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Regaining motor control in musician's dystonia by restoring sensorimotor organisation

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Abstract

Professional musicians are an excellent human model of long term effects of skilled motor training on the structure and function of the motor system. However, such effects are accompanied by an increased risk of developing motor abnormalities, in particular musician's dystonia. Previously we found that there was an expanded spatial integration of proprioceptive input into the hand area of motor cortex (sensorimotor organisation, SMO) in healthy musicians as tested with a transcranial magnetic stimulation (TMS) paradigm. In musician's dystonia, this expansion was even larger, resulting in a complete lack of somatotopic organisation. We hypothesised that the disordered motor control in musician's dystonia is a consequence of the disordered SMO.

In the present paper we test this idea by giving pianists with musician's dystonia 15 min experience of a modified proprioceptive training task. This restored SMO towards that seen in healthy pianists. Crucially, motor control of the affected task improved significantly and objectively as measured with a MIDI piano, and the amount of behavioural improvement was significantly correlated to the degree of sensorimotor re-organisation. In healthy pianists and non-musicians, the SMO and motor performance remained essentially unchanged. These findings suggest a link between the differentiation of SMO in the hand motor cortex and the degree of motor control of intensively practiced tasks in highly skilled individuals.

Keywords

focal hand dystonia; musician; TMS; motor control; sensorimotor; proprioception

Introduction

Motor skill learning induces structural and functional changes in the brain (Kleim et al., 2004; Rosenkranz et al. 2007a). An excellent human model for long-term motor learning are professional musicians, in whom brain changes depend on the age at which musical training commenced (Gaser and Schlaug, 2003; Bengtsson et al., 2005; Rosenkranz et al., 2007b). However, intensive motor training has also been associated with the development of task-specific disorders of motor control, focal hand dystonia (Byl et al., 1995), and professional musicians are more often affected than non-musicians (Altenmüller et al., 2003). Physiological studies suggest that musicians' training leads to reorganisation of sensorimotor

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representations in the cortex that are more pronounced in musician's dystonia than in healthy musicians (Elbert et al., 2005, 2008; Rosenkranz et al., 2005).

In earlier previous study, we tested how experimentally induced proprioceptive movement feedback from the hand muscles is integrated in the motor cortex (sensorimotor organisation, SMO). While healthy non-musicians show a characteristic differential pattern of SMO, with reduced intracortical inhibition in projections to the vibrated muscle and increased intracortical inhibition in “surrounding” projections to the non-vibrated ones, this pattern was less well differentiated in healthy musicians, and lost in musician's dystonia (Rosenkranz et al., 2005). Given the importance of proprioceptive input for motor learning (Pavlides et al., 1993) the changes observed in healthy musicians are likely to have developed during musical skill learning and may be used to support performance at the highest level. However, in musician's dystonia this re-organisation might have gone too far such that it interferes with motor control rather than assists it (Rosenkranz et al., 2005). If this association between the amount of sensorimotor re-organisation and the level of motor control holds true, restoring the “surplus” re-organisation seen in musician's dystonia to that seen in healthy musicians should re-establish motor control.

Several sensory and motor interventions have been used therapeutically in focal hand dystonia to relieve the presence of involuntary contractions (e.g. Zeuner et al., 2002, 2005; Candia et al., 1999). However, the mechanism responsible for any benefit remains unknown since no study has yet established a correlation between intervention-induced neurobiological effects and behavioural improvement. We have shown previously that a 15min intervention with proprioceptive stimulation changes the SMO in musician's dystonia and makes it more similar to that seen in healthy musicians spontaneously (Rosenkranz et al., 2008). Here we expand these findings by investigating whether restoring a more “normal” re-organisation in musician's dystonia by proprioceptive stimulation is associated with an improvement of task-specific motor control. We used a modified version of our previous training paradigm designed to improve the magnitude of the effects on SMO and examined pianists with focal hand dystonia compared to healthy pianist, to avoid confounds by specific brain changes induced by musical training (Bangert et al., 2006).

Methods

Subjects

Six healthy musically naïve subjects (mean age 34 years), eight healthy professional pianists (mean age 31 ± 2 years; see supplemental table 1 for details), and eight professional pianists with musician's dystonia (mean age 33 ± 3 years; see supplemental table 2 for detail) were studied. Groups were matched for age; in addition, healthy and dystonic pianists were matched for age at which piano playing was started and daily practice time. All pianists with musician's dystonia had task-specific symptoms that exclusively occurred during piano playing and involved predominantly the ring finger of the right hand (“pulling-in”) when playing downwards scale-like movements. None of the patients had received botulinumtoxin injections in the hand/forearm muscle before, which could affect neurophysiological findings. All subjects gave informed consent to the study, which was approved by the local ethics committee and conformed to the Declaration of Helsinki.

Transcranial magnetic stimulation (TMS) and EMG recording

TMS was performed using two MAGSTIM 200 stimulators connected by a Y-cable to a figure-of-eight-shaped coil with an internal wing diameter of 7cm (Magstim, Dyfed, U.K.). The coil was held with the handle pointing backwards and laterally approximately 45deg 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) as the main target muscle. The active motor threshold (aMT) defined as the minimum intensity needed to evoke a MEP of >200μV 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 (±SE).

Surface electromyographic (EMG) recordings in a belly-to-tendon montage were made from APB, first dorsal interosseus (FDI), and abductor digiti minimi (ADM). The raw signal was amplified and filtered (30Hz to 1kHz) (Digitimer Ltd.). Signals were digitized at 2kHz (CED Power1401, Cambridge Electronic Design, Cambridge, U.K.) and stored on a laboratory computer for off-line analysis.

Proprioceptive training

Proprioceptive training lasted for 15min and involved repeated cycles of muscle vibration (2s on, 2s off) applied to either the APB, FDI or ADM muscles in random order by using an electromagnetic mechanical stimulator (Ling Dynamics System Ltd., U.K.) with a 0.7cm diameter probe. The amplitude (0.2–0.5mm) of the vibration was adjusted individually to be just below threshold for perceiving an illusory movement (Roll and Gilhodes, 1995; Gilhodes et al., 1986).

