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Pathophysiological differences between musician's dystonia and writer's cramp

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Summary

Focal hand dystonia (FHD) has been suggested to be a maladaptive response of the brain to repetitive performance of stereotyped and attentionally demanding hand movements. However, not all patients with FHD have a strict history of excessive hand use; for example, patients with musician's dystonia (MD) spend many hours per day with their attention focused on instrumental practice, whereas many patients with writer's cramp (WC) have a history of average hand use. The present experiments test whether seven MD and six WC patients have different pathophysiological deficits by examining the spatial pattern of sensorimotor organization in the motor cortex. Two control groups were used, eight healthy non-musicians and eight healthy musicians. The latter served to control for physiological adaptation of the brain to musical training. We used focal vibration of a single hand muscle to produce sensory input whilst the excitability of corticospinal outputs to the vibrated and other hand muscles was evaluated with transcranial magnetic stimulation. In healthy non-musicians, vibration increases the amplitude of motor-evoked potentials and decreases the short-latency intracortical inhibition (SICI) in the vibrated muscle, whilst having the opposite effect on the non-vibrated hand muscles. The pattern of sensorimotor interaction was abnormal in both patient groups. However, the nature of the deficit differed between them. While vibration had little effect on cortical excitability in WC, it strongly reduced SICI in all hand muscles irrespective of spatial organization in MD. In the healthy musicians we found an organization intermediate between that of healthy non-musicians and MD. The data are consistent with a model in which musical practice in healthy musicians leads to beneficial changes in organization of the motor cortex, but in MD these progress too far and begin to interfere with movement rather than assist it. The fact that sensory input had no effect on motor output in patients with WC suggests that sensory information from the hand may play a smaller role in provoking pathological changes in WC than in MD.

Keywords: focal hand dystonia; musician's dystonia; sensorimotor integration; transcranial magnetic stimulation; writer's cramp

Abbreviations: ADJ-SI = adjusted stimulus intensity; ADM = adductor digiti minimi; AMT = active motor threshold; APB = abductor pollicis brevis; BFM score = Burke–Fahn–Marsden score; FDI = first dorsal interosseus; FHD = focal hand dystonia; GABA = gamma-aminobutyric acid; ICF = intracortical facilitation; ISI = interstimulus interval; MD = musician's dystonia; MEP = motor-evoked potential; SI = stimulus intensity; SICI = short latency intracortical inhibition; TMS = transcranial magnetic stimulation; WC = writer's cramp

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Introduction

Writer's cramp (WC), musician's dystonia (MD), embouchure dystonia, telegraphist's cramp or the 'yips', in golfers, are all regarded as task-specific forms of focal hand dystonia (FHD) with symptoms that occur only when patients perform certain tasks, such as writing or playing a musical instrument. Performance of other fine motor tasks, even if they involve the same muscles, can be unimpaired.

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An influential model of FHD based on an animal study by Byl *et al*. (1996) suggests that these forms of dystonia may reflect a maladaptive response of the brain to repetitive performance of stereotyped movements. It postulates that the usual processes of reorganization that accompany learning of new tasks can be pushed to an extreme where they begin to interfere with task performance rather than improving it. The model predicts that the patterns of presymptomatic hand movements, in terms of amount of repetition, complexity, stereotypy and attentional demand, are important factors for the development of dystonia. However, although patients with some forms of FHD have a history of excessive hand use and fit this model, patients with other forms of FHD may use their hands to a similar extent to that seen in normal subjects.

The aim of this study was to examine the pathophysiological changes in two common forms of FHD, WC and MD, in which patients differ considerably in their history of hand use. Many WC patients have a history of average hand use, whereas musicians are spend many hours per day with their attention focused on instrumental practice. The importance of the latter is demonstrated by the fact that MD occurs more often in pianists and classical guitarists, two instruments that are known to be practice intensive (Lim *et al*., 2001). Although WC has been studied by many authors, investigations on MD are rare, even though it often has profound effects on a professional career and is more common amongst professional musicians than is WC in the general population (Altenmueller, 1998).

There is one potential problem in making a direct comparison between these groups. Brain imaging studies show that years of musical training induce changes in the brain's anatomy and function in musicians and these may affect any conclusions that can be drawn. We have therefore included two control groups, one of healthy musicians and one of non-musicians. The healthy musicians were matched to our MD patients for the age at which they started playing their instrument, since this is the most important factor in determining functional and structural changes in the brain (Elbert *et al*., 1995; Amunts *et al*., 1997; Schlaug, 2001; Muente *et al*., 2002).

In the present experiments we examined the pattern of sensorimotor organization in the motor cortex. This is because a large number of recent studies have revealed a variety of sensory deficits in the hands of patients with FHD. For example, patients show impaired performance in spatial and temporal discrimination tasks (Bara-Jimenez *et al*., 2000*a*, *b*; Sanger *et al*., 2001; Tinazzi *et al*., 2002), changes in single and paired somatosensory-evoked potentials (SEPs) (Tinazzi *et al*., 2000; Frasson *et al*., 2001), and alterations in the spatial distribution of SEPs or functional imaging maps, suggestive of changes in the underlying somatosensory maps of the hand (Bara-Jimenez *et al*., 1998; Elbert *et al*., 1998; Butterworth *et al*., 2003). Others have emphasized that the important feature of FHD is an abnormal link between sensory input and motor output. In healthy subjects the pattern of sensorimotor interaction in the hand is relatively focal, with input from one digit having maximum influence on the excitability of muscles that control the same digit (Classen *et al*., 2000; Tamburin *et al*., 2001). In patients with FHD this pattern is less clear and the influence of a focal sensory input much more widespread (Tamburin *et al*., 2002).

The technique we use here was developed in a previous paper (Rosenkranz and Rothwell, 2003) and probes how sensory input interacts with motor output in the hand area of the human motor cortex. Sensory input is provided by short periods of focal muscle vibration applied to one intrinsic hand muscle while corticospinal excitability is tested by measuring the amplitude of motor evoked potentials produced by a standard intensity of transcranial magnetic stimulation (TMS) pulse in both the vibrated and other muscles. We also examine the excitability of local cortical inhibitory circuits using paired pulse TMS methods (short-latency intracortical inhibition, SICI). These are thought to test gamma-aminobutyric acid (GABA)ergic circuits within motor cortex (Ziemann *et al*., 1996; Ilic *et al*., 2002). Results on healthy subjects show that focal sensory input has a spatially specific pattern of effects on vibrated and non-vibrated muscles that we refer to as the sensorimotor organization.

Subjects and methods

Subjects

Eight healthy subjects (three female, five male; age 31 $\pm$ 2 years), eight healthy musicians (five female, three male; age 23 $\pm$ 1 years), seven patients with MD (one female, six male; age 41 $\pm$ 3 years) and six patients with WC (two female, four male; age 44 $\pm$ 4 years) were studied. Two musicians with embouchure dystonia were also tested (aged 43 and 45 years). Inclusion criteria for FHD patients were a strict and exclusively action-induced appearance and task-specificity of symptoms. Patients were not included if they had dystonic symptoms at rest or if they received botulinum toxin injections in the last 6 months preceding the study. Symptoms were assessed using the Burke–Fahn–Marsden (BFM) movement and disability scale (only in WC for the item writing) (for subjects' and patients' details see Tables 1–4).

Subjects gave informed consent to the study, which was approved by the local ethics committee and conformed with the Declaration of Helsinki. Subjects were comfortably seated in an armchair with their forearm pronated on a moulded armrest while forearm and hand muscles were relaxed.

