non-hand dystonia: $P > 0.371$ for both hands; healthy subjects: $P > 0.158$ for both hands).

Proprioceptive drift

On the dominant hand (affected in focal hand dystonia), the factor 'Stroking' was significant [$F(1,51) = 7.49$; $P = 0.009$]. This effect was due to a higher proprioceptive drift after synchronous (mean ± SEM, 3.6 ± 0.7%) compared to asynchronous (1.6 ± 0.7%) stroking. The interaction 'Group' (focal hand dystonia, non-hand dystonia, healthy subjects) × 'Stroking' was also significant [$F(2,51) = 3.27$; $P = 0.046$; Fig. 2A]. *Post hoc* comparisons showed that healthy subjects had a higher proprioceptive drift after synchronous (3.5 ± 1.21%) compared to asynchronous (1.3 ± 1%) stroking ($P = 0.050$). A similar effect was observed in patients of the non-hand dystonia group (synchronous: 5.7 ± 0.9%, asynchronous: 1.5 ± 1.0%; $P = 0.009$). In contrast, patients with focal hand dystonia showed no significant difference between synchronous (1.6 ± 1.1%) and asynchronous (2.1 ± 1.4%) stroking ($P = 0.648$). Of note, this hand was affected in this group. The factor 'Group' was not significant ($P = 0.455$).

On the non-dominant hand (unaffected in focal hand dystonia), the factor 'Stroking' was significant [$F(1,51) = 9.33$; $P = 0.004$]. This effect was due to a higher proprioceptive drift after synchronous (6.3 ± 1.0%) compared to asynchronous (2.6 ± 0.8%) stroking. The interaction 'Group' × 'Stroking' was not significant

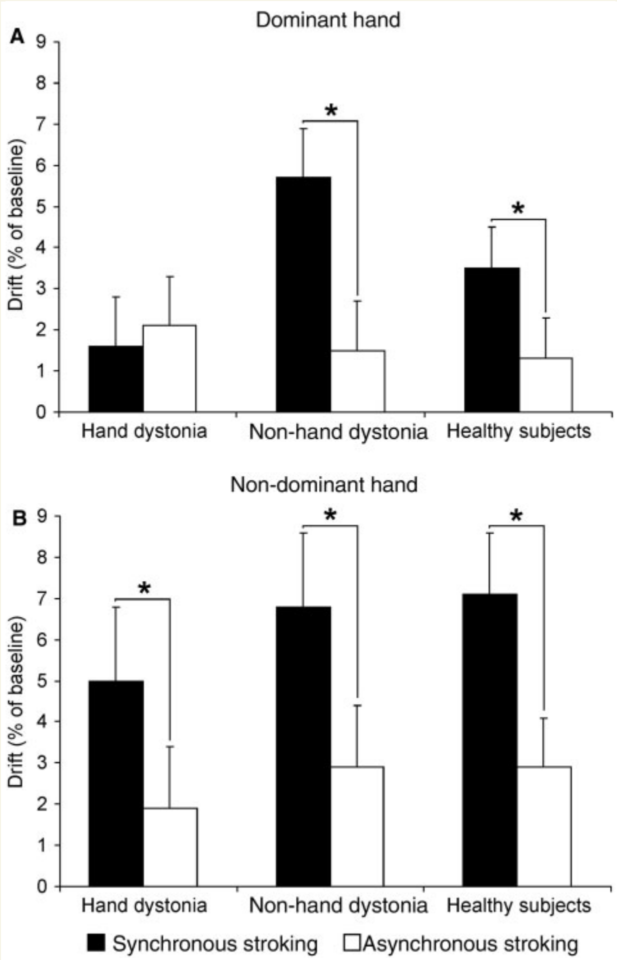

Figure 2 (**A**) Proprioceptive drift of the real dominant hand (affected in focal hand dystonia) towards the rubber hand. The group of patients with focal hand dystonia did not show the typical pattern of the rubber hand illusion in the synchronous compared to the asynchronous condition. (**B**) Proprioceptive drift of the real non-dominant hand (unaffected in focal hand dystonia) towards the rubber hand. In this case, even patients with focal hand dystonia showed the typical pattern of the illusion with synchronous stroking eliciting stronger proprioceptive drift than asynchronous stroking. The non-dominant hand was spared by motor symptoms in all the groups. Values are normalized as percentage change from baseline. Error bars represent standard errors. Asterisks indicate significant comparisons ($P < 0.050$).

