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Sensorimotor reorganization by proprioceptive training in musician's dystonia and writer's cramp



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ABSTRACT

Objective: The sensorimotor organization (SMO) of the motor hand area is abnormal in focal hand dystonia and likely contributes to symptom manifestation. In healthy subjects SMO is changed by training with proprioceptive stimulation. Here we test whether similar interventions reverse the abnormal SMO in musician's dystonia and writer's cramp. If so, they could be developed for therapeutic application.

Methods: In six non-musicians, six professional musicians, six patients with musician's dystonia, and six patients with writer's cramp, SMO was explored by measuring changes in short-interval-intracortical-inhibition (SICI) during short periods of hand muscle vibration before and after two training types: AttVIB, involving attention to 15 minutes vibration of the abductor pollicis brevis (APB); and AttIndex, involving attention to subtle cutaneous stimulation of the index finger.

Results: In healthy non-musicians, baseline SMO is spatially differentiated: SICI is reduced in projections to the vibrated, but enhanced to the non-vibrated muscles. Here AttVIB increased and AttIndex reduced the effect of subsequent APB-vibration on SMO. In healthy musicians, baseline SMO is less differentiated. AttVIB reinstated a more differential SMO pattern while AttIndex attenuated the effect of APB vibration. In focal hand dystonia, SMO is completely dedifferentiated. AttVIB tended to restore a more differential SMO in musician's dystonia but not in writer's cramp while AttIndex failed to induce any changes in both groups.

Conclusion: The intervention effect depends on the pre-interventional sensorimotor organization (SMO). In focal hand dystonia, particularly in musician's dystonia, it is possible to retrain an abnormal SMO toward a more differential pattern, which has potential implications for therapy.

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GLOSSARY

ADM = abductor digiti minimi; **aMT** = active motor threshold; **ANOVA** = analysis of variance; **APB** = abductor pollicis brevis; **AttIndex** = vibration intervention with attention drawn on subtle electrical stimuli applied to the skin overlying the lateral base of the index finger; **AttVIB** = vibration intervention with attention drawn onto subtle changes of vibration frequency; **BFM** = Burke-Fahn-Marsden; **FDI** = first dorsal interosseus; **FHD** = focal hand dystonia; **MEP** = motor evoked potential; **SICI** = short-interval-intracortical-inhibition; **SMO** = sensorimotor organization; **TMS** = transcranial magnetic stimulation.

Abnormalities within and between the sensory and motor systems have been described in patients with focal task-specific hand dystonia, such as writer's cramp or musician's dystonia.¹⁻⁷ Previously, we probed the sensorimotor organization (SMO) of the motor cortical hand area with a paradigm that tests the influence of short periods of proprioceptive stimulation (muscle vibration) to small hand muscles on the excitability of motor cortical projections back to these muscles.^{8,9} In healthy subjects, there is a very specific pattern of organization in which vibration of a muscle increases the excitability of motor cortical projections to the vibrated muscle, while at the same time reducing the excitability of projections to non-vibrated muscles.⁸

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Disclosure: The authors report no conflicts of interest.

Table 1 Characteristics of healthy musicians

Subject	Sex	Age, y	Instrument	Age started, y	Time spent playing, h/day
1	M	31	Trumpet/piano	12	2
2	F	25	Violin/piano	5	4
3	F	27	Violin	7	4
4	M	36	French horn/piano	7	4
5	F	26	French horn/piano	8	3
6	F	28	Clarinet	8	3

The same paradigm also shows that the SMO differs in patients with writer's cramp and musician's dystonia: in the latter, vibration of any one hand muscle increases excitability of projections to all hand muscles, whereas vibration of a muscle in writer's cramp has no effect on any muscle. Long-term motor training in healthy subjects, such as that undertaken by professional musicians, induces structural and functional changes in the sensorimotor cortex.¹⁰⁻¹⁴ In musicians, the SMO lies midway between that in healthy subjects and musicians' dystonia. We hypothesized that the adapted organization of healthy musicians is beneficial for fine motor control, but that in musician's dystonia adaptation might progress too far and interfere with movement rather than assist it. The influence of presymptomatic musical training might explain the differences seen in SMO between musician's dystonia and writer's cramp.⁹

These results suggest that intact motor control is associated with particular patterns of SMO. If so, then it may be possible to im-

prove hand function in focal hand dystonia by retraining the SMO in the hand motor cortex. In previous studies on healthy non-musicians we have shown that the SMO is flexible, and can be modulated in specific ways for at least 30 minutes by short periods (15 minutes) of behavioral proprioceptive training using patterned hand muscle vibration. Depending on whether subjects' attention was focused on the vibration or distracted from it, the pattern of SMO could be specifically changed.^{15,16}

In the present study we extend these findings and investigate whether attended and unattended 15-minute periods of behavioral proprioceptive training can promote reorganization of sensorimotor connections in healthy professional musicians, and patients with musician's dystonia and writer's cramp. If it does, this would show that these patients retain the capability to adapt their sensorimotor connections, which is an important prerequisite for the application of these interventions in rehabilitation of focal hand dystonia.

METHODS Subjects. Six healthy subjects (one woman; age 34 ± 3 years, range 26 to 48 years), six healthy musicians (table 1), six patients with musician's dystonia (table 2), and six patients with writer's cramp (table 3) were studied. Inclusion criteria for focal hand dystonia (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 writer's cramp for the item writing).

Table 2 Characteristics of patients with musician's dystonia

Patient	Sex	Age, y	Instrument	Age started, y	Time spent playing, h/day*	Professional musician?	Symptoms during playing	Duration of symptoms, y	Severity of symptoms (BFM movement scale) [†]	Treatment
1	F	39	Piano	6	4	Yes	Flexion ring and little finger right	8	2	Physio
2	F	42	Piano	5	4	Yes	Flexion ring and little finger right	4	2	Physio
3	M	35	Violin	8	3	Yes	Flexion ring finger left	3	2	Physio
4	M	37	Piano, organ	6	3	Not any more	Flexion of middle finger left	4	2	Physio
5	M	45	Clarinet/saxophone	9	2	Yes	Flexion 4th finger left	12	2	None
6	M	32	Guitar	11	3	Yes	Flexion 3rd finger right	6	2	None

*Estimation for the time period of last 6 months.

[†]Patients with musician's dystonia scored 0 for the item writing on the disability scale of the Burke-Fahn-Marsden (BFM) scale.

Table 3 Characteristics of patients with writer's cramp

Patient	Sex	Age, y	Symptoms during writing	Affected task/side	Duration of symptoms, y	Severity of symptoms (BFM movement/disability scale)	Treatment
1	M	38	Flexion thumb and index	Writing/L	9	2/2	None
2	M	40	Flexion ring and little finger	Writing/R	9	2/1	None
3	M	25	Flexion thumb and index; wrist extension	Writing/R	6	2/2	None
4	F	38	Flexion thumb and index	Writing/R	6	2/1	BTX, last 6 months ago
5	M	51	Flexion thumb and index	Writing/R	3	2/2	BTX, last 7 months ago
6	F	39	Flexion thumb and index	Writing/R	15	2/1	None

BFM = Burke-Fahn-Marsden; BTX = botulinum toxin.