TMS

TMS was performed using two MAGSTIM 200 stimulators connected to a figure-of-eight-shaped coil with an internal wing diameter of 7 cm by a Y-cable (Magstim, Dyfed, UK). The coil was held with the handle pointing backwards and laterally $\sim$45° to the interhemispheric line to evoke anteriorly directed current in the brain and was optimally positioned to obtain motor-evoked potentials (MEPs) in first dorsal interosseus muscle (FDI). The active motor threshold (AMT) defined as the minimum intensity needed to evoke a MEP of >200 μV in five out of 10 trials was measured in the tonically

Table 1 *Characteristics of patients with MD*

Patient No.	Male/ female	Age (years)	Instrument	Started at age (years)	Time spent playing (hours/day)*	Professional musician?	Symptoms during playing	Start of symptoms (years ago)	Severity of Symptoms (BFM movement scale)†	Treatment
1	M	32	Guitar	11	0.5	Not any more	Flexion 3rd digit right	4	2	None
2	M	39	Guitar/violin	6	1	Yes	Flexion of 4th digit left	10	2	BTX‡
3	M	59	Piano	8	1.5	Yes	Flexion 3rd digit right	2	1.5	None
4	M	35	Drum	10	1.5	Yes	Loss of control 4th + 5th digit left	6	2	BTX‡
5	F	35	Piano	3	2.5	Yes	Flexion index right	4	2	Physio
6	M	44	Saxophone	16	2	Yes	Flexion 4th digit left	14	2	None
7	M	43	Guitar	11	0.5	Not any more	Flexion 3rd–5th digit left	8	2	BTX‡
8	M	45	Trombone	10	2	Yes	Embouchure	2	1	None
9	M	43	French horn	12	2	Yes	Embouchure	6	0.5	None

*Estimation for the time period of last 6 months. †MD patients score 0 for the item 'writing' on the disability scale. ‡For patients treated with injections of botulinum toxin (BTX) the last injections were in all cases >6 months prior to testing. The results of the two patients with embouchure dystonia (cases 8 and 9) are reported but not included in the statistical analysis. M = male; F = female.

Table 2 *Characteristics of patients with WC*

Patient No.	Male/ female	Age (years)	Symptoms during writing	Affected task/side	Start of symptoms (years ago)	Severity of symptoms (BFM movement/ disability scale)	Treatment
1	F	35	Flexion of wrist and fingers, tight grip of pen	Writing right	4	2/1.5	None
2	M	40	Flexion of wrist, thumb and index, tight grip of pen	Writing right	6	2/2	BTX*
3	M	35	Right index finger flexion	Writing/typing right	10	2/2	BTX*
4	M	60	Slight flexion of wrist, tight grip of pen	Writing right	9	2/2	None
5	M	46	Flexion of wrist, tight grip of pen	Writing right	9	1/1	None
6	F	50	Slight flexion of wrist, tight grip of pen	Writing/typing right	15	2/1	None

*For patients treated with injections of botulinum toxin (BTX) the last injections were in all cases more than 6 month prior to testing. M = male; F = female.

Table 3 *Characteristics of healthy musicians*

Subject	Male/ female	Age (years)	Instrument	Started at age (years)	Time spent playing (hours/day)
1	F	22	Flute	10	3
2	M	25	Violin	10	5
3	M	24	Flute/clarinet	6	4
4	F	22	Violin/piano	4	2 (each instrument)
5	F	27	Violin/piano	5	1 (each instrument)
6	F	24	Violin	3	5
7	M	19	Piano/trombone	5	3
8	F	21	Harp	3	6

M = male; F = female.

Table 4 *Characteristics of healthy non-musicians*

Subject	Male/female	Age (years)	Handedness
1	M	26	Right
2	M	32	Right
3	M	34	Right
4	F	30	Right
5	F	27	Right
6	F	32	Right
7	M	26	Right
8	M	41	Right

M = male; F = female.

active FDI (~20% of maximal contraction as assessed visually on an oscilloscope). Stimulation intensities are quoted in the text as a percentage of maximal stimulator output (±SE) or percentages of AMT (±SE) (see below).

Electromyographic recording

Surface electromyographic (EMG) recordings in a belly-to-tendon montage were made from abductor pollicis brevis (APB), FDI and abductor digiti minimi (ADM). FDI was chosen as the target muscle for defining TMS parameters (see Study protocol). The raw signal was amplified and filtered (30 Hz to 1 kHz) (Digitimer Ltd). Signals were digitized at 2 kHz (CED Power1401; Cambridge Electronic

Design, Cambridge, UK) and stored on a laboratory computer for off-line analysis.

Muscle vibration

Trains of muscle vibration (frequency 80 Hz) of 1.5 s duration were applied every 5 s to the muscle belly of a relaxed hand muscle using an electromagnetic mechanical stimulator (Ling Dynamics System Ltd, UK) with a 0.7 cm diameter probe. The amplitude (0.2–0.5 mm) of the vibration was adjusted individually to be just below threshold for perceiving an illusory movement (Gilhodes *et al*., 1986; Roll *et al*., 1989; Roll and Gilhodes, 1995; Gruenewald *et al*., 1997). During vibration we monitored the EMG for any muscle contraction indicating, besides possible voluntary activation, the occurrence of the tonic vibration reflex (Lance *et al*., 1966; Hagbarth and Eklund, 1968; Marsden *et al*., 1969). TMS stimuli were given 1 s after the start of muscle vibration.

Study protocol

Intracortical excitability was investigated using the paired-pulse paradigm described by Kujirai *et al*. (1993) with a subthreshold conditioning magnetic stimulus preceding a suprathreshold test stimulus. Five different interstimulus intervals (ISI) were tested: ISI of 2, 3 and 4 ms were measured to evaluate SICI, and ISI of 10 and 15 ms for intracortical facilitation (ICF). The experiment was performed under four different experimental conditions: rest, and during vibration of each hand muscle (APB, FDI and ADM) in turn. The intensity of the conditioning stimulus was set to evoke a 50% inhibition of the test MEP. The stimulus intensity (SI) of the test pulse was adjusted so as to produce an MEP of $\sim$1 mV in the target muscle in resting (SI 1 mV) and vibration conditions [adjusted stimulus intensity (ADJ-SI) 1 mV]. The experiments were also repeated using a stimulus intensity of SI 1 mV in the vibration conditions. For each experimental condition, six randomly intermixed conditions were presented 10 times each: the five different double-pulse conditions and the test stimulus alone. The interval between each consecutive trial was 5 s.

Data analysis and statistics

The data for the two musicians with embouchure dystonia were not included in the group of MD either for statistical analysis or to illustrate the results; their results are reported separately. The comparability of the subject groups for AMT, conditioning stimulus intensity, SI 1 mV, all ADJ-SI 1 mV and subjects' age was tested by a one-way analysis of variance (ANOVA) (factor: 'group'). Unpaired *t*-tests were used to compare the age at which instrumental playing started in healthy musicians and MD and to compare the BFM scores in MD and WC.

The amplitudes of single-pulse MEPs during vibration are given either as raw data (mV) or expressed as percentages of the mean value obtained without vibration (normalized data). A three-way ANOVA with factors 'group', 'muscle' and 'vibration condition' was performed on the normalized MEP data. Further two-way ANOVAs ('muscle' $\times$ 'vibration condition') were performed for the data of each group separately. Furthermore, for each group dataset paired *t*-tests were performed on the data from each hand muscle to compare MEPs during vibration with MEPs without vibration.