($P = 0.937$), suggesting that a similar effect of stroking was present in all the three groups, as shown in Fig. 2B. The factor 'Group' was not significant ($P = 0.609$).

Questionnaire ratings

On the dominant hand (affected in focal hand dystonia), the factor 'Stroking' was significant in the first three statements strictly regarding the subjective experience of feeling ownership over the rubber hand [Statement 1: $F(1,51) = 12.3$; $P = 0.001$; Statement 2: $F(1,51) = 12.2$; $P = 0.001$; Statement 3: $F(1,51) = 8.6$; $P = 0.005$]. These effects were due to the fact that, in general, participants gave higher scores to the three statements after synchronous (Statement 1: 6.1 ± 0.6, Statement 2: 4.9 ± 0.6, Statement 3: 2.7 ± 0.5) compared to asynchronous (Statement 1: 4.6 ± 0.6, Statement 2: 3.1 ± 0.5, Statement 3: 1.6 ± 0.4) stroking. The lack of significance of the factor 'Group' ($P > 0.359$, for all three statements) and of the interaction 'Group' × 'Stroking' ($P > 0.516$, for all three statements) suggests that a similar effect of stroking was present in all the groups (Fig. 3A).

In the control Statement 6 we found a significant 'Group' × 'Stroking' interaction on the dominant hand [$F(2,51) = 4.1$; $P = 0.022$]. *Post hoc* comparisons showed that after synchronous stroking patients with focal hand dystonia gave a lower score (0.7 ± 0.4) to this sentence than patients with non-hand dystonia (3.4 ± 3.7) ($P = 0.040$). Moreover, patients of the focal hand dystonia group tended to give a higher score to this statement after asynchronous (1.9 ± 0.9) than synchronous stroking ($P = 0.051$). Finally, in the control Statement 9, the factor 'Stroking' was significant [$F(1,51) = 5.45$; $P = 0.024$] (Fig. 4A). This effect was due to the fact that, in general, participants gave higher scores to this sentence after synchronous (3 ± 0.5) compared to asynchronous (1.9 ± 0.4) stroking, in line with the notion that sense of ownership might cause perceived similarity (Longo *et al.*, 2009). The factor 'Group' ($P = 0.712$) and the interaction 'Group' × 'Stroking' ($P = 0.423$) were not significant for this statement.

On the non-dominant hand (unaffected in focal hand dystonia), the factor 'Stroking' was significant in the first three statements [Statement 1: $F(1,51) = 32.2$; $P < 0.001$; Statement 2: $F(1,51) = 13.2$; $P = 0.001$; Statement 3: $F(1,51) = 18.3$; $P < 0.001$]. These effects were due to higher scores to the after synchronous (Statement 1: 6.8 ± 0.5, Statement 2: 5 ± 0.6, Statement 3: 3 ± 0.5) compared to asynchronous (Statement 1: 3.8 ± 0.6, Statement 2: 2.8 ± 0.5, Statement 3: 1.2 ± 0.3) stroking. Again, the lack of significance of the factor 'Group' ($P > 0.197$, for all the three statements) and of the interaction 'Group' × 'Stroking' ($P > 0.240$, for all three statements) suggests that a similar effect of stroking was present in all of the groups (Fig. 3B).