Subjects were asked to focus their attention on the vibrated muscle and to discriminate subtle changes of vibration frequency occurring during the vibration period. In 75% of trials at random the frequency of the vibration was changed from 80Hz to 67.5Hz, 72.5Hz, or 77.5Hz for the last 300ms of the 2s-train. In the 2s 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 hand. They were instructed to be as accurate rather than as quick as possible. After each trial auditory feedback of whether their answer was correct or not was given.

Experimental parameters

Sensorimotor organisation (SMO)—The SMO was measured following previously described protocols (Rosenkranz and Rothwell, 2003, 2006a,b; Rosenkranz et al., 2005, 2008). In brief, single (test pulse alone) or pairs of pulses (conditioning and test pulse, interstimulus interval 3ms; Kujirai et al., 1993) to measure the short-interval-intracortical inhibition (SICI) were applied randomly every 5s. The intensity of the test stimulus was set to evoke an MEP of about 1mV peak-to-peak amplitude, and the subthreshold conditioning stimulus was set to evoke a 50% inhibition of the test MEP (about 80% aMT). On one quarter of trials each, stimuli were applied either in the presence of APB vibration (vibAPB), FDI vibration (vibFDI), ADM vibration (vibADM) or without vibration (novib). Using the same parameters and probe positions as mentioned above, the muscle vibration was applied in trains of 1.5s duration and the TMS single pulse or test pulse was applied 1s after the onset of vibration. During vibration EMG was monitored for any muscle contraction indicating, besides possible voluntary activation, the occurrence of the tonic vibration reflex (Hagbarth and Eklund, 1968; Marsden et al., 1969). A total of 80 trials were collected with 10 trials of each condition.

Although measurement of SICI involves recording the response to single-pulse MEPs, in the present study we focussed on SICI since this is a better measure of the purely cortical effect of proprioceptive training (DiLazzaro et al., 1998).

It should be noted that although short-term vibration increases the amplitude of the test MEP, we have previously shown that the percent SICI during vibration is unaffected by

variations in MEP amplitude over this range in healthy subjects, healthy musicians and patients with musician's dystonia (Rosenkranz and Rothwell, 2003; Rosenkranz et al., 2005). Thus, it was not necessary to adjust the test pulse intensity to evoke MEPs of matching size (1mV peak-to-peak amplitude).

Piano performance test—To objectively evaluate the piano performance, subjects were asked to play 10 cycles of a five-finger exercise (figure 1) on a MIDI-piano (Yamaha Clavinova CLP170) following a metronome set at 200bpm (1 note per beat). Two different levels of loudness (*pianissimo – mezzoforte*) and musical notation (*staccato – legato*) were tested for the right hand. The loudness level was verified by comparing the velocity of key press, which was not significantly different between groups. Furthermore, *staccato* and *legato* were verified by the absence or presence of overlay between successive notes, respectively. Healthy non-musician subjects were given 10-15min tuition on the task until their performance was stable. All healthy and dystonic pianists were given time to familiarise themselves with the particular mechanics of this piano. The duration of the key press was measured for each individual finger during the cycle, distinguishing between upward (thumb to little finger) and downward (little finger to thumb) movements. The coefficient of variance (CoVar) for the duration of keypress was calculated as a measure of performance variability. In order to give an additional simple summarising measure the mean CoVar (duration) averaged over all finger movements was calculated for each subject.

Self-assessment of piano performance—All participants were asked to express on a visual-analogue scale (VAS) whether they felt their performance of the five-finger exercise on the piano to be better or worse than before the proprioceptive training (VAS (change in performance); see supplemental figure 1A). For analysis the items were translated into a score with “0” indicating “no change”, and the numbers “1”, “2” and “3” describing that the performance was “slightly”, “moderately” or “strongly” changed with positive/negative values indicating improvement/worsening. Additionally, musician's dystonia patients were asked to rank their level of impairment on a VAS (impairment) scale ranging from “none” to “absolute” before and directly after each performance of the five-finger exercise. For analysis, the items were scaled from “0” (none) to “6” (absolute) (supplemental figure 1B).

Clinical evaluation—While the assessment of piano performance was based on the objectively assessed performance on the MIDI piano, hand motor control was additionally assessed before and after proprioceptive training using the Burke-Fahn-Marsden (BFM) and Tubiana-Chamagne Scales (TCS; Tubiana 1993; see supplemental table 3) for reasons of comparability to other clinically oriented studies on hand dystonia.

Vibration discrimination data—During the proprioceptive training, subtle changes of vibration frequency had to be discriminated (see above). These behavioural data were digitised and stored on the computer for off-line analysis and the number of errors performed per condition (frequency interval) and muscle were calculated.

Protocol

At the start of the experiments all participants performed the five-finger exercise on the MIDI piano, after which the patients were asked to subjectively assess their level of impairment on the VAS (impairment). Then, the participants were prepared for the TMS experiment and baseline SMO was recorded. Following this, proprioceptive training was performed for 15min. After a break of 10min, the SMO was recorded again, before the EMG electrodes were removed, and after a further break of 15min the participants were asked to perform the piano exercise again.

All participants were then asked to rate their performance on the VAS (change of performance), and additionally, musician's dystonia patients on the VAS (impairment). The patients were then asked to continue playing at home some repertoire of their choice, to repeat the five-finger exercise and their self-rating via VAS (impairment) at least 6 hours and 24 hours after the end of proprioceptive training and to report back via telephone.

Data analysis and statistics

Subjects' age and TMS parameters, the vibration discrimination data and the VAS (change of performance) scores were compared between all groups, and the clinical scores (BFM/TCS) and VAS (impairment) were compared in musician's dystonia before/after training by use of ANOVA, and parameteric (t-tests) or non-parametric tests (Wilcoxon's) where necessary (see Results for detail).

Neurophysiological and piano performance data—For data analysis and presentation the neurophysiological data was simplified. After establishing that the MEPs obtained in all hand muscles without vibration before and after the intervention were not significantly different (paired t-tests), the amount of SICI measured during vibration of APB, FDI, or ADM was expressed as a percentage of SICI without vibration. Statistical analysis was performed on this normalised SICI (see figure 2).