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

Transcranial magnetic stimulation. Transcranial magnetic stimulation (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 approximately 45 deg to the interhemispheric line to evoke anteriorly directed current in the brain and was optimally positioned to obtain motor evoked potentials (MEPs) in abductor pollicis brevis muscle (APB) of the right hand in healthy subjects and the affected hand in patients. The active motor threshold (aMT) defined as the minimum intensity needed to evoke a MEP of $>200 \mu\text{V}$ in 5 out of 10 trials was measured in the tonically active APB (20% of maximal contraction as assessed visually on an oscilloscope). Stimulation intensities are quoted in the text as a percentage of maximal stimulator output ($\pm\text{SE}$) or percentages of aMT ($\pm\text{SE}$).

EMG recording. Surface EMG recordings in a belly-to-tendon montage were made from APB, first dorsal interosseus (FDI), and abductor digiti minimi (ADM). APB 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 either APB or FDI using an electromagnetic mechanical stimulator (Ling Dynamics System Ltd., UK) with a 0.7 cm diameter probe. The amplitude (0.2 to 0.5 mm) of the vibration was adjusted individually to be just below threshold for perceiving an illusory movement.^{17,18} During vibration we monitored the EMG for any muscle contraction indicating, besides possible voluntary activation, the occurrence of the tonic vibration reflex.^{19,20} TMS stimuli were given 1 s after the start of muscle vibration.

Experimental parameters. The measures were designed to explore the basic pattern of SMO in the three hand muscles. In previous studies⁹ we had measured with and without vibration of the FDI or APB muscle, the peak-to-peak ampli-

tude of MEPs after single TMS pulse as well as short interval intracortical inhibition (SICI) using a subthreshold conditioning stimulus.²¹ In general, the changes in MEP during vibration mirrored those in SICI: when vibration increased the MEP in a muscle, the level of SICI was reduced. However, the size of the MEP can be affected by changes in spinal as well as cortical excitability, whereas changes in SICI are generally thought to reflect purely cortical effects.²²

Although measurement of SICI involves recording the response to single-pulse MEPs, in the present study we focused on SICI since this is a better measure of the purely cortical effect of our training protocols.

The SMO was measured following the previously described protocols.^{15,16} In brief, single (test pulse alone) or pairs of pulses (conditioning and test pulse) were applied randomly every 5 s. On one third of trials each, stimuli were applied in the presence of FDI vibration, APB vibration, or without vibration. A total of 60 trials were collected with 10 trials of each condition. It should be noted that although short-term vibration increases the amplitude of the test MEP, we have previously shown that the percent SICI is unaffected by variations in MEP amplitude over this range in healthy subjects, healthy musicians, and patients with musician's dystonia and writer's cramp.⁸ Therefore, an adjustment of the test pulse intensity to evoke MEPs of matching size (1 mV peak-to-peak amplitude) was not necessary.

Interventions with behavioral proprioceptive training. All interventions lasted for 15 minutes and involved repeated cycles of vibration (2 s on, 2 s off) applied to the APB muscle alone. Vibration was applied with the same parameters (80 Hz, amplitude 0.2 to 0.5 mm [individually adapted]) and the same position of probe as used in the main testing protocol above.

Two different types of intervention were explored. They differed in the focus of attention: vibration of APB with attention drawn onto subtle changes of vibration frequency (AttVIB) and vibration of APB with attention drawn on subtle electrical stimuli applied to the skin overlying the lateral base of the index finger (AttIndex).

AttVIB. In 66% of trials at random the frequency of the vibration was changed from 80 Hz to 65 Hz, 67.5 Hz, 70 Hz, 72.5 Hz, 75 Hz, or 77.5 Hz for the last 300 msec of the 2 s train. In the 2 s rest period between vibration, subjects had to report whether they perceived a change or not by pressing buttons on a response box with their left/unaffected hand. There were twice as many trials with frequency changes as without (150 trials with change, 75 without). They were instructed to be as accu-

Table 4 Transcranial magnetic stimulation parameters (\pm SE) defined in the abductor pollicis brevis in all groups and statistical results

	Age, y	AttVIB			AttIndex		
		aMT	Cond. SI	Test SI	aMT	Cond. SI	Test SI
Healthy subjects	34.3 \pm 3.5	30.5 \pm 3.1	27.2 \pm 2.3	50.3 \pm 5.2	29.8 \pm 3.0	26.7 \pm 2.4	49.0 \pm 4.9
Healthy musicians	28.8 \pm 1.7	31.2 \pm 1.8	27.7 \pm 1.7	51.5 \pm 3.7	31.7 \pm 1.3	28.3 \pm 1.4	52.3 \pm 3.7
Musician's dystonia	38.3 \pm 1.9	29.2 \pm 1.6	24.2 \pm 1.6	45.8 \pm 2.2	29.7 \pm 2.1	25.2 \pm 2.0	47.5 \pm 3.0
Writer's cramp	38.5 \pm 3.4	30.3 \pm 2.0	26.2 \pm 1.7	47.5 \pm 3.9	30.7 \pm 1.9	25.8 \pm 1.6	48.0 \pm 3.6
ANOVA (group)							
F(3;20)	2.75	0.14	0.70	0.44	0.17	0.53	0.32
p	0.070	0.934	0.562	0.729	0.912	0.664	0.811

The means of the aMT, the stimulus intensity of the test pulse which produces a motor evoked potential (MEP) of 1 mV peak-to-peak amplitude without vibration (test SI), and of the conditioning pulse intensity that produces a 50% inhibition of this test MEP are given in percentage of stimulator output. Within each group aMT, cond. SI, and test SI were not significantly different in the AttVIB and AttIndex experiments (paired *t* tests; NS).

AttVIB = attention drawn onto subtle changes of vibration frequency; AttIndex = attention drawn on subtle electrical stimuli applied to the skin overlying the lateral base of the index finger; aMT = active motor threshold; Cond. SI = conditioning stimulus intensity; Test SI = test stimulus intensity; ANOVA = analysis of variance.

rate rather than as quick as possible. Auditory feedback of whether their answer was correct or not was given after each trial. These data were digitized and stored for off-line analysis.

AttIndex. Subjects had to press a button with their left/unaffected hand as rapidly as possible in response to subtle cutaneous stimuli (just above sensory threshold) applied via a pair of electrodes to the skin overlying the FDI muscle. Subjects were given auditory feedback when their reaction occurred within a time window of 300 msec after the cutaneous stimulus. Stimuli occurred randomly during the vibration or during the vibration free interval, with one stimulus within each 4 s cycle (2 s APB vibration 2 s interval). This condition was performed as a reaction time task to match the level of attentional demand to the AttVIB condition, to give subjects feedback about their performance and to keep them motivated to perform as well as possible. The reaction time data were digitized and stored for off-line analysis.