The factor 'Stroking' on the non-dominant hand was significant in the control Statements 6 and 9 [Statement 6: $F(1,51) = 6.96$; $P = 0.011$; Statement 9: $F(1,51) = 4.66$; $P = 0.036$]. These effects were due to the fact that participants generally gave higher scores to these two sentences after synchronous (Statement 6: 2.4 ± 0.4, Statement 9: 2.8 ± 0.5) compared to asynchronous (Statement 6: 1.5 ± 0.3, Statement 9: 1.8 ± 0.4) stroking (Fig. 4B). The factor 'Group' ($P > 0.082$, for both statements) and the interaction 'Group' × 'Stroking' ($P > 0.332$, for both statements) were not significant for these two statements on the non-dominant hand. No other significant effects have been found. Performance to the other control statements of the questionnaire (Statements 4, 5, 7 and 8) is reported Supplementary Fig. 1.

Correlation analysis

The main analysis described above showed a lack of proprioceptive drift after synchronous stroking on the affected hand of patients with focal hand dystonia. The amount of proprioceptive drift, however, did not correlate with the severity of disease

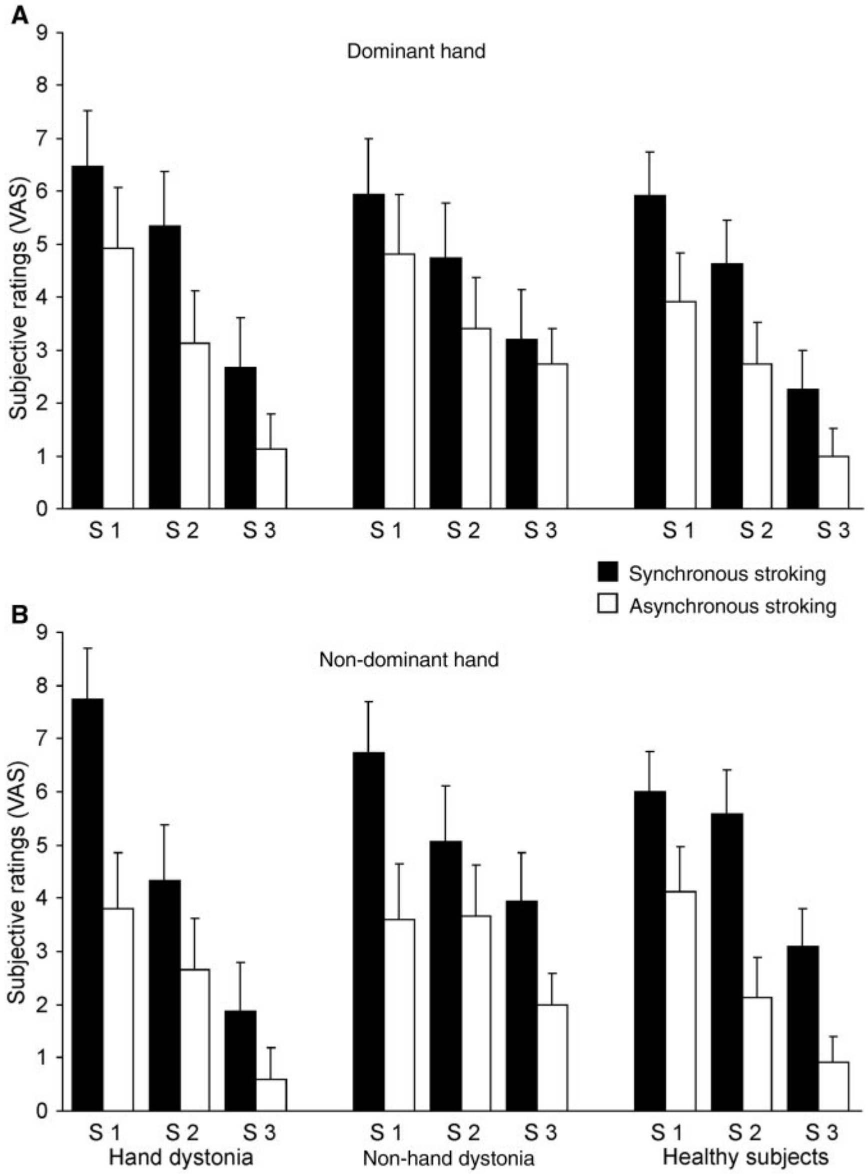

Figure 3 Questionnaire ratings of the three groups on the dominant (**A**) and non-dominant (**B**) hands after synchronous (black bars) and asynchronous (white bars) stroking in the three sentences related to the subjective experience of feeling ownership over the rubber hand (Statement 1: 'It seemed as if I were feeling the touch of the paintbrushes in the location where I saw the rubber hand touched'; Statement 2: 'It seemed as though the touch I felt was caused by the paintbrushes touching the rubber hand'; Statement 3: 'I felt as if the rubber hand was my own hand') (Botvinick and Cohen, 1998). Subjective ratings are higher after the synchronous than the asynchronous stroking, in all the three groups. Error bars represent standard errors. S = statement; VAS = visual analogue scale.

(Spearman's Rho = -0.232; $P = 0.406$), suggesting that, although the lack of drift is localized to the affected hand, it is independent from the severity of the motor deficit (Supplementary Fig. 2). The group of patients with non-hand dystonia did not show any significant correlation.

Discussion

The principal finding of this study is a highly specific impairment of the rubber hand illusion elicited in the dystonic hand of patients with focal hand dystonia. More precisely, during the synchronous stroking patients did not feel their own affected hand displaced towards the rubber hand, whereas they subjectively experienced the illusory ownership (Statements 1–3). As will be outlined below, the specific pattern of failure of limb recalibration, but not of the subjective feeling of ownership, and the fact that this abnormality was confined to the impaired body district may have important implications for understanding the pathophysiology of focal hand dystonia.

Healthy participants and patients with dystonia not affecting the hand, i.e. torticollis and blepharospasms, displayed the typical