Analysis of variance (ANOVA) was used for the statistical analysis of the neurophysiological and piano performance data, followed by t-tests where necessary. The factors used for the analysis of the neurophysiological data were TRAINING (before/ after training), MUSCLE (APB, FDI, ADM) and VIBRATION CONDITION (vibAPB, vibFDI, vibADM). The analysis of the piano performance data was performed for the two conditions (mezzoforte, pianissimo) separately on the parameters duration and CoVar (duration) with the factors TRAINING and FINGER MOVEMENT.

The between-group statistics on neurophysiological and behavioural data could be confounded by the baseline differences between the groups, especially when including the factor TRAINING. Therefore, the between-group analysis was performed on the data obtained either before or after the proprioceptive training. In order to minimise this confound further, we have performed two different analyses involving the factor GROUP, one including the groups of healthy subjects and healthy musicians (HS/HM) only, and another including healthy musicians and musician's dystonia (HM/MD).

Correlation of SMO and piano performance data in musician's dystonia—In order to get a summarising measure of the changes of SMO after proprioceptive training (SMOchange) the difference (after – before proprioceptive training) of the normalised SICI data (vibrated/non-vibrated; as shown in figure 2) were calculated. To provide a single value for the homotopic (effect of vibration on the vibrated muscle), the near heterotopic (effect of vibration on the near-by non-vibrated muscle; e.g. vibAPB on FDI, vibFDI on APB) and far heterotopic (effect of vibration on the far non-vibrated muscle; e.g. vibADM on APB or FDI) effects, the data obtained in APB and FDI were averaged. The distinction between near and far heterotopic effects was made since the effect of proprioceptive training on the “far” heterotopic effect was expected to be stronger than that on the the “near” heterotopic. The data obtained in the ADM was not included, since both heterotopic effects induced by APB and FDI vibration could be considered as “far”, and therefore would have contributed an unequal amount of observations.

The averaged SMOchange was correlated with the difference (after – before proprioceptive training) of the mean key press duration (DURchange) and CoVar (COVARchange) for

each finger movement in the mezzoforte and pianissimo condition separately. The r^2 values were calculated and statistical analysis performed using t-tests.

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 and Wilcoxon's test.

Results

Subjects' and TMS parameters

The mean age, the active motor threshold (aMT) and the stimulus intensities used for test (test SI) and conditioning pulses (cond. SI) were not different between the groups (ANOVA (GROUP); $F(2;18)>0.07$; $p>0.3$) (table 1). The age at which instrumental playing started and the amount of actual daily playing were similar in healthy musicians and musician's dystonia (t-test; $p=0.6$ for starting age; $p=0.8$ for practice time). Furthermore, in all groups the amplitudes of the test MEPs and SICI recorded in all muscles without vibration before and after proprioceptive training were similar (ANOVA (GROUP); $F(2;18)>0.071$; $p>0.09$), thus allowing for a simplification of the data set as described above (see methods).

Neurophysiological data

Baseline Sensorimotor organisation—Figure 2 shows SICI during vibration as a percentage of the amount of SICI obtained without vibration for each group before and after proprioceptive training. Decreases of SICI (i.e. less inhibition) are plotted as columns going up, increases as columns going down.

At baseline, in healthy subjects muscle vibration reduced SICI in the vibrated muscle, whilst having the opposite effect on 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. However, vibration of ADM did enhance the SICI in the non-vibrated muscles. In musician's dystonia, vibration of one muscle reduced SICI in all recorded muscles. These results confirm our previous findings obtained in different groups of patients (Rosenkranz et al., 2005; 2008).

A within-group two-way ANOVA with the factors MUSCLE and VIBRATION CONDITION showed a significant interaction in healthy subjects ($F(4;20)=498.8$; $p<0.0001$) and healthy musicians ($F(4;20)=314,64$; $p<0.0001$), but not in musician's dystonia. This indicates that in the latter, vibration of any muscle had a similar effect on SICI recorded in all muscles.

The three-way interaction of the factors MUSCLE and VIBRATION CONDITION with either HS/HM ($F(4;40)=87,6$; $p<0.00001$) or HM/MD ($F(4;52)=65.84$;$p<0.00001$) as between group factors were significant, which indicates that the effect of vibration on the hand muscles is significantly different in healthy subjects compared with healthy musicians, as well as in healthy musicians compared with musician's dystonia.

Within-group effect of proprioceptive training on sensorimotor organization—After proprioceptive training, the differential pattern of SMO was sharpened in healthy subjects: the effect of vibration on the vibrated (homotopic) and on the non-vibrated (heterotopic) muscles became stronger (figure 2). In healthy musicians, there was less co-facilitation of vibAPB or vibFDI on APB and FDI muscles after proprioceptive training and the heterotopic effects of vibAPB on FDI and vibFDI on APB became stronger.

After proprioceptive training, the musician's dystonia patients showed a clear differential modulation in the effect of vibration on SICI. While the homotopic effect was little changed,

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there was a clear increase of SICI in the non-vibrated muscles (heterotopic effects), which was strongest in muscles farther away from the vibrated one (e.g. SICI increase in ADM during vibAPB and vibFDI).

A three-way ANOVA performed with the factors TRAINING, MUSCLE and VIBRATION CONDITION showed a significant three-way interaction in healthy subjects ($F(4;20)=39.83$; $p<0.0001$), in healthy musicians ($F(4;20)=19.6$; $p<0.0001$), and particularly in musician's dystonia patients ($F(4;32)=55.1$; $p<0.0001$).

Between-group effect of proprioceptive training on sensorimotor organisation—Table 2 displays the statistical results in detail. An ANOVA performed with VIBRATION CONDITION and MUSCLE as within-, and HS/HM as between-group factor showed significant interactions and main effects at baseline and after proprioceptive training. Therefore, the baseline differences in the effect of vibration on SICI in healthy subjects and healthy musicians persisted after proprioceptive training.