For SICI and ICF, single-trial peak-to-peak MEP amplitudes were measured and averaged for each ISI separately and their size expressed as a percentage of the mean test MEP. Statistical analysis was performed either on the individual ISIs or after grouping them to give a single value for SICI (ISIs of 2, 3 and 4ms) and ICF (10 and 15 ms). A three-way ANOVA with the factors 'muscle', 'vibration condition' and 'test SI' was performed for each group separately. Since the factor 'test SI' had no significant main effect or influence on an interaction, data obtained with SI 1 mV and with ADJ-SI 1 mV were pooled for further analysis. Three-way ANOVA with the factors 'group', 'muscle' and 'vibration condition' was performed for the SICI and ICF data. This analysis was specified by further two-way ANOVAs with the factors 'group' and 'muscle' tested for each vibration condition, and 'group' and 'vibration condition' tested for each muscle separately. To test for the comparability of the SICI/ICF data obtained without vibration between the groups, two-way ANOVA with the factors 'group' and 'ISI' were performed on the data of each muscle separately. Where necessary, *post hoc t*-tests were performed as indicated in the text or figure legends.

The significance level was set at $P \leqslant 0.01$ in order to reduce the probability of detecting false positives in this complex statistical design. Data are given as mean $\pm$ SE.

Results

Subjects' and TMS parameters

The mean stimulus intensities used for test and conditioning pulses are given for each group in Table 5. There were no statistically significant differences in the intensities used in each group. However, the subject groups did differ in age [ANOVA; $F(3,15) = 9.9$; $P < 0.001$]. The healthy musicians, who were all students completing training at the Royal College of Music, were younger than the other groups; however, there was no significant age difference between patient groups. The age at which instrumental playing began was similar in healthy musicians and MD. The dystonic symptoms as assessed by the BFM score were of similar severity in both patient groups.

MEPs

Figure 1 illustrates examples from each of the subject groups of MEPs evoked in the FDI muscle after a single TMS pulse. Each trace shows the responses with and without vibration of each hand muscle. In healthy subjects, vibration of the FDI increased MEPs in that muscle whilst they were suppressed by vibration of either the APB or ADM. The healthy musicians behaved slightly differently in that the FDI MEP increased not only during vibration of FDI, but also during vibration of APB; however, it was still suppressed by vibration of ADM. Both MD and WC patients were characterized by lack of suppression after vibration of any of the muscles. Indeed, in WC, FDI responses were facilitated during vibration of any hand muscle.

Figure 2 summarizes the data from all three hand muscles. Graphs on the left plot the absolute amplitude of the MEPs in mV, whereas those on the right show the same data normalized to the amplitude of control responses without vibration. In healthy subjects, muscle vibration increased MEPs in the vibrated muscle, whilst at the same time decreased it in non-vibrated muscles. This pattern was less distinctive in healthy

Table 5 *TMS parameters defined in the FDI in all groups*

	AMT (% stimulator output)		SI of cond. stimulus (% stimulator output; % of AMT)				SI 1 mV (% stimulator output)		ADJ-SI 1 mV, vib FDI (% stimulator output)		ADJ-SI 1 mV, vib APB (% stimulator output)		ADJ-SI 1 mV, vib ADM (% stimulator output)	
	Mean	SE	Mean	SE	Mean	SE	Mean	SE	Mean	SE	Mean	SE	Mean	SE
Healthy subjects	36.6	2.6	32.6	2.4	89%	1%	56.8	4.0	52.5	3.6	56.3	4.3	56.4	3.9
Healthy musicians	31.0	1.1	27.1	0.8	88%	2%	54.5	2.3	52.9	2.9	55.8	2.5	56.6	3.0
MD*	34.4	2.6	26.7	2.1	77%	2%	53.6	3.1	54.6	2.9	54.7	2.9	56.3	3.5
WC	36.5	2.2	29.0	2.0	80%	3%	59.5	4.4	60.5	4.0	61.8	4.3	61.0	4.7

The mean (±SE) of the AMT, the intensity of the conditioning pulse in percentage stimulator output (left) and percentage of AMT and the test stimulus intensities which produces a MEP of 1 mV peak-to-peak amplitude without vibration (SI 1 mV), with vibration (ADJ-SI 1 mV) of APB, FDI or ADM are given. *Excluding embouchure dystonia patients. vib ADM = vibration of ADM; vib APB = vibration of APB; vib FDI = vibration of FDI.

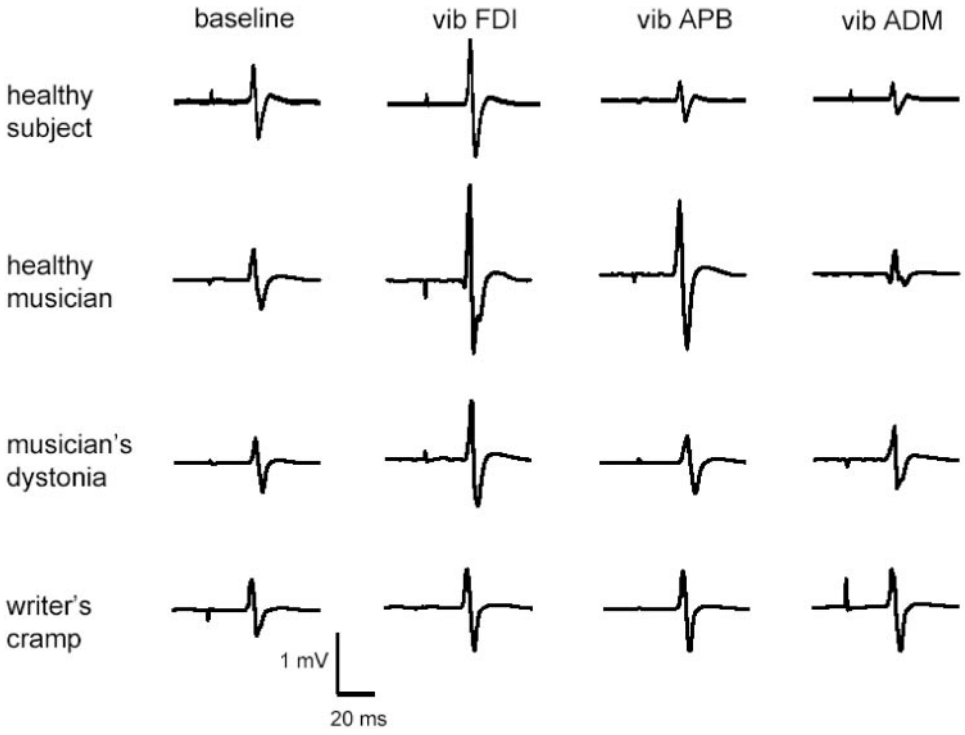

Fig. 1 Average MEP recordings from the FDI showing the effect of vibration form one representative individual of each subject group. MEPs are shown at rest without vibration (baseline) and during vibration of each hand muscle in turn. In healthy subjects, vibration of the FDI increased MEPs in that muscle while they were suppressed by vibration of either the APB or ADM. The healthy musicians responded slightly differently in that the FDI MEP increased not only during vibration of FDI, but also during vibration of APB; however, it was still suppressed by vibration of ADM. In MD, the FDI MEP was facilitated during vibration of FDI, but there was no suppression with vibration of either APB or ADM. In WC FDI MEPs were mildly facilitated during vibration of any hand muscle.

musicians. Here, vibration of either APB or FDI facilitated the MEPs in both FDI and APB, but not the ADM. In contrast, vibration of ADM only facilitated the MEPs in ADM and suppressed those in the APB and FDI. The two groups of dystonia patients differed from both sets of healthy subjects in that vibration never produced suppression of MEPs in any muscle. In MD patients, vibration of a hand muscle facilitated the MEP in the vibrated muscle, but there was no effect on other muscles. In WC, vibration of any muscle mildly facilitated MEPs in all muscles.