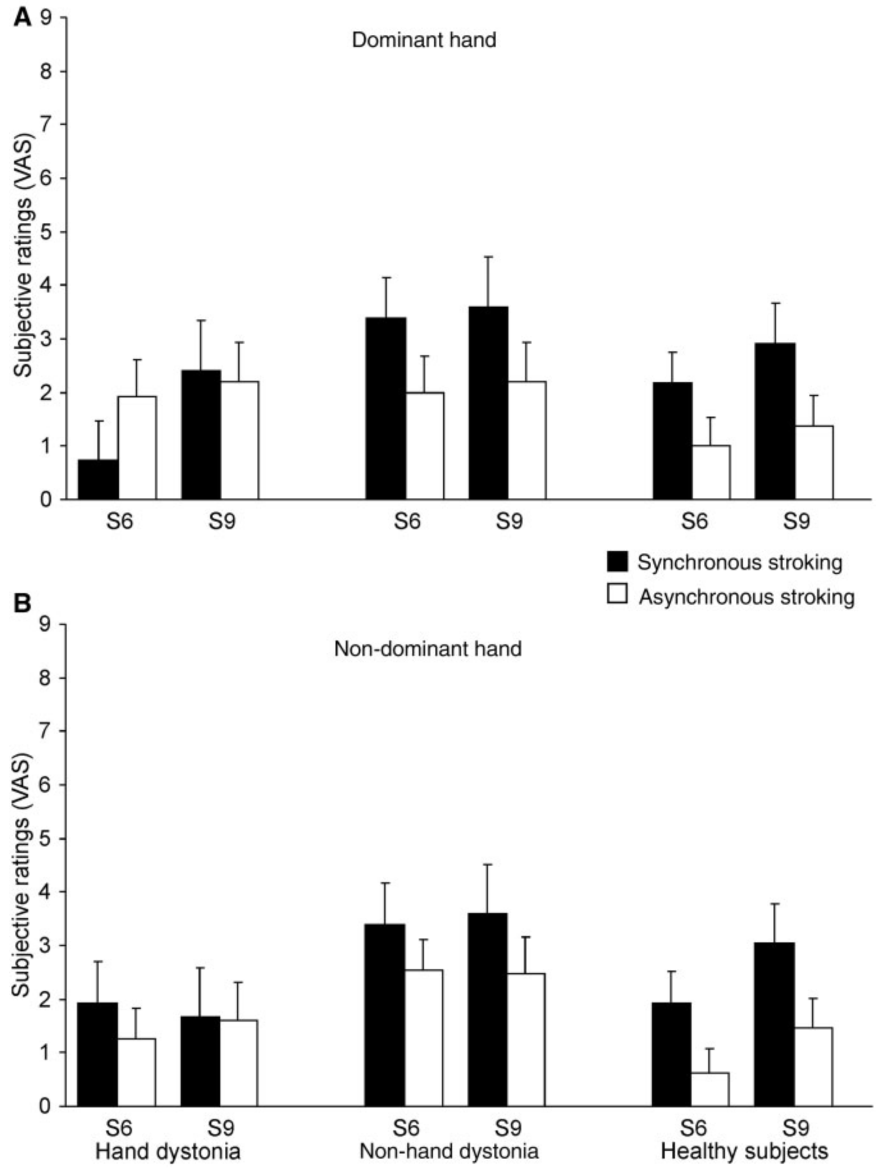

Figure 4 Questionnaire ratings of the three groups on the dominant (**A**) and non-dominant (**B**) hands after synchronous and asynchronous stroking in two control statements of the questionnaire (Statement 6: 'It seemed as if the touch I was feeling came from somewhere between my own hand and the rubber hand'; Statement 9: 'The rubber hand began to resemble my own hand') (adapted from Botvinick and Cohen, 1998). Error bars represent standard errors. Note that subjective ratings of focal-hand dystonia patients to Statement 6 are lower after synchronous than asynchronous stroking on the affected hand. S = statement; VAS = visual analogue scale.

pattern of the rubber hand illusion on both hands (Botvinick and Cohen, 1998; Ehrsson *et al*., 2004; Tsakiris and Haggard, 2005; Longo *et al*., 2008). After synchronous stroking, the first three statements, which strictly related to the illusion, received higher rating scores (indicating subjective feeling of ownership over the rubber hand) and the perceived position of the hand was nearer to the rubber hand (indicating a hand proprioceptive drift towards the rubber hand) than after asynchronous stroking. The apparently stronger illusion on the non-dominant compared to the dominant hand, qualitatively observed in all three groups (Figs 2 and 3), might be related to the relevance of the right hemisphere in the rubber hand illusion (Ocklenburg *et al*., 2010). A normal pattern of the rubber hand illusion was observed in the non-dystonic hand of patients with focal hand dystonia. This suggests that the sense of body ownership elicited by the rubber hand illusion is not generally disturbed by the dystonic pathology *per se*.