Using HM/MD as between-group factor, the three-way ANOVAs showed a significant three-way interaction and a significant main effect of HM/MD only for the baseline data. For the data obtained after proprioceptive training, no interaction or main factor reached significance. Similarly there was no difference when comparing the data obtained in musician's dystonia *after* the proprioceptive training with those obtained in healthy musicians at *baseline*. In summary, these results show that the effect of vibration on SICI differed in healthy musicians and musician's dystonia at baseline, however, after proprioceptive training there was no significant difference between these two groups, which is likely due to the fact that the SMO in musician's dystonia became more differentially organised and thus more similar to that seen in healthy musicians.

Piano performance data

The detailed description, statistical analysis and discussion of the piano performance data was carried out on the data obtained during *staccato* playing. The data obtained during *legato* playing was similarly changed and given as supplemental material (see supplemental figures 3 and 4).

Baseline performance parameters—Figures 3 and 4 display the duration of key press (left column) and the coefficient of variance (CoVar) of the duration of keypress (right column) for each key press performed in the test sequence, distinguishing between upward (thumb to little finger) and downward (little finger to thumb) movements while the subjects were asked to play *staccato mezzoforte* (figure 3) or *staccato pianissimo* (figure 4).

Baseline piano performance before the application of proprioceptive training was quite different between the groups (figures 3A,B and 4A,B). As expected, the mean key press duration was generally shortest in healthy musicians in both performance conditions (*mezzoforte* and *pianissimo*), but showed also some slight prolongation in the ring and little finger. A one-way ANOVA with the factor FINGER MOVEMENT was significant for the duration data in both performance conditions ($F(7;35)>6.8$; $p<0.001$). However, the variability of performance (CoVar) was lowest in healthy musicians and did not show significant differences between single finger movements.

The musician's dystonia patients showed clear differences between the fingers, with the ring and little fingers showing the longest durations and the highest variability. Here the one-way ANOVAs with the factor FINGER MOVEMENT on duration and CoVar (duration) data were significant in the *mezzoforte* and *pianissimo* condition ($F(7;56) >31.6$; $p<0.001$).

Healthy (non-musician) subjects showed longer key press durations and the variability of performance (CoVar) was high, especially in the more difficult *pianissimo* condition (figure 4 A, B). There were slight performance differences between finger movements, with the "ring up", "little finger", "ring down" finger movements showing the longest duration and the highest variability. However, this was not confirmed statistically since the one-way ANOVAs with the factor FINGER MOVEMENT was not significant in either performance condition for the duration of keypress or the CoVar (duration).

Within-group effect of proprioceptive training on piano performance—Healthy musicians showed no change in their performance parameters after the proprioceptive training. A two-way ANOVA with the factors TRAINING and FINGER MOVEMENT revealed no significant interaction for either the duration or the CoVar (duration) data in both performance conditions (*mezzoforte* and *pianissimo*). Similar to their results at baseline, the duration of key press was slightly prolonged in the ring and little fingers ((FINGER MOVEMENT); $F(7;35)>3.2$; $p<0.01$), but there was no finger-movement-specific effect on the CoVar (duration).

In musician's dystonia patients, however, the prolonged duration and increased CoVar (duration) were clearly reduced after training, especially in the ring and little fingers. Two-way ANOVAs with the factors TRAINING and FINGER MOVEMENT showed a significant interaction for the duration and CoVar (duration) data, in the *mezzoforte* and *pianissimo* performance conditions ($F(7;56)>6,4$; $p<0.001$) and significant main effects of the factor TRAINING ($F(1;8)>23.4$; $p<0.002$). In addition, the mean CoVar (duration) was significantly reduced after the proprioceptive training in both the *mezzoforte* and *pianissimo* performance conditions (figure 3E and 4E, paired t-tests; $p <0.001$).

In healthy subjects, piano performance appeared to be slightly improved after proprioceptive training with a reduction in the duration of key press and CoVar (duration). The two-way ANOVA with the factors TRAINING and FINGER MOVEMENT showed no significant interaction. However, there was a significant significant reduction of the mean CoVar (duration) (figure 3E, paired t-test: $p<0.01$) in the *mezzoforte*, condition, indicating that piano performance was less variable after proprioceptive training.

Between-group comparison of the effect of proprioceptive training on piano performance—Before the proprioceptive training the piano performance of musician's dystonia patients clearly differed from that of healthy musicians (figures 3A,B and 4A,B). In the *mezzoforte* and *pianissimo* performance conditions, the duration of key press was longer in musician's dystonia and the variability of performance higher. The difference was particularly striking in the ring and little fingers, which the patients had most difficulties in controlling. The two-way ANOVAs performed on the duration and CoVar (duration) data with HM/MD as between-group and FINGER MOVEMENT as within-group factor showed significant interactions for the *mezzoforte* and *pianissimo* conditions, and also significant main effects of the factor HM/MD (see Table 3 for details of the statistics).

However, after the proprioceptive training, the performance in musician's dystonia patients changed and tended to become more like that of healthy musicians, particularly in the key press duration data. The same two-way ANOVAs as performed on the baseline performance data above were now calculated for the data after the proprioceptive training, and also on the data obtained in musician's dystonia *after* the training compared to those in healthy musicians *before* the training. In contrast to the findings in the baseline performance data, after the training there were neither significant interactions nor main effect of HM/MD for the duration of key press and CoVar (duration) in the *mezzoforte* or the *pianissimo* conditions (see Table 3 for details of the statistics). These statistical results confirm that

particularly for the duration of key press, the performance of musician's dystonia patients after the proprioceptive training was more similar to that of healthy musicians either before or after the training.

Comparing the data of healthy musicians and non-musicians, in the latter, in general, the duration of key press was longer and the variability higher. Before and after proprioceptive training, the two-way ANOVAs with HS/HM as between-group factor and FINGER MOVEMENT as within-group factor showed significant interactions for duration and CoVar (duration) in the *mezzoforte* and *pianissimo* conditions ($F(7;72)<2,9$: $p<0.01$), with HS/HM having a significant main effect ($F(1;12) >13.5$; $p<0.001$).