These impressions were borne out in the statistical analysis. A three-way ANOVA showed a significant interaction between the main factors 'group', 'muscle' and 'vibration condition' [ANOVA; $F(12,69) = 7.36$; $P < 0.000001$]. Within each group, the interaction of factors 'muscle' and 'vibration condition' was significant in healthy subjects, healthy musicians and MD (ANOVA; $P < 0.003$), but not in WC. This was because in patients with WC vibration had the same effect (facilitation of MEPs) on all muscles, whereas in the other groups, vibration had a specific

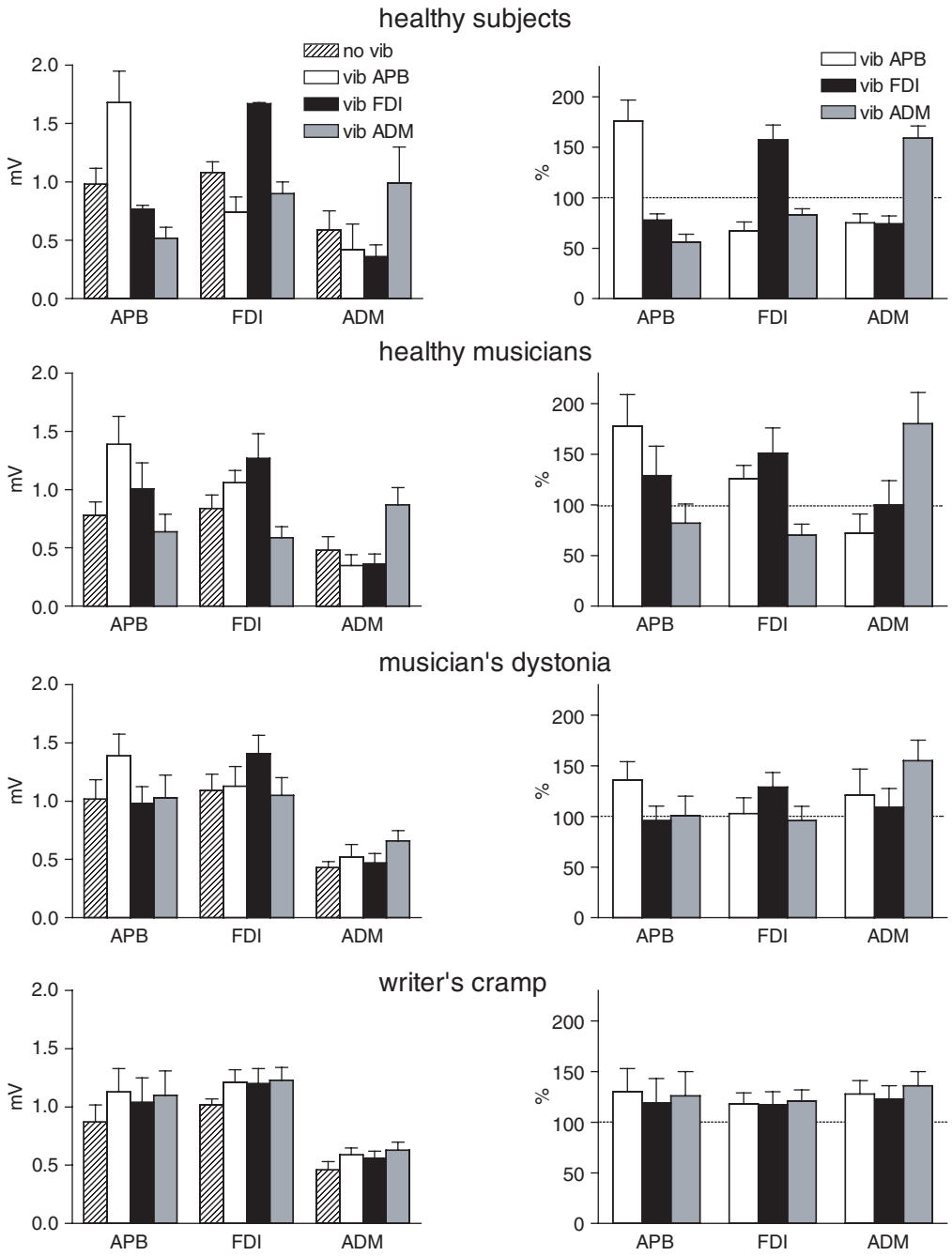

Fig. 2 Mean MEP responses to single TMS stimuli (SI 1 mV) in all vibration conditions. The left panel shows mean MEP amplitudes (±SE) obtained with SI 1 mV in the hand muscles in the conditions without vibration (no vib), with vibration of APB (vib APB), with vibration of FDI (vib FDI) and with vibration of ADM (vib ADM) given for all subject groups. The TMS intensity was adjusted to produce an MEP of 1 mV peak-to-peak amplitude in the FDI as target muscle. The right panel show the same data normalized to the amplitude of control responses without vibration. MEPs obtained without vibration in all three hand muscle were not different in the groups. In healthy subjects, the MEP increased in the vibrated muscle, whereas they decreased in the non-vibrated muscle. In healthy musicians, vibration of the either the FDI or APB increased MEPs in both muscles but not in the ADM, whereas vibration of ADM still had an inhibitory effect on MEPs in FDI and APB. In MD, vibration increased the MEPs in the vibrated muscle whereas the inhibitory effect on non-vibrated muscles was absent. In WC patients vibration had almost no effect on either vibrated and non-vibrated muscle apart from a slight, non-significant increase in all muscles in all vibration conditions.

pattern of effects that depended on which muscle had been vibrated.

We explored other differences between groups by performing three-way ANOVAs (factors 'group', 'muscle' and 'vibration condition') on datasets of two of the groups in turn. Effectively, this asks whether the spatial pattern of vibratory effect is the same or different between the groups. There was a significant three-way interaction between healthy subjects and

healthy musicians [ANOVA; $F(4,28) = 4.74$; $P < 0.005$]. This was due to the fact that vibration of FDI and APB had opposite effects in healthy subjects but similar effects in healthy musicians. There was also a significant three-way interaction between healthy musicians and MD and between healthy subjects and WC (ANOVA; $P < 0.0002$), both caused by the lack of any vibratory inhibition in the patient groups. There was no significant interaction between MD and WC.

SICI and ICF

The paired-pulse TMS experiments with vibration of each hand muscle in turn were performed twice: (i) with the intensity of the test pulse set to evoke an MEP in the FDI muscle of 1 mV peak-to-peak in the absence of any vibration (SI 1 mV); and (ii) with test pulse intensities adjusted to give a 1 mV MEP during vibration (ADJ-SI 1 mV). An ANOVA (with the factors 'muscle', 'vibration condition' and 'test SI') performed on the data of each group in turn showed that adjusting the intensity of the test pulse had no effect on the amount of SICI/ICF. This confirms the previous observations of Rosenkranz and Rothwell (2003), who made separate analyses of data obtained with non-adjusted and adjusted SI. In view of this we have taken the mean of the data from the two experiments and presented the combined analysis in the results. We have confirmed that the same conclusions would have been reached if we had conducted separate analyses of each dataset.

Figure 3 shows the percentage SICI (left panel) and ICF (right panel) in the three hand muscles for each subject group separately. In each histogram the four bars represent the data of the different experimental conditions: baseline without vibration, during vibration of APB, during vibration of FDI and during vibration of ADM.

Healthy subjects showed the same spatial pattern of modulation as reported previously (Rosenkranz and Rothwell, 2003). Vibration of one muscle reduced SICI in the same muscle and increased SICI in the non-vibrated muscles. In healthy musicians this pattern was less clear. As with the effect of vibration on MEPs, vibration of either FDI or APB decreased the SICI in both muscles equally, but still increased SICI in the ADM. However, as in healthy subjects, vibration of the ADM only decreased SICI in the ADM whilst increasing it in FDI and APB. In MD, vibration of a hand muscle had no differential effect at all; instead it decreased SICI in all hand muscles to the same extent. In contrast, in WC vibration of hand muscles had no effect on SICI in any muscle.