The breakdown of limb recalibration in focal hand dystonia was present only unilaterally, on the affected hand. The lack of correlation between severity scores and the proprioceptive drift may suggest that failure in recalibrating the limb, although lateralized to the affected body district, is not a direct expression of the process that causes the motor symptoms, but occurs independently from it. It is conceivable that this failure in focal hand dystonia is due to a kinaesthetic dysfunction. Support of this hypothesis comes from previous studies showing that kinaesthesia (sense of movement) is impaired in patients with focal hand dystonia, despite a normal joint position sense (Grunewald *et al*., 1997; Rome *et al*., 1999; Yoneda *et al*., 2000). Our results are in line with this evidence. Namely, we found that the position sense of the real hand before stroking was accurate, whereas hand displacement during stroking, which might imply intact kinaesthetic signals to inertly shift the real hand towards the rubber hand, was lacking. It is noteworthy that contrary to previous studies, in which proprioceptive abnormalities have been described bilaterally and symmetrically in focal hand dystonia (Grunewald *et al*., 1997; Rome *et al*., 1999), in our study the lack of proprioceptive drift was present only unilaterally. This divergent finding might depend on the different tasks used, i.e. movement illusion induced by tendon vibration in the previous studies versus illusory limb recalibration induced by the rubber hand illusion in our study. Moreover, in the previous studies, patients had to track the amplitude or speed of the passively moved limb with the other limb and therefore any subclinical dysfunction of the tracking arm might have influenced the performance. Conversely, in our study, we tested the rubber hand illusion effect on one hand at a time. Furthermore, it should be noted that in the rubber hand illusion not only proprioception, but also other sensory modalities (visual and tactile) are involved and integrated (Botvinick and Cohen, 1998; Ehrsson *et al*., 2004). The illusion, indeed, can only occur if proprioception is distorted by the synchronous visual and tactile inputs. Therefore, the lack of hand relocation could, in principle, be ascribed to purely visual or tactile dysfunctions, to a deficit in integrating visual and tactile inputs or to a deficit in overwriting the visual-tactile input on the proprioceptive information. In this regard, previous studies have shown that while the processing of visual inputs is accurate in focal hand dystonia, the elaboration of tactile stimuli and the integration of visual and tactile inputs are impaired (Fiorio *et al*., 2003). These deficits, however, have been found both on the dystonic and healthy hand (Fiorio *et al*., 2003), whereas in the current study, impairment of limb relocation was present only in the affected hand. Moreover, we did not find impairment of limb recalibration in patients with cervical dystonia and blepharospasm, in spite of deficits of visual-tactile integration previously described in these groups (Tinazzi *et al*., 2004; Fiorio *et al*., 2008*b*). Based on these considerations, we consider it most likely that the selective breakdown of limb recalibration of the dystonic hand is due to a failure in integrating the synchronous visual-tactile input with the proprioceptive location sense arising from an underlying kinaesthetic deficit.

Interestingly, some marginal aspects of the subjective experience of ownership were compromised on the dystonic limb of patients with focal hand dystonia. In particular, it is interesting to note that patients gave higher scores for Statement 6 ('... touch ... came from somewhere between my own hand and the rubber hand') after asynchronous than synchronous stroking on the affected hand. Although this question was originally thought as control (Botvinick and Cohen, 1998), it refers to a sense of touch localized in-between the real and the rubber hand. An abnormal pattern at this statement might be in line with the lack of proprioceptive drift of the affected hand towards the rubber hand and it might suggest that patients did not subjectively feel the hand displacement, despite feeling the rubber hand like part of their body (Statement 3). In the non-affected hand, instead, patients with focal hand dystonia showed a similar pattern of results to the other two groups. This suggests an asymmetrical rubber hand illusion effect on the two hands of patients with focal hand dystonia, with the affected hand having an abnormal pattern compared to the non-affected hand. Furthermore, a qualitative inspection of Fig. 4 suggests that, in contrast to the other two groups, patients with focal hand dystonia appear to be less susceptible to judge the rubber hand as similar to their own hand (Statement 9). Finding an impairment in some secondary aspects of the subjective experience of the illusion (Statements 6 and 9) might hint at a slight damage of the higher order construct of the body. Hence, given that body ownership may 'arise[s] as an interaction between multisensory input and modulation exerted by stored on-line internal models of the body' (Tsakiris, 2010), we assume that in focal hand dystonia, a failure might be present in integrating visual-tactile and proprioceptive information with the internal representation of the affected body side, thus hindering the updating of the current body state to the position of the rubber hand. Nevertheless, the fact that patients declared to have sensed the rubber hand as their own hand (Statement 3) might suggest that they are still able to incorporate an external body part in their own body (Tsakiris, 2010). Reliance on visual information (in spite of proprioceptive deficits) (Fiorio *et al*., 2003), could have been sufficient to induce the subjective experience of the illusion when associated with synchronous tactile feeling (Botvinick and Cohen, 1998; Botvinick, 2004; Hagura *et al*., 2007). We would argue that to some extent, the subjective feeling of ownership is still possible due to the integration of the spare visual information with a feeble internal body representation of the affected side.