Correlation of SMO and piano performance data in musician's dystonia

Figure 5 displays the relationship between changes in SMO (SMOchange) and piano performance data (DURchange; COVARchange) in the nine musician's dystonia patients. The significant correlations between SMOchange (see methods) in the heterotopic near (Figure 5A) and far (Figure 5B) effects with DURchange and COVARchange (see methods) in the ring finger downwards movement and little finger ($p<0.05$) are displayed. These results show that the restoration of a heterotopic (near and far) inhibitory effect in the SMO is associated with an improvement of control of ring and little finger movements, which were most affected by the dystonic symptoms (see Figure 5 for results of r^2).

Effect of proprioceptive training on self-assessment and clinical scales

Three out of six healthy subjects and one out of eight healthy musicians perceived their piano performance as slightly improved after the training. However, all musician's dystonia patients reported a significant subjective improvement of motor performance that in some cases lasted up to 24 hours. This was paralleled by a significant improvement in the BFM and TCS scores (for further details see supplemental table 4).

Vibration discrimination data

In all groups, discrimination was more difficult when there were smaller differences to the baseline vibration frequency; furthermore, there appeared to be clear differences between the groups, with musician's dystonia and also healthy non-musicians performing significantly worse than healthy musicians, independent of the muscle to which vibration was applied. The individuals' discrimination ability was not correlated to either motor performance on the piano or SMO data. Details of the results and the statistics are provided in supplementary figure 2.

Discussion

Patients with musician's dystonia have a highly disorganised pattern of sensorimotor organisation in the motor cortex hand area. Proprioceptive training in pianist's dystonia restored a differential spatial pattern similar to that seen in healthy pianists, and, crucially, led to an objective improvement of piano playing which was significantly correlated with the degree of sensorimotor re-organisation. In healthy musicians and non-musicians SMO was slightly more differentiated after proprioceptive training, but motor performance remained essentially unchanged. We hypothesise that motor control in musician's dystonia is regained through restoring sensorimotor re-organisation to the level seen in healthy musicians.

SMO and hand motor control

SMO describes how short periods of hand muscle vibration affect MEPs and SICI in different hand muscles (Rosenkranz and Rothwell, 2003). We concentrate here on reporting

changes in SICI since these are likely to reflect changes in cortical rather than subcortical circuits (DiLazzaro et al., 1998). In healthy subjects, input from one muscle facilitates motor output to that muscle (“homotopic” effect) by decreasing SICI, whereas it reduces motor output to other muscles (“heterotopic” effect) by increasing SICI. Low-amplitude muscle vibration predominantly excites Ia-afferents (Roll et al., 1989) and produces proprioceptive input from a resting muscle that may resemble that of an ongoing contraction (Albert et al., 2006). Proprioceptive input directly activates area 4 of the motor cortex (Hore et al., 1976; Fromm et al., 1984; Huffmann & Krubitzer, 2001; Burton et al., 2008; Golaszewski et al., 2002) and is of particular relevance for motor learning (Pavlides et al., 1993). This makes the SMO particularly well suited as a measure of sensorimotor interactions in the human motor cortex that are relevant for hand motor control and motor learning.

In professional musicians, the (baseline) pattern of SMO is less differentially organized than in non-musicians. In them, proprioceptive input from muscles that are functionally related, such as APB and FDI, facilitates motor output to these muscles, while it suppresses the output to functionally unrelated ones, such as ADM (Rosenkranz et al., 2005). We have speculated that this has behavioural advantages since it may facilitate motor control of adjacent fingers, e.g. for the playing of fast passages.

However, in musician's dystonia patients, the re-organisation of SMO goes one step further: spatial differentiation disapperars; instead, muscle vibration increases the excitability of projections to all hand muscles (Rosenkranz et al., 2005; 2008). Although this excess reorganisation is associated with loss of task-specific motor control it is not possible to say whether it causes the break down in motor control, or whether it is consequence of persistent abnormal movement patterns. Several studies have considered a disorganisation of sensorimotor integration, amongst other features, to be an “endophenotypic trait” in dystonia (Quartarone et al., 2006). Since, however, these features can also be induced in healthy humans by short-or long-term motor learning (Rosenkranz et al., 2006b, 2007a), and are found in highly trained professional musicians (Rosenkranz et al., 2007b), it cannot be excluded that they might represent an adaptation to movement patterns rather than being the cause of their development. Nevertheless it is likely that alterations in cortical sensorimotor interactions influence motor control, so that the association of changes in SMO and the level of motor control is relevant irrespective of its causality.

Effect of proprioceptive training on SMO

The way sensory representations are changed by sensory interventions depends on stimulation parameters such as attentional focus, timing and location. While synchronous stimulation leads to spatially separate representations being integrated into a single locus, asynchronous stimulation leads to separation (Xerri, 2008). In previous studies we showed that similar factors determine the effect of interventions with muscle vibration on SMO in healthy human subjects (Rosenkranz and Rothwell, 2004, 2006a). In a comparative study on healthy non-musicians, musicians, musician's dystonia and writer's cramp patients we found that the effect of vibration interventions depends on the baseline pattern of SMO (Rosenkranz et al., 2008). While the differential SMO in healthy subjects becomes undifferentiated by an intervention with vibration applied to the APB alone, the undifferentiated pattern seen in musician's dystonia regained some differentiation. Taking the findings in the animal literature into account (Xerri, 2008) we used here an intervention that applied vibration to three hand muscles randomly and asynchronously (one muscle at a time), with a concurrent discrimination task (proprioceptive training). We hypothesised that switching the “sensory input channel” and also the attentional focus would further sharpen the differential pattern of SMO in all groups. This reasoning was confirmed by the results. Proprioceptive training sharpened the differential profile of SMO particularly in the musician's dystonia patients. By strengthening the inhibitory heterotopic effects of

proprioceptive input on the non-vibrated muscles it restored a differential pattern of SMO similar to that seen in healthy musicians. In healthy musicians and non-musicians, the effect of proprioceptive training was much weaker. Importantly, the slightly de-differentiated baseline SMO of healthy musicians remained basically unchanged. We hypothesise, that their SMO represents a stable and behaviourally beneficial pattern, established through long-term learning, which in contrast to the excessive SMO re-organisation in musician's dystonia, is not subject to short-term changes.