In this condition, the subjects' attention was directed away from the APB vibration, and focused on a different modality of input in a different location on the hand. We did not give both stimuli (vibration and cutaneous) to the same location (e.g., the APB muscle) because this made it much more difficult than the AttVIB task. Any changes observed might then have been due to changes in the level of attention between tasks.

Protocol. Each subject participated in two experiments testing the effects of each intervention separately. The order of interventions was randomized and the experiments were performed at least 1 week apart from each other. In all of them, we tested the sensorimotor organization in intrinsic hand muscles before and after one of the interventions described above.

Data analysis and statistics. *Analysis of the neurophysiologic data.* *Within group statistics.* Paired *t* tests were performed in order to compare aMT, conditioning, and test pulse intensities obtained in both experimental parts; further paired *t* tests were performed to compare the MEPs obtained in all hand muscles without vibration before and after the intervention. There was no significant difference in stimulus parameters (aMT, conditioning, and test pulse intensities)

and MEPs without vibration obtained before or after the interventions. This allowed for two simplifications of the data set: 1) to pool the baseline data obtained before the interventions and 2) to express the SICI measured during vibration of APB or FDI as a percentage of SICI without vibration. Paired *t* tests comparing these normalized vibration SICI at baseline and after the interventions were performed and the results are shown as asterisks in figures 2 and 3.

Separate repeated measures analyses of variance (ANOVAs) with the factors intervention (baseline/AttVIB or baseline/AttIndex), muscle (APB, FDI, ADM), and vibration condition (vibAPB, vibFDI) were performed with subsequent two-way analyses (tables e-1 through e-4 on the *Neurology*[®] Web site at www.neurology.org).

Between group statistics. A one-way ANOVA with factor group was performed on the parameters age, aMT, conditioning, and test stimulus intensities as obtained for both parts of the experiments (table 4). *t* Tests were used to compare the age at which instrumental playing was started in healthy musicians and musician's dystonia, as well as to compare the BFM scores in musician's dystonia and writer's cramp.

For the baseline data, repeated measures ANOVA with the factor group as between group factor, and muscle and vibration condition as within group factors were performed and followed up by subsequent two-way ANOVAs (table e-5).

Since the interaction between the factors group and intervention could be confounded by group differences in sensorimotor organization at baseline, this analysis was only performed for the groups of healthy musicians vs musician's dystonia, who showed similar baseline sensorimotor organization patterns. A repeated measures ANOVA with the factors healthy musician/musician's dystonia as between group factor and intervention: baseline/AttVIB or baseline/AttIndex and vibration condition as within group factors was calculated for the data obtained in each hand muscle separately. Further two-way ANOVAs were performed (table e-6).

Analysis of the behavioral data. For the data obtained during the AttVIB and AttIndex interventions, the number of errors per minute was displayed. A one-way ANOVA with

the factor time was calculated for each group separately to control for changes in error rates over time.

For the AttVIB behavioral data, the percentage of errors performed per condition (interval) was calculated. Two-way ANOVAs with the factors group and interval as well as one-way ANOVAs for each group separately were performed.

On the average reaction time data per condition obtained during the AttIndex intervention a two-way ANOVA with the factor group and stimulation time as well as subsequent one-way ANOVAs for the data of each group separately were performed. Separate two- and one-way ANOVAs were performed for the average reaction time data in conditions during the vibration phase (200 to 1,800 msec).

The significance level was set at $p \leq 0.01$ for ANOVAs in order to correct for multiple comparisons, and to $p \leq 0.05$ for t tests.

RESULTS **Subjects and TMS parameters.** Table 4 shows the mean age, as well as the values for mean stimulus intensities used for test (test SI) and conditioning pulses (cond. SI), and the active motor thresholds (aMT) for each group. Apart from healthy musicians being younger than patients with musician's dystonia (t test; $p = 0.004$), there were no significant differences between the groups in any of these parameters (ANOVA results see table 4). The age at which instrumental playing started was similar in healthy musicians and musician's dystonia (t test; $p = 0.8$). Furthermore, in all groups the amplitudes of the test MEPs recorded in all muscles without vibration before the interventions were similar [ANOVA (group \times muscle) $F(6;88) = 1.01$; $p = 0.424$] (figure e-1). The dystonic symptoms as assessed by the BFM score were of similar severity in both patient groups (t test; $p = 0.99$).

Neurophysiologic data. Sensorimotor organization at baseline (before interventions). Figure 1 displays the amount of SICI in each of the four groups of subjects expressed as (conditioned MEP/test MEP) in percent. In each muscle, the amount of SICI was measured in three different conditions: without vibration (no vib) and during short-term vibration of the APB (vib APB) or FDI (vib FDI).

In healthy subjects, muscle vibration reduced SICI in the vibrated muscle, while having the opposite effect on the non-vibrated muscles. This pattern was less distinctive in healthy musicians. Here, vibration of either APB or FDI reduced SICI in both FDI and APB, while still increasing SICI in ADM. In musician's dystonia, vibration reduced SICI in all recorded muscles, whereas in writer's cramp vibration had no effect on SICI (see statistics in tables e-1 through e-4 for within group statistics on the baseline data). These results confirm our previous findings obtained in different patients.⁹ A three-way

ANOVA with group as between-group factor and muscle as well as vibration condition as within group factors revealed a significant three-way interaction [$F(6;88) = 172.6$; $p < 0.0001$] (table e-5).

Common effects for all groups after both interventions. There were no significant differences either within or between any of the groups in the amount of SICI obtained without vibration before and after the interventions (paired t tests; NS). This allowed for a simplification of the data set by calculating the percentage change in SICI when vibration was applied. In addition, since the baseline sensorimotor organization obtained before the two interventions was the same (paired t tests; NS) these values were pooled to provide a single baseline. The following description and analysis of the results will refer to this simplified data set (figures 2 and 3).

Intervention effects within each group. First the effects of both interventions are described separately within each group before group differences are presented. Details of the statistical results for the within group analyses are given in tables e-1 through e-4; the statistical results of paired t tests comparing baseline data with data obtained after the interventions are shown as asterisks in figures 2 and 3 (with $*p \leq 0.05$ and $**p \leq 0.001$).