Evidence that the personal experience of the illusory ownership sensation and illusory spatial displacement of the limb might be two dissociate aspects of the rubber hand illusion, with different neural underpinnings, derives from behavioural, psychometric, imaging and transcranial magnetic stimulation studies in healthy subjects (Ehrsson *et al*., 2004, 2005; Longo *et al*., 2008; Kammers *et al*., 2009*a*, *b*). In particular, imaging studies have demonstrated a positive correlation between activity in the ventral premotor cortex, but not other activated cortical regions, and the subjective ratings of the illusion, thus suggesting that this region, but not others, is implicated in the subjective sense of body ownership (Ehrsson *et al*., 2004, 2005). Even more direct evidence supporting the hypothesis that limb recalibration and subjective feeling of ownership might have distinct neuronal underpinnings has been demonstrated in a study utilizing a virtual-lesion approach in healthy subjects (Kammers *et al*., 2009*a*). Disruption of the inferior parietal lobule by repetitive transcranial magnetic stimulation resulted in impaired hand relocation, without impairing the subjective feeling of ownership over the rubber hand (Kammers *et al*., 2009*a*). This work suggests that the inferior parietal lobule might be specifically involved in the process of limb recalibration during the rubber hand illusion, although it did not exclude that other regions might be involved.

Against this background in healthy subjects, the present findings may be the first to demonstrate that the dissociation between subjective body ownership and impaired limb recalibration is pathophysiologically relevant. The predominant failure of the rubber hand illusion to generate a proprioceptive drift in the dystonic hand may suggest an abnormality in the brain regions associated with recalibration of limb positioning, such as the intraparietal cortex, the dorsal premotor cortex, the supplementary motor area, the cerebellum, the putamen and the ventral thalamus (Ehrsson *et al*., 2004, 2005). Some of these regions conspicuously overlap with a brain network implicated by recent models of the pathogenesis of dystonia (Eidelberg *et al*., 1998; Trošt *et al*., 2002; Carbon *et al*., 2004, 2010; Delmaire *et al*., 2007; Argyelan *et al*., 2009). In particular, a parallel can be drawn between hyperactivation of the inferior parietal lobule and cerebellar abnormalities in different forms of dystonia (Eidelberg *et al*., 1998; Delmaire *et al*., 2007; Argyelan *et al*., 2009; Carbon and Eidelberg, 2009; Carbon *et al*., 2010) and the involvement of these regions in the limb recalibration process during the rubber hand illusion (Ehrsson *et al*., 2004, 2005; Kammers *et al*., 2009*a*). The parietal cortex and the cerebellum are involved in processing kinaesthetic information (Naito *et al*., 2005; Proske and Gandevia, 2009) and the cerebellum is also involved in updating limb position (Hagura *et al*., 2009). As the inferior parietal lobule and the cerebellum are connected (Clower *et al*., 2001), these observations strengthen the hypothesis that dysfunctions in a circuit involving these two structures might have impaired a proper limb recalibration during the rubber hand illusion in patients with focal hand dystonia. On the other side, since the feeling of body ownership (Statements 1–3) was present in the dystonic hand, we would suggest that the ventral premotor cortex is functioning. However, the precise contribution of this region to our findings is not completely clear, as some aspects of the illusory subjective feeling (Statement 6) were also found to be impaired.

Together, our findings may represent evidence of dissociation between the subjective feeling of ownership and the proprioceptive feeling of displacement, with impairment of the latter being associated with motor symptoms in focal hand dystonia. This may indicate that the mechanisms underlying the two dimensions of the rubber hand illusion are different. Dystonic motor symptoms may selectively impair the limb recalibration process, possibly due to underlying deficits in integrating the visual-tactile input with the proprioceptive information. Impairment of limb recalibration may point to dysfunction in a neural network involving the inferior parietal lobule and the cerebellum. Whether dystonia is the cause or the effect of the inability to displace the real dystonic hand towards the rubber hand cannot be decided on the basis of the present data and deserves further investigation.

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Supplementary material

Supplementary material is available at *Brain* online.

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