Effect of proprioceptive training on piano performance

Since studies of behavioural effects especially in patients often rely on investigator-dependent measures, such as clinical scales, special emphasis was given to employ an objective measure of task-specific motor performance on the MIDI-piano. Rather than a whole scale (Jabusch et al., 2004), we asked the subjects to play a five-finger exercise, which, firstly, was manageable by all subjects, and secondly, ensured an equal number of observations per finger movement for data analysis.

As expected, the performance of this five-finger exercise was worse in pianists with musician's dystonia than in healthy pianists, particularly when they used the ring and little fingers, whereas the performance of the other fingers (thumb, index, middle) was almost similar to healthy musicians. Proprioceptive training had an immediate effect on performance in all musician's dystonia patients, which was seen best as a large reduction in variance of the ring and little finger movements to a level similar to that in the unaffected fingers. These findings support the reliability of the piano performance task in quantifying the degree and change of impairment, which is crucial for the assessment of any behavioural change (Zeuner and Molloy, 2008; Spector and Brandfonbrener, 2007). These objective results were paralleled by a substantial improvement in the patients' self-rating of performance, lasting for up to 24 hours, and in the significant changes in the BFM and TCS scores.

Proprioceptive training had no influence on piano performance in healthy musicians, while in healthy non-musicians, whose piano performance was much worse than that of musicians, it tended to improve performance slightly. Further control experiments would be needed to examine whether this was a within-session learning effect or whether proprioceptive training supported the consolidation of the newly learnt motor skill.

Does the sensorimotor re-organisation induce the behavioural effect in musician's dystonia?

A clear finding of this study is that restoration of a more differentiated pattern of SMO was associated with improved motor performance on the piano in musician's dystonia. Furthermore, the degree of normalisation of the heterotopic effect was significantly correlated to the decrease of key press duration and coefficient of variation in those finger movements, which were most affected in the patients.

The immediate and strong effect of proprioceptive training is striking compared to training protocols using cutaneous stimulation (e.g. Zeuner *et al.*, 2002, 2005), and might be due to differences in the central processing and integration of proprioceptive input in the motor cortex (see above).

Like many patients with pianists dystonia, all the patients in this study had dystonia that involved “curling-in” of their ring (and little) finger. Since these movements are produced mainly by contraction of superficial and deep finger flexors in the forearm how could our proprioceptive training involved only inputs from three hand muscles affect motor control of such distant muscles? In fact, one of the muscles we studied was the ADM which is a flexor

of the proximal phalanx of the little finger, and can readily be palpated to contract when pressing a piano key with the little finger. Its disordered SMO could therefore contribute directly to the dystonic contraction of that finger. We can only speculate on reasons for involvement of the ring finger. However, the most likely explanation relates to the fact that the motor cortex consists of a mosaic of intermingled output zones that each project to one or more different muscles (Schieber, 2002). Performance of discrete finger movements requires that particular spatial patterns of output are recruited within this mosaic. In patients with musician's dystonia, lack of differentiated SMO means that sensory input from one muscle, rather than facilitating the zones that control output to that muscle and inhibiting others, will facilitate wide output areas. This is likely to "defocus" any attempts to control spatial patterns of activity beyond the three muscles we have examined here and will contribute to the symptoms of dystonia.

In this respect, we postulate that in musician's dystonia the enhanced baseline variability in motor performance was due to unfocussed sensory feedback to motor output zones during finger movements. Proprioceptive training restored a more normal focussed input which then improved the quality and variability of movement. Since the effect occurred quickly we presume that it was caused by plastic changes in the strength of existing synaptic connections rather than growth of new connections.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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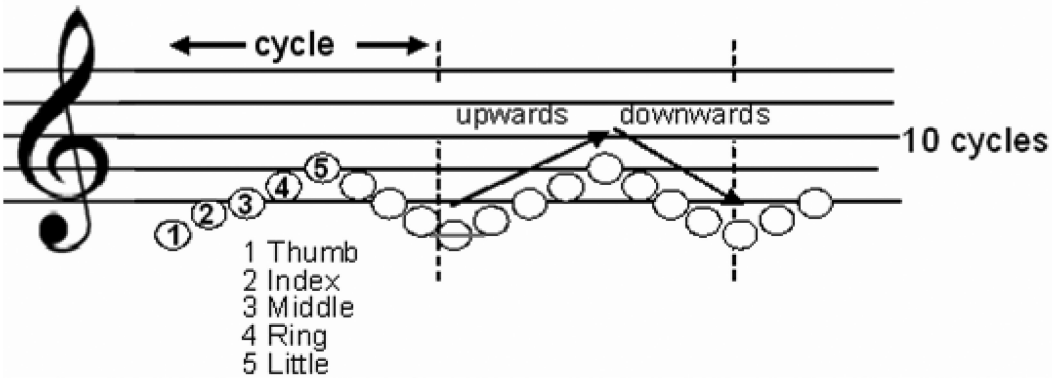

Figure 1.

Five-finger exercise performed on a MIDI-piano (Yamaha Clavinova CLP170). This involved playing the first 5 notes of the C major scale using all five fingers of the right hand, starting with the thumb to the little finger and vice-versa. 10 cycles were performed following a metronome set at 200bpm (1 note per beat). Two different levels of loudness (*pianissimo – mezzoforte*) and musical notation (*staccato – legato*) were tested. The loudness level was verified by comparing the velocity of key press, which was not significantly different between groups. Furthermore, *staccato* and *legato* were verified respectively by the absence or presence of overlay between successive notes.