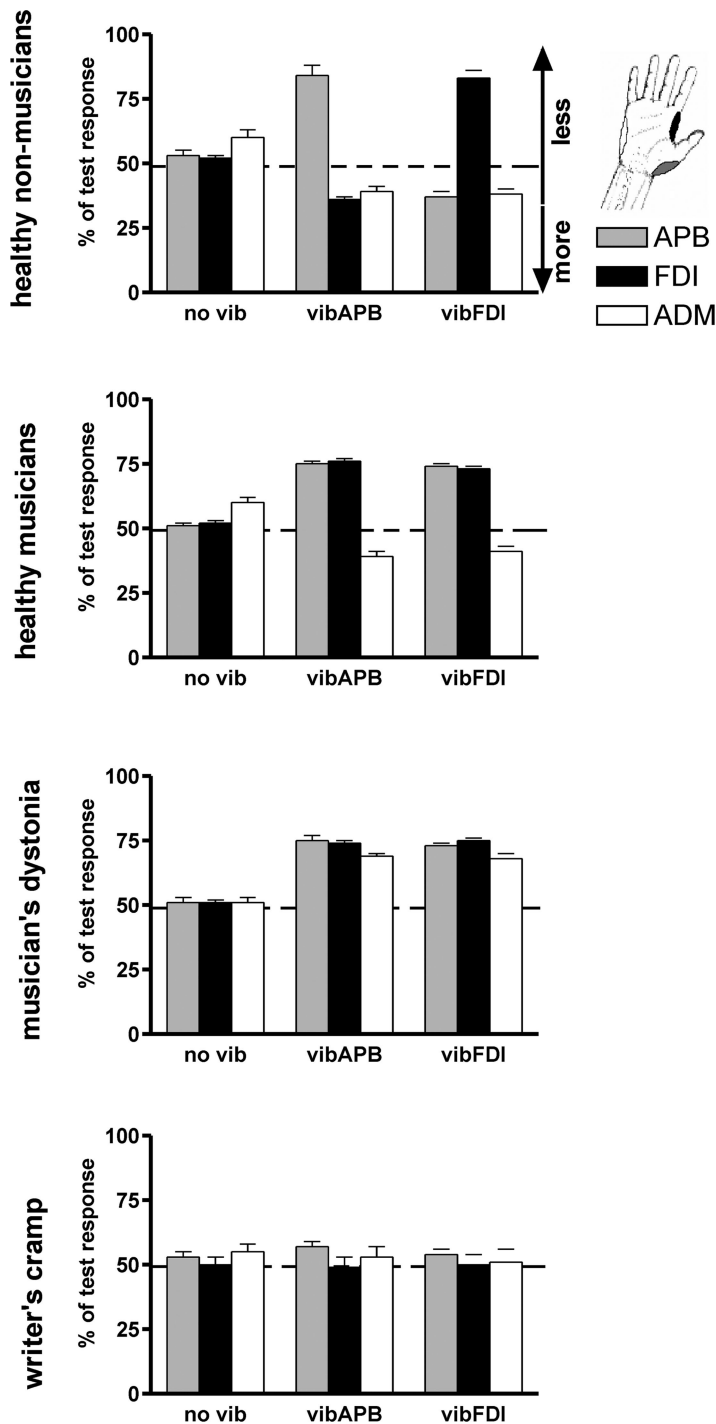
AttVIB. The results in healthy non-musicians are similar to those described previously.¹⁶ In brief, after AttVIB intervention the effect of vibAPB on SICI in APB (homotopic effect) was unchanged. Before the intervention SICI in FDI was increased by vibAPB; however, afterwards it was decreased (paired t tests; see figure 2). The results in ADM remained unchanged.

Before intervention, vibFDI decreased SICI in FDI (homotopic effect), whereas afterwards it had no effect. The results in APB and ADM remained unchanged. Effectively, it is as if the homotopic effect of vibAPB had expanded to FDI while the homotopic effect of vibFDI on FDI was reduced. A three-way ANOVA with the factors intervention: baseline/AttVIB, muscle, and vibration condition showed a significant interaction [$F(2;22) = 44.8$; $p < 0.0001$].

As in healthy non-musicians, in healthy musicians the AttVIB intervention did not change the effect of vibAPB on SICI in APB. Prior to intervention, vibAPB reduced SICI also in FDI in this group of subjects. This effect was smaller after the intervention. The results in ADM remained unchanged.

There were similar changes for the vibFDI effect. Here the homotopic effect became stronger; that is, vibFDI reduced SICI in FDI to a greater extent after

Figure 1 Baseline sensorimotor organization in healthy subjects, healthy musicians, musician's dystonia, and writer's cramp



Short-interval-intracortical-inhibition (SICI) (\pm SE) expressed as percentage inhibition relative to unconditioned control values. Each of the three columns of graphs shows data obtained without muscle vibration (no vib), during vibration of abductor pollicis brevis (APB) (vibAPB), and during vibration of first dorsal interosseus (FDI) (vibFDI) in the hand muscles (APB, FDI, abductor digiti minimi [ADM]). In healthy subjects the effect of short-term vibration is differential, showing a decrease of SICI in the vibrated muscle, while having the opposite effect in the non-vibrated muscles. In healthy musicians, short-train vibration of APB and FDI decrease SICI in APB and FDI, and enhanced it in ADM. However, in musician's dystonia and writer's cramp there was no differential effect; short-train vibration of APB and FDI decreased SICI in all hand muscles, whereas in writer's cramp short-train vibration had no effect on SICI. The baseline data obtained in both parts of the experiments before the two vibration interventions (AttVIB, AttIndex) was not different in any of the groups and was pooled to provide a single data set, which is displayed here.

AttVIB than before. In contrast, the previously abnormal reduction of SICI in APB by vibFDI was less evident after AttVIB. The parameters measured in ADM did not change. A three-way ANOVA with the factors intervention: baseline/AttVIB, muscle, and vibration condition showed a significant three-way interaction [$F(2;22) = 55.2; p < 0.0001$].

Before the intervention, vibAPB in musician's dystonia reduced SICI in all three hand muscles. After AttVIB the effect of vibAPB became more focused on APB, and was significantly attenuated in FDI (paired t test; $p \leq 0.001$) as well as ADM ($p \leq 0.001$). Similarly, before intervention, vibFDI reduced SICI in all muscles. After AttVIB, it reduced SICI even more in FDI ($p \leq 0.05$), whereas it had significantly less effect on SICI in APB and ADM. Thus, after AttVIB, both vibAPB and vibFDI tended to induce a pattern that resembles the pre-intervention state in healthy non-musicians. A three-way ANOVA with the factors intervention: baseline/AttVIB, muscle, and vibration condition showed a significant three-way interaction [$F(2;22) = 52.0; p < 0.0001$].

In writer's cramp, vibAPB and vibFDI did not influence SICI in any hand muscle before the interventions. Afterwards, there was a significant change in the effect of vibAPB on APB, but no other effect. A three-way ANOVA with factors intervention: baseline/AttVIB, muscle, and vibration condition showed no significant interaction.