These impressions were supported by the statistical analysis. There was a highly significant interaction between the main factors 'group', 'muscle' and 'vibration condition' [ANOVA; $F(12,324) = 57.2$; $P < 0.00001$]. Follow-up analysis on each group separately showed that this was probably because there was a significant interaction of the factors 'muscle' and 'vibration condition' only for healthy subjects and healthy musicians [ANOVA; $P < 0.00001$], but not for MD and WC. In other words, whereas muscle vibration produced a particular spatial pattern of effects on SICI in healthy subjects and healthy musicians, in the patients, muscle vibration had the same effect (or no effect in WC) on all muscles.

We explored other differences between groups by performing three-way ANOVAs on data from pairs of groups in turn. As with the MEPs, this asks whether the spatial pattern of vibratory effect is the same or different between the groups. The interactions were significant between healthy subjects and healthy musicians (owing to the lack of differential effect between the effects of FDI and APB vibration in the musicians), between healthy musicians and MD, and between healthy subjects and WC (the control groups have a spatial pattern of vibratory effects whereas the latter do not) (ANOVA; $P < 0.00001$). There was no significant interaction comparing MD and WC (ANOVA; $P < 0.03$); however, there was a strong effect of the main factor 'group' (ANOVA; $P < 0.00001$). This might be explained by the fact that on both groups of patients, vibration of one hand muscle had the same effect on all muscles, but in MD this was because vibration reduced SICI in all muscles, whereas in WC vibration had no influence on SICI in any muscle.

The results of healthy subjects, healthy musicians and MD give the impression of a continuum, with the differential activation pattern evoked by muscle vibration in healthy subjects gradually breaking down such that the effect of vibration spreads further and further from the site of vibration in the two groups of musicians. Thus, in healthy musicians, vibration of FDI reduces SICI not only in FDI itself, but also in APB (and *vice versa* for vibration of APB). In MD this effect spreads even further and reduces SICI even in the ADM (and *vice versa*). The results in WC patients do not seem to fit into this continuum since they lack any modulation of SICI in response to vibration.

The ICF data as shown for each group in the right column of Fig. 3 was less modulated by vibration compared with SICI. Two-way ANOVAs with the factors 'muscle' and 'vibration condition' performed on the data of each group separately revealed no significant interaction in any group.

Figure 4 illustrates the SICI/ICF data in a different way. The graphs plot the time course of SICI and ICF in the FDI muscle in each of the four different vibration conditions. The top graph plots the baseline data of each group obtained without vibration. Note that the intensity of the conditioning stimulus had been adjusted in each group to produce ~50% SICI at and ISI of 2 ms. There was no significant difference [ANOVA ('group' × 'ISI'); $F(12,60) = 1.07$; $P = 0.4$] between the groups and in the lower three graphs, the grand mean time course from all groups has been plotted as thick line. Figure 4B plots the data during vibration of FDI. In all groups apart from WC, vibration reduced SICI. During vibration of APB (Fig. 4C) SICI (ISI 2–4 ms) was enhanced in healthy subjects, whereas in healthy musicians and MD it was reduced. There was no significant effect on WC. Vibration of ADM (Fig. 4D) enhanced SICI in healthy subjects and healthy musicians, whereas it was reduced in MD. Again, in WC, SICI was not significantly affected by ADM vibration.

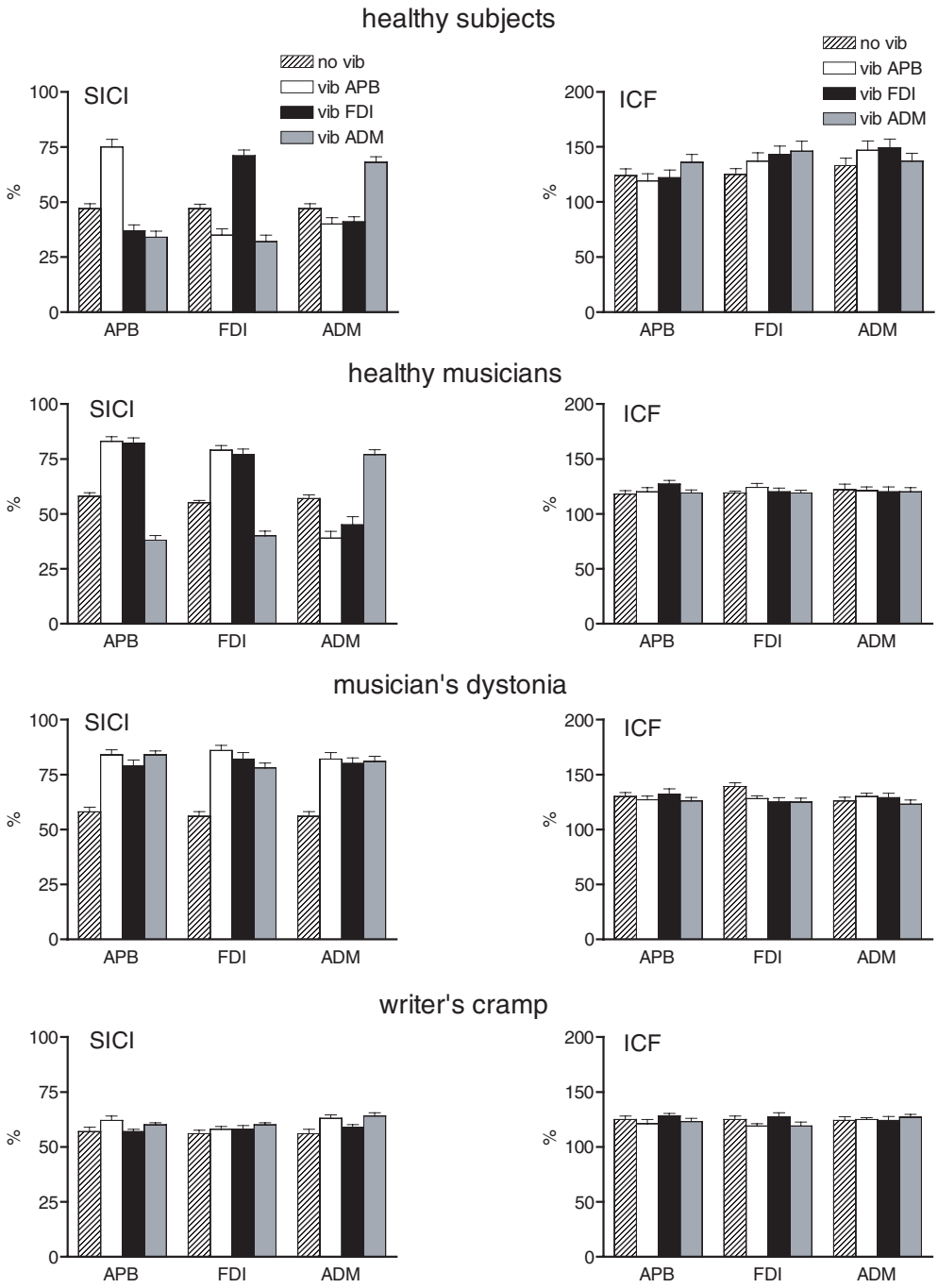

Fig. 3 SICI (*left* column) and ICF (*right* column) in each hand muscle in all four groups of subjects without (no vib) and with vibration of APB (vib APB), FDI (vib FDI) or ADM (vib ADM). Data points at ISIs 2, 3 and 4 ms were averaged to yield a single mean value for SICI, and data points from ISIs of 10 and 15 ms averaged to yield a mean value for ICF. Data obtained with adjusted and non-adjusted test SI in each vibration condition were pooled since they were not significantly different. In healthy subjects vibration reduces SICI in the vibrated muscle and an increases itin the non-vibrated muscles. In the healthy musicians, this pattern is less focal. Vibration of either APB or FDI reduces the SICI in both muscles, whereas vibration of the ADM has the same effect as in non-musicians: it reduces SICI only in ADM and increases SICI in APB and FDI. In MD, vibration applied to any one of the muscles suppresses SICI in all of them, whereas in WC, vibration has no effect on SICI in any muscle. The *right* column displays the ICF data for all groups separately, which was not significantly changed by muscle vibration in any of them. Data are means ± SE.