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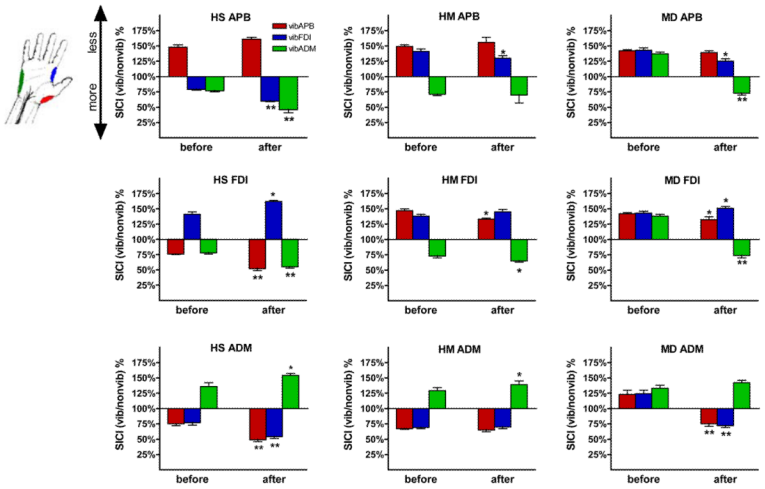

Figure 2.

SICI during vibration as a percentage of the SICI obtained without vibration. The three columns display data for healthy subjects (HS), healthy musicians (HM) and musician's dystonia (MD) whilst the rows show SICI recorded in the three different hand muscles (APB, FDI, ADM), before and after proprioceptive training. The coloured bars show the normalised SICI with vibration of APB (vibAPB, red bars), of FDI (vibFDI, blue bars) or ADM (vibADM, green bars). Decreases of SICI are plotted as columns going up (i.e. less percentage inhibition of the test response), increases as columns going down. Statistical results of paired t-tests comparing baseline data (before) with data obtained after proprioceptive training are shown as asterisks (with * $p \leq 0.05$; ** $p \leq 0.001$).

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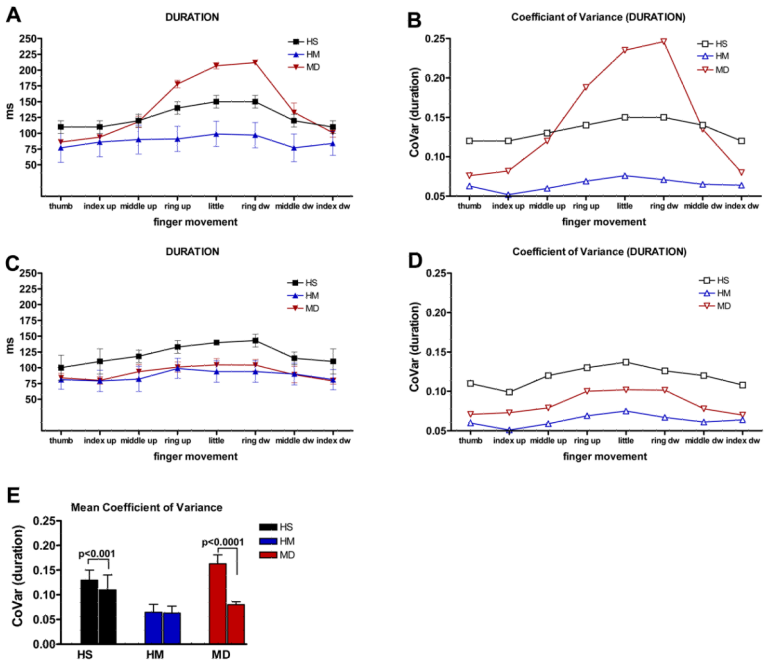

Figure 3.

The duration of key press (**A**,**C**; left column) and the coefficient of variance of the duration of keypress (**B**,**D**; right column) for each finger movement of the test sequence, distinguishing between parts of the cycle when the finger was used in the ascending portion of the scale (thumb up, index up, middle up, ring up, little finger) or the descending portion (little finger, ring dw, middle dw, index dw, thumb). Subjects were asked to play staccato mezzoforte. The data obtained in healthy subjects (HS, black), healthy musicians (HM; blue) and musician's dystonia (MD; red) before (**A**,**B**; upper panels) and after (**C**,**D**; lower panels) the proprioceptive training was given. **E** displays the mean coefficient of variance averaged over all finger movements before (left column) and after (right column) the proprioceptive training in healthy subjects (HS), healthy musicians (HM) and musician's dystonia (MD). Statistical results of paired t-tests comparing the data obtained before and after proprioceptive training are given.

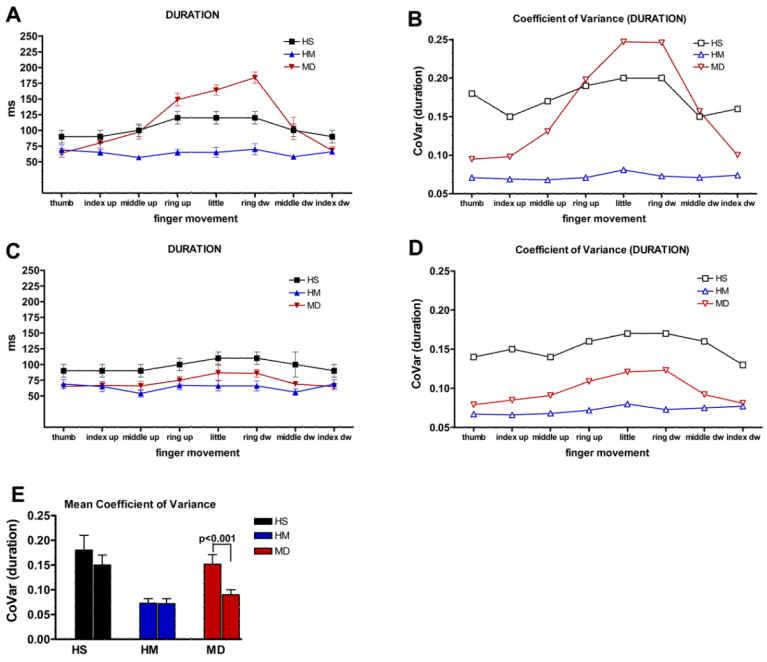

Figure 4.