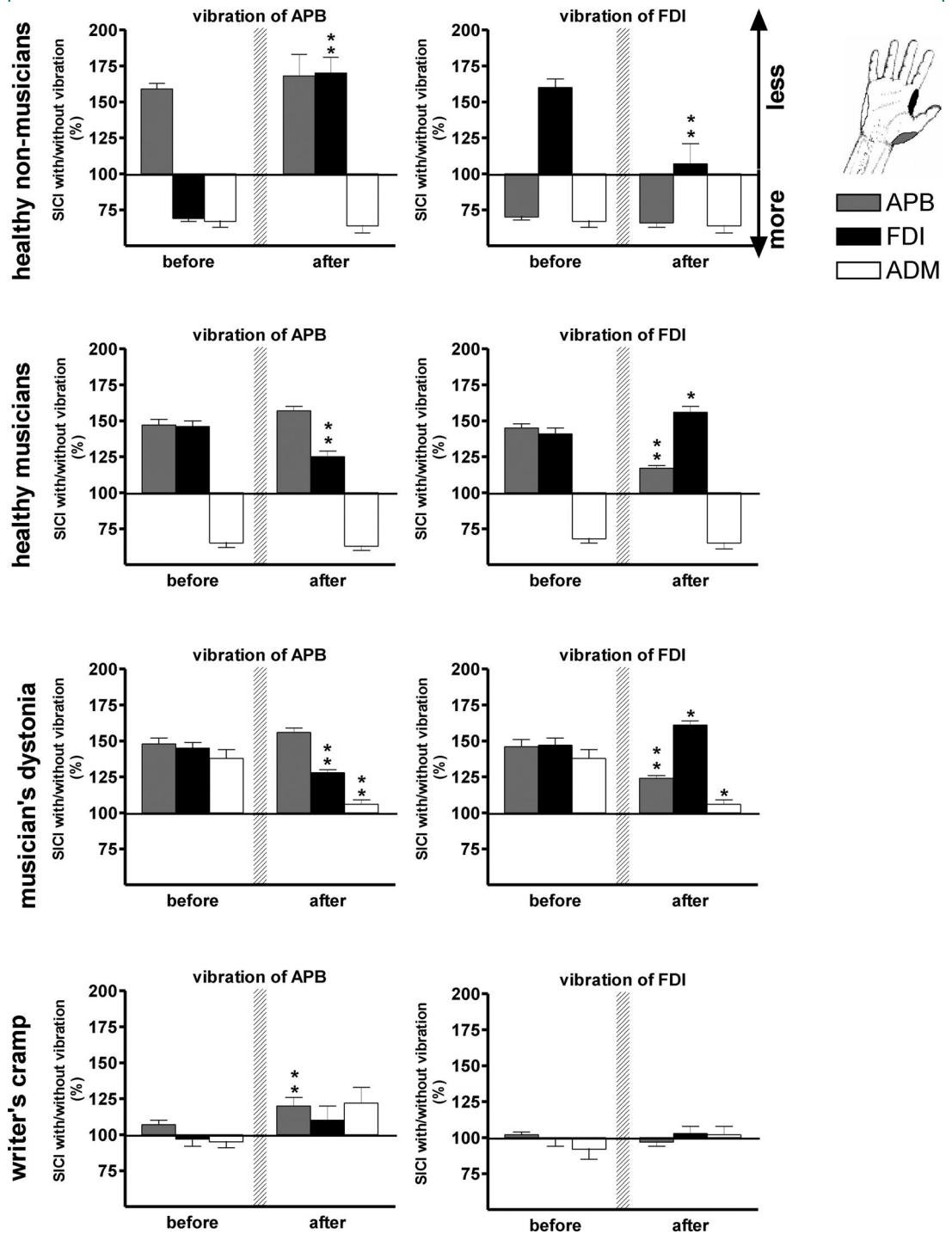
AttIndex. In healthy non-musicians the AttIndex intervention abolished the effect of vibAPB on APB and FDI (paired t tests, see figure 3), but had no influence on the effect of vibFDI. The statistical analysis showed a significant three-way interaction of the factors baseline/AttIndex \times muscle \times vibration condition [$F(2;22) = 52; p < 0.0001$].

In healthy musicians prior to the intervention, vibAPB decreased SICI in APB and FDI, and increased SICI in ADM. After AttIndex all these effects were significantly reduced in APB and FDI, but not for ADM (paired t test, see figure 3). Prior to intervention, vibFDI reduced SICI in both APB and FDI. After AttIndex, vibFDI decreased SICI even more in FDI while it produced less effect on SICI in APB. There were no significant changes in ADM. The statistical analysis showed a significant three-way interaction of the factors baseline/AttIndex \times muscle \times vibration condition [$F(2;22) = 39.4; p < 0.0001$].

In musician's dystonia and writer's cramp the AttIndex intervention had no effect on baseline parameters.

Comparison of intervention effects between groups. Direct comparison of the changes induced by

Figure 2 Effect of the vibration intervention with attention drawn onto subtle changes of vibration frequency (AttVIB) on sensorimotor organization in all groups