Figure 5 illustrates the results from two professional musicians with embouchure dystonia, which were not included in the MD group of dystonia affecting the hand for data display or analysis. Because of the small number of subjects, no statistical analysis has been performed. Interestingly, the effect of vibration on MEPs (Fig. 5A) and SICI (Fig. 5B) was quite similar to the results of healthy musicians rather than to MD. As in the results of the other groups, ICF (Fig. 5C)

was not modulated by vibration. These results suggest that the complete loss of sensorimotor organization in the hand area as seen in MD is localized to the area representing the muscles that are involved in the symptoms.

Discussion

As we have described previously (Rosenkranz and Rothwell, 2003), the present data using a vibratory paradigm show that there is a spatially focal pattern of sensorimotor interaction in the hand area of the cortex in healthy non-musicians. The new findings are that this pattern is not only abnormal in both patient groups with FHD, but that the pattern of abnormality differs in patients with WC from that in MD. Sensory input in the latter group has a strong but unfocused influence on motor output, whereas in WC sensory input appears to have little if any effect on motor output. A second finding is that the pattern of sensorimotor interaction in musicians differs from that of non-musicians. We hypothesize that this is the consequence of the intense and repetitive training of hand movements experienced by professional musicians over many years. The fact that the reorganization in MD appeared to be an exacerbation of this 'healthy' training effect suggests that the pattern of presymptomatic use of the hand may determine the eventual pattern of sensorimotor organization that is seen in the cortex of patients with FHD.

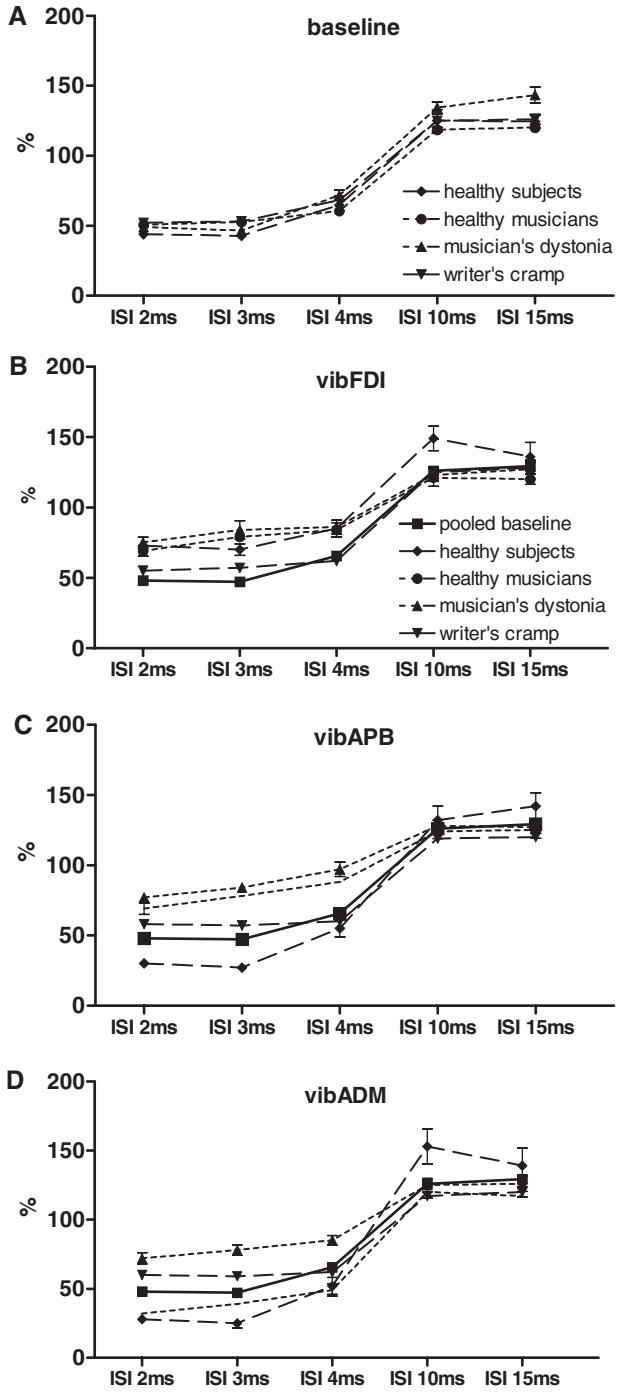

Fig. 4 Mean time-course of SICI and ICF in the FDI muscle of the different patient groups. **A** shows the baseline time course obtained in the absence of vibration. The size of the conditioned response is expressed as a percentage of the control MEP for the four groups of patients. The curves are quite similar in all groups. To simplify the comparison of data obtained while vibration was applied to different muscles (**B**, **C** and **D**), these group baselines were pooled to provide a single grand mean time-course of SICI/ICF which is plotted as the thick line in the graphs below. Note that the time courses of the effects during vibration are the mean of data obtained with adjusted and non-adjusted test SI, since the intensity of the test stimulus had no influence on SICI and ICF. **B** shows the SICI and ICF in FDI during vibration of the FDI (vib FDI). SICI is markedly reduced in healthy non-musicians and musicians, as well as MD, but there is only a slight decrease in WC. **C** shows SICI and ICF in FDI during vibration of the APB. Compared to the pooled baseline, SICI was increased in healthy non-musicians, but decreased in healthy musicians and MD patients. In WC, SICI appeared to be uninfluenced by vibration of APB. **D** shows SICI and ICF in FDI during ADM vibration (vib ADM). In both healthy control groups ADM vibration increased SICI, but in MD SICI was reduced, and there was virtually no effect in WC. There was no clear effect on ICF during vibration in any subject group. Data are means ± SE.

Sensorimotor interactions: cortical or subcortical?

Our test of sensorimotor interaction measures the amplitude of MEPs and the level of SICI/ICF in three different hand muscles while sensory stimulation (in the form of 1.5 s low-amplitude vibration) is applied to one of them. It differs from other tests of sensorimotor organization in that: (i) the sensory input is produced by stimulation of sensory receptors (Burke *et al*., 1976*a*, *b*; Roll *et al*., 1989) rather than electrical stimulation of sensory afferent fibres (Classen *et al*., 2000; Tamburin *et al*., 2001, 2002); and (ii) the input is present during measurement of the MEP parameters rather than at different times after a phasic sensory input. The results show that in healthy subjects focal vibration of a hand muscle facilitates MEPs and decreases SICI in the vibrated muscle, whilst the opposite occurs in the non-vibrated muscles: MEPs are suppressed and SICI increased.