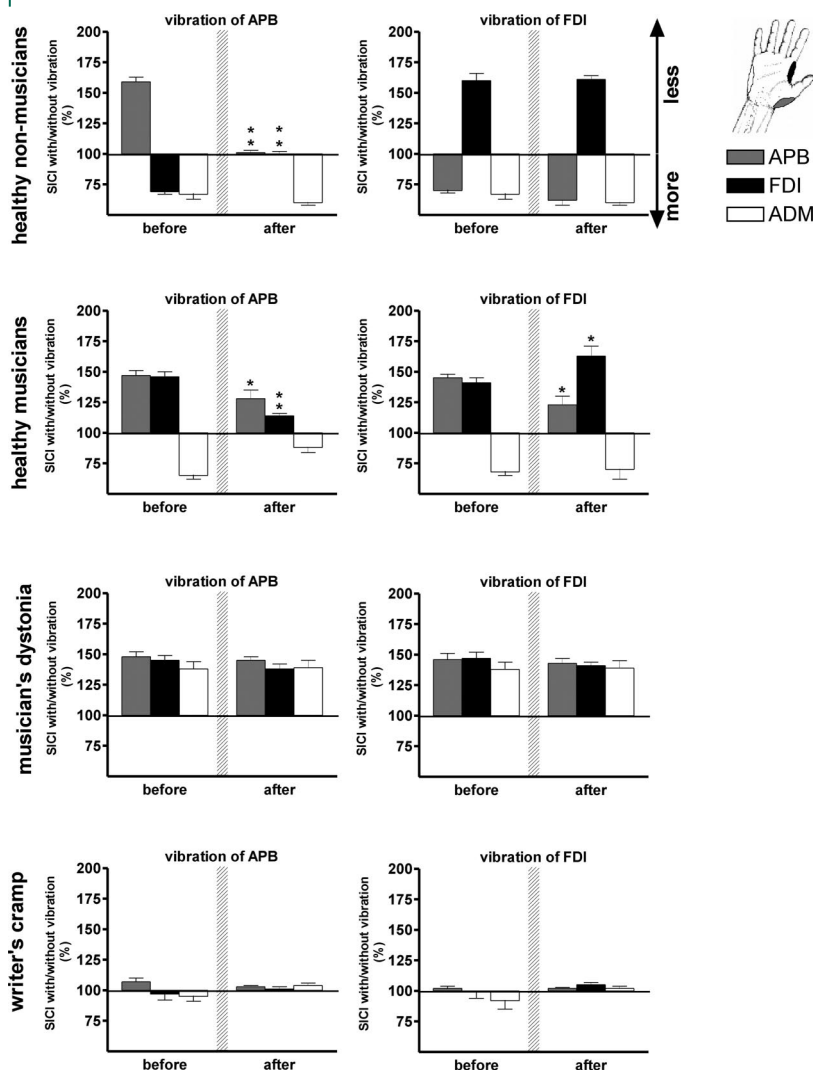


The data sets from each of the four groups of subjects consist of two rows that display the results of short-interval-intracortical-inhibition (SICI) (\pm SE) for the two vibration conditions, vibration of abductor pollicis brevis (APB), and vibration of first dorsal interosseus (FDI), separately. Each graph shows data of the three intrinsic hand muscles (APB, FDI, abductor digiti minimi) (ADM) before and after the intervention. Changes in SICI during vibration of either APB or FDI are plotted relative to the SICI obtained without vibration. Statistical results of paired *t* tests comparing baseline data with data obtained after AttVIB are shown as asterisks (with * $p \leq 0.05$; ** $p \leq 0.001$). For details see Results.

AttVIB and AttIndex in the groups is limited, since they are confounded by differences in their sensorimotor organization prior to intervention. However, it is possible to compare

healthy musicians and musician's dystonia, since in these groups the baseline data obtained in APB and FDI was not significantly different (unpaired *t* tests; $p > 0.05$).

Figure 3 Effect of the vibration intervention with attention drawn on subtle electrical stimuli applied to the skin overlying the lateral base of the index finger (AttIndex) on sensorimotor organization in all groups



For further details refer to the legend of figure 2.

The effect of the AttVIB intervention in healthy musicians and musician's dystonia appears to be quite similar. The AttIndex intervention changed the effect of subsequent vibAPB quite differently in the two groups. The effect of vibAPB was attenuated in healthy musicians in APB and FDI, whereas it was unchanged in musician's dystonia. Similarly, the effect of vibFDI changed in healthy musicians but not in musician's dystonia. There were significant three-way interactions of baseline/AttIndex \times vibration condition \times healthy musicians/musician's dystonia for both muscles [$F(2;45) > 7.1; p < 0.002$].

Behavioral data. AttVIB. Figure 4A displays the number of errors per minute training for each group, which is relatively constant in each group during the 15 minutes training, indicating that the

subjects' level of attention was probably constant during the training period.

A two-way ANOVA with group as between group and time as within group factor showed no significant interaction or main effect of these factors [ANOVA group \times time; $F(3;20) = 0.46; p = 0.7$]. Subsequent one-way ANOVAs for each group separately showed no significant main effect of the factor time [ANOVAs; $F(14;70) \geq 0.5; p \geq 0.05$].

In figure 4B, these data are plotted to show the percentage errors performed per condition. The x-axis displays the differences from the baseline frequency (80 Hz) that the subjects had to perceive, with 15 Hz being the biggest and 2.5 Hz the smallest difference. In all groups the percentage of errors increased with smaller frequency differences. However, while the results in healthy subjects, healthy musicians, and patients with musician's dystonia are relatively similar, the patients with writer's cramp only managed to discriminate the two widest intervals with accuracy similar to healthy subjects.

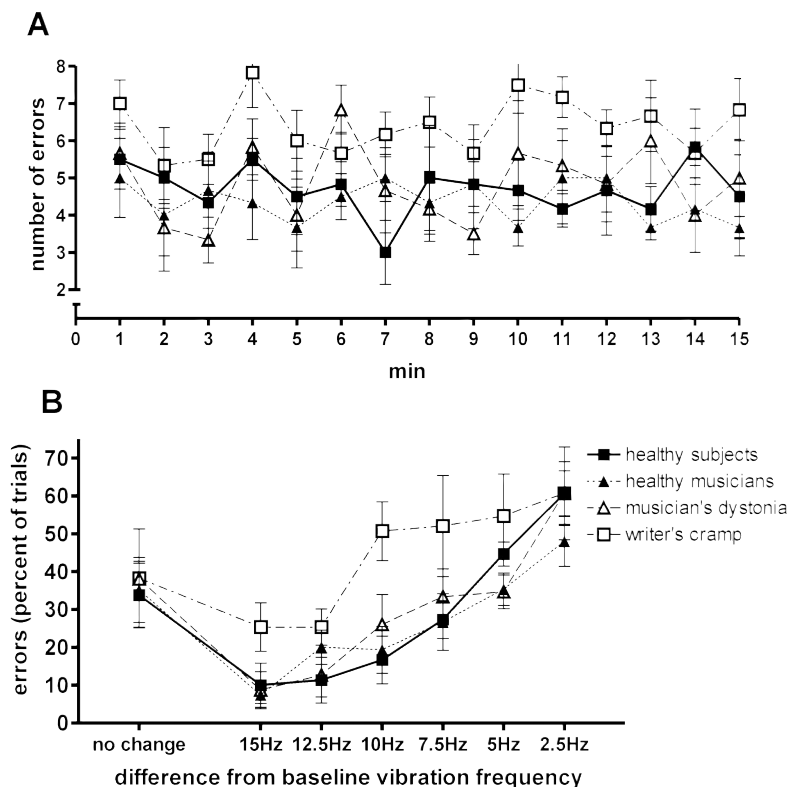
A two-way ANOVA performed with group as between group factor and interval as within group factor showed a significant main effect for group [ANOVA; $F(3;20) = 4.58; p = 0.01$] and interval [ANOVA; $F(6;120) = 18.67; p = 0.001$], but no significant interaction. Subsequent one-way ANOVAs performed on the data of each group separately showed significant effect of the factor interval in healthy subjects, healthy musicians, and musician's dystonia [ANOVAs; $F(6;30) \geq 7.3; p \leq 0.0001$], but not in writer's cramp.

AttIndex. Figure 5A displays the average reaction time per minute during the 15 minutes training for all groups. A two-way ANOVA with group as between- and time as within-group factor showed no significant interaction or main effects [ANOVA group \times time; $F(42;280) = 1.14; p = 0.26$]. Subsequent one-way ANOVAs performed for each group separately showed no significant effect of time in either of them [ANOVA; $F(14;70) \geq 0.6; p \geq 0.05$].

Figure 5B displays the same data expressed as the average reaction time per condition. The x-axis shows the timing (ms) of the cutaneous stimulus in relation to the onset of APB vibration, which was presented from 0 to 2,000 msec. In all groups the mean reaction times during the vibration phase (200 to 1,800 msec) were longer compared to the vibration free interval (2,200 to 3,400 msec) (paired t tests; $p \leq 0.03$).

A two-way ANOVA with group as between- and stimulus time as within group factor showed

Figure 4 Behavioral data from the vibration intervention with attention drawn onto subtle changes of vibration frequency (AttVIB)



Subtle changes of vibration frequency that occurred at the end of each 2 s-vibration phase had to be discriminated. A displays the mean number of errors (\pm SE) made per minute during this 15 minutes intervention for each group of subjects. The performance was relatively stable during the intervention in all groups (see Results), indicating that attention was kept at a similar level. B plots the same data expressed as number of errors per frequency difference (Hz; \pm SE) for each group separately. Healthy subjects, healthy musicians, and patients with musician's dystonia performed relatively well on this task, while patients with writer's cramp only managed to discriminate the two widest intervals with accuracy similar to healthy subjects.

no significant interaction, but a significant main effect of stimulus time [ANOVA; $F(8;160) = 34.01$; $p \leq 0.0001$]. There was no significant main effect of the factor group which might be due to the fact that in all groups the mean reaction times to stimuli applied in the vibration free interval were relatively similar. However, a subsequently performed one-way ANOVA on the pooled mean reaction times obtained during vibration showed a significant effect of group [ANOVA; $F(3;140) = 10.35$; $p \leq 0.0001$].

DISCUSSION These experiments tested the effect of 15 minutes attended or unattended vibratory stimulation on the pattern of SMO in healthy non-musicians, healthy musicians, patients with musician's dystonia, and patients with writer's cramp. In confirmation of our previous results, baseline SMO differed among the groups⁹ and could be influenced in healthy non-musicians by these 15 minutes interventions.¹⁶ The new findings in the present data are that the same interven-

tions have a different effect on SMO in healthy musicians, patients with musician's dystonia, and patients with writer's cramp.

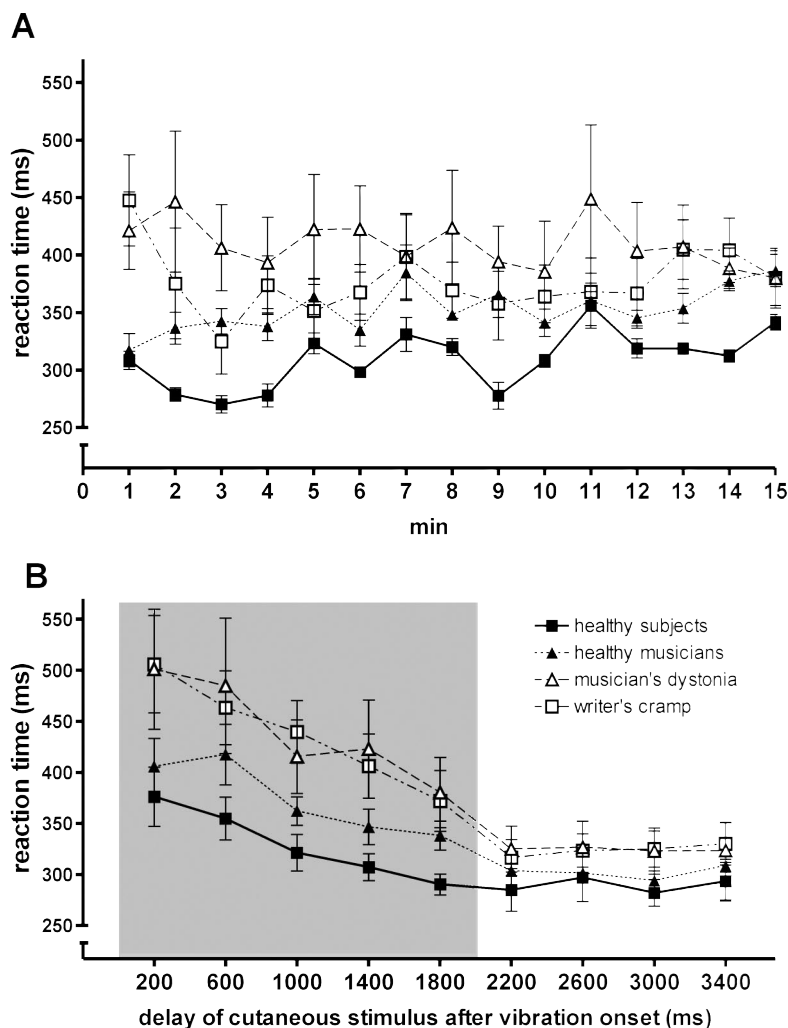
As we have argued before, the SMO, which describes the influence of short periods of muscle vibration on MEPs and SICI in hand muscles, can be seen as a measure of the input-output relation of sensory and motor cortex.^{8,15,16} The differential effect that is seen (focal activation of projections to the vibrated muscles, opposite effect on non-vibrated muscles) does not occur for cutaneous inputs and may therefore be related to the fact that proprioceptive inputs have direct projections to area 3a^{23,24} and area 4.²⁵

In the present article we have reported data on the SMO of SICI whereas in previous work we also included data on MEPs. The reason for this is that the effects of short periods of vibration on MEPs can involve both cortical and subcortical mechanisms. In order to limit discussion to cortical changes we concentrate on SICI, which is recognized to involve synaptic interactions within the cerebral cortex.²² In the text that follows we refer to increases in SICI (i.e., more inhibition) as inhibitory, and decreases in SICI (i.e., less inhibition) as facilitatory.

The effects of the 15 minutes interventions that we saw in healthy subjects confirm previous findings.¹⁶ After the AttVIB intervention the facilitatory effect of subsequent short-term APB vibration expanded from APB onto the FDI, while the effect of FDI input onto FDI was reduced, thus suggesting a competition between both effects. The AttIndex intervention had almost the opposite effect; subsequent short-term vibration of APB had almost no effect on either APB or FDI. The changes induced by both interventions seem to be quite focused, since the parameters in ADM were not modified. As discussed in our previous article, we hypothesize that attending to APB vibration during the intervention might have enhanced its efficacy by selecting and recruiting interneuronal circuits that are responsive to APB input but project also to the neighboring FDI.¹⁶

The baseline SMO is different in healthy musicians and non-musicians. In musicians there is a co-facilitatory effect of APB and FDI vibration on these two muscles, whereas the heterotopic inhibitory effect on ADM is preserved (see also⁹). Depending on the age at which instrumental playing was started, structural and functional alterations in the sensorimotor cortex of professional musicians have been described.¹⁰⁻¹⁴ We suggest that this adaptation of SMO reflects a higher synaptic

Figure 5 Behavioral data from the vibration intervention with attention drawn on subtle electrical stimuli applied to the skin overlying the lateral base of the index finger (AttIndex)



In this task, subjects had to detect subtle electrical stimuli applied to the skin overlying the first dorsal interosseus (FDI) muscle, that were applied randomly during vibration of abductor pollicis brevis (APB) or the vibration free interval. A displays the mean reaction times per minute (\pm SE) during the 15 minutes interventions for all groups. The reaction times did not change during the intervention, indicating a relatively constant level of attention throughout the task in all groups. B plots the same data expressed as the average reaction time per condition. The x-axis shows the timing (ms) of the cutaneous stimulus in relation to the onset of APB vibration, which was presented from 0 to 2,000 msec. In all groups the mean reaction times during the vibration phase (20 to 1,800 msec; shaded area) were longer compared to the vibration free interval (2,000 to 3,400 msec) (paired t tests; $p \leq 0.03$). Musician's dystonia and writer's cramp both had difficulties in discriminating and reacting to the cutaneous stimulus during the 2 s vibration phase. Interestingly, the healthy musicians also performed worse than healthy subjects on this task, perhaps indicating subclinical sensory abnormalities.

connectivity of sensorimotor areas representing neighboring muscle projections, which may be an advantage for fine movement control in musicians.