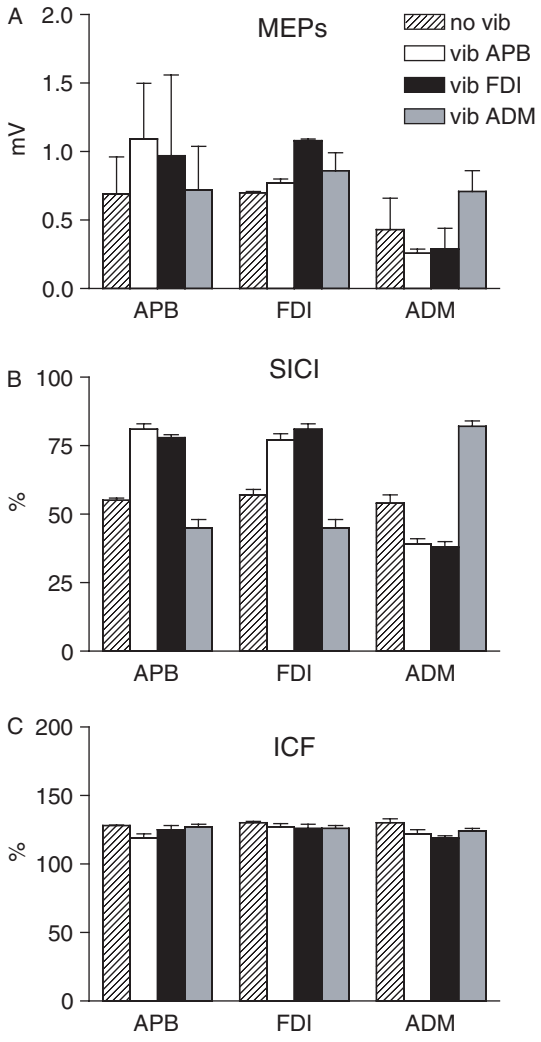

Fig. 5 (**A**) MEPs, (**B**) SICI and (**C**) ICF obtained in the two patients with embouchure dystonia. MEPs are displayed as in Fig. 2, and SICI and ICF are displayed as in Fig. 4. In these two professional musicians (one brass, one woodwind player), the dystonic symptoms affected their embouchure only while playing their instruments and there was no involvement of the hands. The results are similar to those in healthy musicians.

Although cutaneous inputs have been reported to have spatially specific effects on the corticospinal excitability of nearby hand muscles (Classen *et al*., 2000; Tamburin *et al*., 2001), they do not have opposite effects on distant hand muscles as found here with vibration. This maybe because the muscle spindles that are predominantly activated by vibration (Burke *et al*., 1976*a*, *b*; Roll *et al*., 1989) have a more specific and direct effect on motor cortical circuitry than cutaneous inputs (Heath *et al*., 1976; Hore *et al*., 1976; Jones and Porter, 1980).

As we have argued previously (Rosenkranz and Rothwell, 2003), it is likely that the effect of vibration on SICI occurs because of changes in excitability of intrinsic GABAergic circuits in motor cortex (Ziemann *et al*., 1996; DiLazzaro *et al*., 1998; Ilic *et al*., 2002). The mechanism of vibratory effects on the MEP (and possibly ICF) is less clear and may in addition involve spinal pathways (Claus *et al*., 1988*a*, *b*; Kossev *et al*., 1999). It should also be noted that the effects on SICI/ICF persisted when the intensity of the test stimulus was adjusted to compensate for vibratory effects on baseline MEP size. This makes it unlikely that they result from vibration-induced changes in the recruitment of corticospinal volleys (Rosenkranz and Rothwell, 2003; Rosenkranz *et al*., 2003).

In all experiments we adjusted the initial intensities of the conditioning stimulus to produce an ∼50% inhibition of the test MEP in the target muscle. The mean intensities, expressed either as absolute values, or relative to AMT, were the same in all groups. Therefore, we presume that the excitability of the SICI circuit is similar in all groups. However, several previous studies have found that the amount of SICI at a given intensity of conditioning stimulus is smaller in patients with WC than in healthy subjects (Ridding *et al*., 1995; Gilio *et al*., 2000), and that the threshold for evoking SICI is higher in patients (Stinear and Byblow, 2004*a*). One possibility for why such a difference was not seen in the present group of WC is that our patients had milder symptoms than those of previous groups. This is because only patients with an action-induced and task-specific dystonia were included in order to match with the MD patients.

Unfortunately, our groups were not well age-matched. Because the healthy musicians were all recruited from the Royal College of Music, they were generally in their early twenties and younger than the group of patients with MD. Nevertheless, structural and functional changes of the brain in musicians depend on the age at which instrumental playing was started (Elbert *et al*., 1995; Amunts *et al*., 1997; Schlaug, 2001). Since this was the same in healthy musicians and MD, we presume that despite the absolute age difference, the groups had a comparable CNS adaptation to instrumental playing. The healthy musicians were also younger than our healthy non-musicians. Corticospinal and intracortical excitability tends to decrease with age (Peinemann *et al*., 2001), but this should have been compensated for by the fact that we adjusted the intensities of conditioning and test pulse in each individual so that the MEP size and the percentage SICI was similar in all cases. Importantly, there was no significant age difference between the two patient groups.

Differences in sensorimotor organization in WC

Unlike the results in healthy subjects, vibration had no spatially specific effects in WC. Stimulation of one muscle had the same effect on all three hand muscles: it marginally facilitated MEPs but had no effect on SICI. This lack of spatial specificity of sensory input on corticospinal excitability is in some respects similar to the lack of somatotopic effect in WC seen by Tamburin *et al*. (2002) using electrical stimulation of digital nerves as a conditioning input.

A similar loss of specificity in WC has been reported in the context of fine motor acts performed with the hand (Stinear and Byblow, 2004*b*). Focal contraction of a hand muscle

normally is accompanied by a decrease in SICI in the same muscle and an increase of SICI in other hand muscles that are not activated in the task. Patients with WC fail to modulate SICI in any muscle, even when they perform the task as well as controls.

Both studies imply that the usual spatial specificity of interaction between sensory input and motor output to intrinsic hand muscles is disrupted in FHD. This might be due to a failure to focus sensory input on the appropriate motor output and prevent the selection of the intended movement and suppression of unintended movements (Mink, 1996).

Interestingly we have recently shown that a similar pattern of sensorimotor organization can be induced transiently in healthy subjects by applying vibration simultaneously to the FDI and APB muscles for 15 min (Rosenkranz and Rothwell, 2004). For 30 min afterwards, sensory input from the vibrated muscles no longer had any effect on corticospinal excitability. It was as though the system had adapted to or 'ignored' an irrelevant input. Whether a similar adaptation occurred in WC as a mechanism to 'filter out' irrelevant or excessive feedback that occurs during dystonic contractions is a possibility, although this would require further investigations.

Differences in sensorimotor organization in MD and comparison with healthy musicians

As in WC, there is a loss of the normal spatial pattern of sensorimotor interaction in MD. However, the direction of the change is quite different in the two groups and can be seen most clearly in the SICI data, which is the most direct measure of changes at the level of the motor cortex. In MD, SICI was strongly reduced in all hand muscles, irrespective of which hand muscle was vibrated. To understand this difference between the patient groups, it is helpful to consider the data from healthy musicians. Interestingly, healthy musicians differed from non-musicians in the pattern of sensorimotor interaction between the APB and FDI. In musicians, vibration applied to either muscle alone had a similar and not opposite effect on both MEPs and SICI in both of them. In contrast, the pattern of effect both onto and from the ADM muscle was the same as in non-musicians. Precisely why musicians show this overlap of effects in APB and FDI is unclear. We presume that it is linked to the long process of practicing complex movement patterns, which might involve functional coupling of muscle pairs like the APB and FDI. Certainly, several studies on healthy musicians have highlighted functional and structural changes in their brains, particularly the sensorimotor cortices (Amunts *et al*., 1997; Bangert *et al*., 2001; Muente *et al*., 2002; Nordstrom and Butler, 2002) that are likely to reflect training-induced adaptations. The lack of a differential effect between the closely functionally coupled muscles might indicate an increased functional connectivity between these muscle representations, which could be advantageous for the performance of complex movements.

A similar pattern of sensorimotor integration as shown here in healthy musicians can be induced in healthy non-musicians by simultaneously vibrating the APB and FDI muscles for 15 min with the subjects' attention drawn to vibration (Rosenkranz and Rothwell, 2004). This demonstrates that attended sensory input can induce changes in organization and reinforces the hypothesis that the results seen in healthy musicians are caused by their training rather than being inherent.