Interestingly, in healthy musicians the result of the AttVIB intervention on SMO was quite different. Here, there was no expansion of the effect of subsequent APB vibration; on the contrary, the expanded (compared to non-musicians) facilitatory effects of APB vibration onto FDI and of FDI

vibration onto APB were strongly reduced, thereby focusing the effects of short-term APB and FDI vibration onto the homotopic muscle, and restoring a more normal pattern. The interventions that we use are applied for only 15 minutes, so that the changes they induce are more likely to reflect changes in synaptic efficacy by potentiation/depotentiation or by unmasking of pre-existing synaptic connections, than by formation of new synapses. In line with the concept of homeostatic synaptic plasticity,²⁶⁻³⁰ we suggest any further strengthening of these already facilitated connections by the AttVIB intervention is occluded, and results in the opposite effect.

As reported previously,⁹ SMO in musician's dystonia lacked the usual differential organization seen in healthy non-musicians. Vibration of either APB or FDI increased excitability in all muscles rather than being focused on the vibrated muscle. We suggested that this pattern represents a further progression of the adapted SMO seen in healthy musicians that may eventually be associated with maladaptive behavioral consequences. The patients with musician's dystonia were on average older than the healthy musicians, resulting in a longer exposure to intense practice. However, experimental evidence shows that structural and functional brain adaptations to musical practice are determined by the age at which instrumental playing started,^{10-12,14} and this was similar in both groups. It is therefore unlikely that differences in the total amount of practice caused the difference in baseline SMO in healthy musicians and patients with musician's dystonia. However, in the absence of longitudinal studies it remains unclear whether the pattern seen in musician's dystonia is secondary to the development of dystonic symptoms or primary.

As in healthy musicians, the AttVIB intervention in patients with musician's dystonia had a reverse effect to that seen in healthy non-musicians. Interestingly, here the effect expanded to the ADM, and therefore induced a more physiologic pattern of SMO in all three hand muscles. We suggest that a similar homeostatic-like mechanism as discussed above for healthy musicians may occur here. Most importantly, these results show that the dedifferentiated SMO we see in musician's dystonia is not a fixed pattern, but can be modified by vibration interventions. However, the effect of the AttIndex intervention differed from that seen in healthy musicians. Patients with musician's dystonia did not show any changes in their baseline SMO, thus, the effect of subsequent APB vibration was not attenuated at all. It seems

as if they have difficulties in switching off sensory inputs.

As described previously, prior to any interventions, patients with writer's cramp showed no change in SICI during short-term vibration. We suggested that unlike musician's dystonia, who showed dedifferentiated facilitation in all hand muscles during short-term vibration of any muscle, patients with writer's cramp seem to be insensitive to vibration. Although both hand dystonia groups show a dedifferentiated SMO, it seems as if in musician's dystonia there is excess sensory coupling to motor output, whereas in patients with writer's cramp, sensory influences on motor output are attenuated.

Most importantly, as in musician's dystonia, SMO in writer's cramp was not fixed but could be changed by the AttVIB intervention, although to a much lesser extent. Subsequent APB vibration reduced SICI in all three hand muscles. Although this effect was strongest and significant in APB, it was far from inducing a physiologic differential pattern of SMO as seen in healthy subjects. As in musician's dystonia, the AttIndex intervention did not induce any change in SMO in writer's cramp, which is probably due to the fact that vibration has no effect in the baseline state, and hence cannot be reduced further.

Several studies have highlighted the impaired spatial and temporal sensory discrimination of patients with focal hand dystonia.^{3-6,31-35} Our study extends these findings to the sensory tasks studied in our vibration interventions. Here, we tested the subjects' ability to discriminate subtle changes in vibration frequency (AttVIB), as well as their ability to defocus from the proprioceptive input and react to cutaneous stimulation applied nearby. All groups showed a constant error rate over the duration of the task suggesting that their level of attention remained relatively constant throughout. Patients with writer's cramp were more impaired in their ability to discriminate vibration frequencies than patients with musician's dystonia, even though they both had similar difficulties in defocusing from the vibration in order to discriminate the cutaneous stimulus. To our knowledge, this is the first description of a difference in performance of patients with musician's dystonia and writer's cramp in a sensory discrimination providing further evidence that their pathophysiology may also differ. Interestingly, healthy musicians performed slightly better than healthy subjects in discriminating vibration frequencies; however, their ability to detect cutaneous stimuli during vibration lay between that of

healthy non-musicians and the patients with dystonia. It seems as if the slightly increased ability to differentiate vibration frequencies comes at a cost of their ability to defocus from the vibration and react to cutaneous inputs. It is possible that the subjects' task performance predicts/influences the effect of the vibration interventions on SMO. Although this cannot be completely ruled out, there is no clear correlation between performance and induced changes in physiology. The performance of patients with writer's cramp in discriminating frequency changes was the poorest among all groups, as was their performance in detecting cutaneous stimuli while defocusing from the ongoing vibration. However, the AttVIB intervention still changed in SMO in writer's cramp patients, which might argue against a strict behavioral/neurophysiologic correlation.

Our results show that the SMO of hand muscle control is flexible not only in healthy subjects, but also in healthy musicians, patients with musician's dystonia, and patients with writer's cramp. However, the way in which SMO responds to behavioral proprioceptive training is influenced by the baseline pattern of SMO, which itself is determined by the musician's status and the presence of focal hand dystonia. Thus therapeutic paradigms that attempt to restore physiologic patterns of SMO in patients may need to be adapted to the baseline state of the individuals being treated rather than relying on observations made in healthy subjects. Finally, the differences we noted in sensory discrimination during behavioral training together with the fact that the behavioral proprioceptive training induces different patterns of SMO effects in writer's cramp and musician's dystonia is compatible with the idea that they do not share the same pathophysiology. Further studies will now address the question whether the prolonged application of behavioral proprioceptive training improves hand motor function in focal hand dystonia.

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Sensorimotor reorganization by proprioceptive training in musician's dystonia and writer's cramp

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