We speculate that the data from patients with MD represents a further 'progression' of this basic pattern of reorganization. Rather than similar effects occurring from vibration of just APB and FDI, in MD this spreads to involve the ADM with the result that the usual pattern of spatial specificity is completely lost. Parallels could be drawn to studies on the organization of finger representation in the sensory cortex, in which there is an (orderly) increase of representational fields in healthy musicians, but an overlap and fusion in MD (Elbert *et al*., 1995, 1998). Interestingly, the two musicians with embouchure dystonia that we studied did not show a complete loss of sensorimotor organization in the hand area, thus suggesting that in MD the loss of sensorimotor organization is specific for the representation of the part of the body where the symptoms manifest.

There is some evidence that prolonged training of cortical circuits can increase the capacity for further reorganization. Ragert *et al*. (2004) found that professional musicians not only had a superior two-point discrimination threshold in the fingers, but that they could also be trained to improve this to a greater extent than non-musicians using standard protocols. This could be related to the fact that in healthy musicians afferent input from the APB or FDI vibration produces a more widespread reduction in SICI than normal. SICI is thought to depend on GABAergic mechanisms and intracortical representations are shaped by GABAergic inhibitory circuits (Jacobs and Donoghue, 1991). A reduction in GABAergic activity might be one factor that contributes to their increased sensitivity to training and increases the chances of some of them developing dystonia. Indeed, the development of dystonic symptoms is often triggered by minor alterations of playing technique, instrument or minor injuries that might require adjustments in sensorimotor reorganization (Lim *et al*., 2001).

Conclusions

Patients with different forms of FHD share a variety of abnormalities in sensory processing, sensorimotor organization and in motor excitability (Hallett, 1995; Berardelli *et al*., 1998; Abbruzzese *et al*., 2001; Tinazzi *et al*., 2003) which suggest that they share a common pathophysiology. However, the recent finding that patients with the DYT1 mutation do not show some of the usual sensory deficits (Molloy *et al*., 2003) indicates that this may not always be the case. The present results extend this to WC and MD. These are both FHD, but they differ in the effect vibration has on motor excitability. Despite both of them showing a loss of spatial organization of sensorimotor interactions, in MD the sensory input still

influences GABAergic inhibition, whereas it has no effect in WC. Patients with MD have usually spent many hours every day for several years practising their instruments, and this requires a high level of sensory feedback control. In contrast, most patients with WC have used their hands in the usual manual tasks performed by healthy subjects. Our hypothesis is that the final pattern of sensorimotor organization in MD and WC reflects these differences in hand use before the development of dystonic motor symptoms and the different role of sensory feedback from the hand in the pathophysiology.

Figure 6 summarizes the results diagrammatically in terms of the effects of focal vibratory input on SICI in the three hand muscles. We have chosen to illustrate the effects on SICI because of the possibility that non-cortical changes could contribute to the differences in spatial effects on the MEP. In this simplified diagram, the muscle representations of the hand muscle are displayed as concentric circles with the APB and FDI considered being 'near' neighbours, whereas ADM is considered 'far'. We should stress that this is not meant to reflect the anatomical distance between muscle representations in the cortex, since these are well known to be highly intermingled. It is instead intended to reflect the effective functional connectivity between muscles, with connections between APB and FDI being more prominent that those between ADM and FDI (for example). In healthy subjects, focal vibratory input to one muscle reduces SICI in that muscle and increases it in other muscles. In healthy musicians, SICI in both 'near' muscles is suppressed by vibration applied to either of them, whilst in MD vibration of any muscle suppresses SICI in all of them. WC patients show no modulation of SICI by vibration of any muscle. We hypothesize that long hours of practicing complex movements first produce the modulation of sensorimotor interaction seen in the healthy musicians, and that this later progresses into the non-focal pattern of MD. The result is that the GABAergic circuits responsible for SICI retain their responsiveness to sensory input in MD, whereas this is lost in WC.

The present results raise the possibility that MD is a form of training-induced dystonia comparable to that described in the animal model of Byl *et al*. (1996). In susceptible individuals an initially beneficial adaptation of sensorimotor organization may progress too far and lead to problems in targeting motor commands. The influence of presymptomatic hand training on the pathophysiology of MD suggests that appearance of symptoms might be delayed or prevented by modifying training schedules to reduce repetition and increase

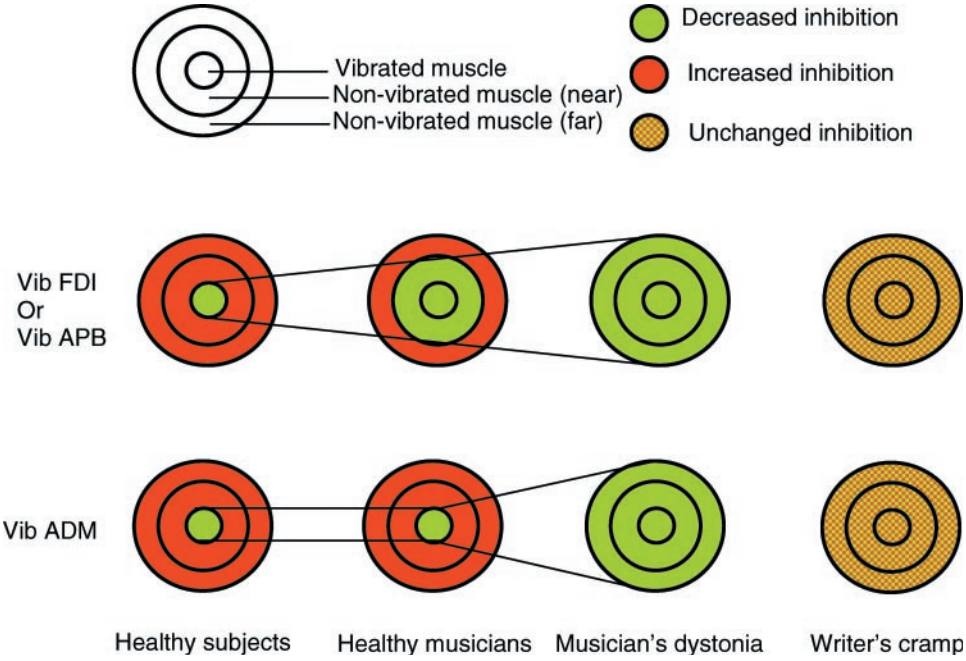

Fig. 6 Schematic summary of the effects of focal vibratory input on SICI in the three hand muscles. In this diagram, the hand muscle representations are drawn as circles with the vibrated muscle in the centre, and the 'near' and 'far' non-vibrated muscles surrounding it. APB and FDI are considered to be 'near' neighbours, whereas ADM is considered 'far'. This illustration is intended to reflect the effective functional connectivity between muscles, rather than anatomical distances between muscle representation in the cortex. Colours represent the level of SICI: green symbolizes a reduction of SICI, red an increase, and red and green intermingled an unchanged SICI compared with the non-vibration condition. Two cases are distinguished, vibration applied to FDI or APB (vib FDI, vib APB) (as one of the 'near' neighbours) and vibration of ADM (vib ADM) ('far'). In healthy subjects, focal vibratory input to one muscle reduces SICI in that muscle and increases it in other muscles, as symbolized here by the green centre surrounded by red in the 'near' and 'far' muscle. In healthy musicians, SICI in both 'near' muscles is reduced by vibration applied to either of them, whilst it is increased in the 'far' one. In contrast, vibration of the ADM reduces SICI in ADM but increases SICI in FDI and APB. In MD, vibration of any muscle reduces SICI in all of them, as symbolized by green in all muscle representations. WC patients show no modulation of SICI by vibration of any muscle; the SICI remains unchanged compared with baseline levels.

variability of the movements that are practised. The lack of sensory modulation of motor excitability in WC suggests that sensory input from the hand may play a different role in provoking pathological changes in WC than in MD.

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