The duration of key press and the coefficient of variance of the duration of key press while subjects were asked to play staccato pianissimo. For further details refer to the legend of Figure 3 since the layout is similar.

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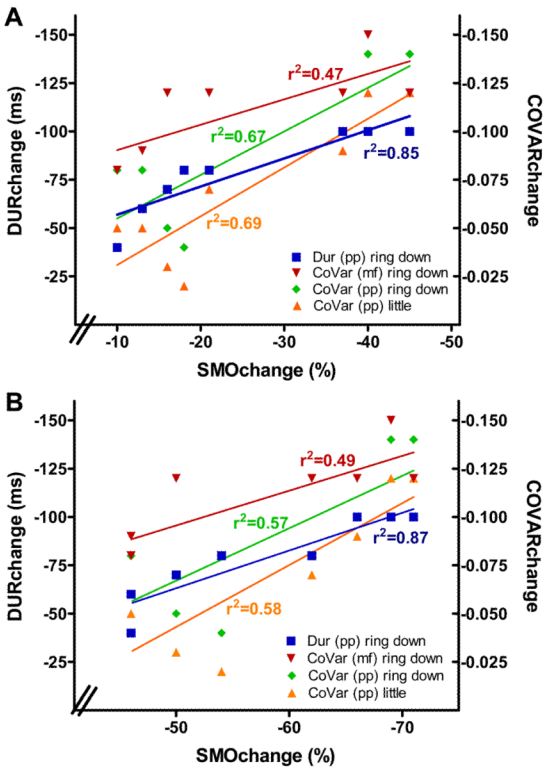

Figure 5.

Correlation of the changes in SMO (SMOchange) and piano performance (DURchange and COVARchange) after proprioceptive training in the musician's dystonia patients. DURchange or COVARchange are calculated as the difference (after – before proprioceptive training) of the mean key press duration or coefficient of variance (duration) for the ring finger downwards and little finger movement for the *mezzoforte* and *pianissimo* condition separately. These values are correlated to SMOchange, which is calculated as the difference (after – before proprioceptive training) of the normalised SICI data as displayed in figure 3. **A** displays the correlations with the near heterotopic effect averaged for the data obtained in APB and FDI; **B** similarly for the far heterotopic effect. The r^2 values are given for the significant correlations ($p < 0.05$).

The amount of change in the heterotopic near and far effects of SMO are both significantly correlated to performance improvement in the most affected ring finger downwards movement in the five-finger-exercise.

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Table 1

Subjects' age and transcranial magnetic stimulation (TMS) parameters defined in the abductor pollicis brevis (APB).

	age (years)	aMT	cond.SI	test SI
healthy subjects	34.0 ± 2.3	36.7 ± 3.4	29.8 ± 2.7	56.2 ± 5.6
healthy musicians	31.43 ± 2.3	32.8 ± 1.7	26.4 ± 0.9	54.8 ± 3.6
musician's dystonia	33. ± 2.5	35.0± 1.9	29.0 ± 1.5	54.5 ± 3.9
ANOVA (GROUP)				
F(2;18)	1,12	0,52	0,81	0,10
p	0,37	0,59	0,48	0,89

TMS parameters are given in percent stimulator output.

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Table 2

Statistical results of the ANOVAs on sensorimotor organisation (SMO).

A	three-way interaction HS/HM × muscle × vibration condition		main effect HS/HM	
	F (4;48)	**p**	**F (1;12)**	**p**
HS before/ HM before	88.3	< 0,0001	15,6	0,003
HS after/ HM after	35,6	< 0,0001	21,2	0,001

B	HM/MD × muscle × vibration condition		HM/MD	
	F (4;56)	**p**	**F (1;14)**	**p**
HM before/ MD before	68,9	< 0,0001	120,9	< 0,0001
HM after/ MD after	21,1	0,039	2,8	0,19
HM before/ MD after	3,8	0,041	0,02	0,97

Table showing three-way ANOVAs on the SMO data obtained in healthy subjects (HS), healthy musicians (HM) and patients with musician's dystonia (MD). Separate three-way ANOVAs are performed with either the data of healthy subjects and healthy musicians (HS/HM; **A**) or the data of healthy musicians and musician's dystonia patients (HM/MD; **B**) as between-group factors, and MUSCLE and VIBRATION CONDITION as within-group factors. Separate analyses were performed on the data obtained before or after the proprioceptive training. Furthermore, the data obtained in healthy musicians before, and in musician's dystonia after proprioceptive training, were compared. The F and p values for the three-way interaction (middle sets of columns) and the main effect of the between-group factor (right sets of columns) are given.

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Table 3

Statistical results of the two-way ANOVAs on the duration and coefficient of variation (duration) data during piano performance

A Duration		two-way interaction HM/MD × finger movement		main effect HM/MD	
		F (7;98)	**p**	**F (1;14)**	**p**
MF	**HM before/ MD before**	18,8	<0,0001	9,6	0,008
	HM after/ MD after	3,6	0,012	0,1	0,710
	HM before/ MD after	3,2	0,027	0,2	0,700
PP	**HM before/ MD before**	25,4	<0,0001	34,8	<0,0001
	HM after/ MD after	4,4	0,026	5,5	0,179
	HM before/ MD after	4,7	0,026	5,7	0,063

B CoVar		two-way interaction HM/MD × finger movement		main effect HM/MD	
		F (7;98)	**p**	**F (1;14)**	**p**
MF	**HM before/ MD before**	21,2	<0,0001	122,7	<0,0001
	HM after/ MD after	2,7	0,020	91,8	0,016
	HM before/ MD after	2,1	0,060	127,5	0,017
PP	**HM before/ MD before**	19,3	<0,0001	140,3	<0,0001
	HM after/ MD after	5,1	0,015	34,6	0,014
	HM before/ MD after	6,2	0,012	33,2	0,013

Table showing two-way ANOVAs on the piano performance data obtained in healthy musicians (HM) and musician's dystonia patients (MD) with HM/MD as between-group factor and FINGER MOVEMENT as within-group factor for the parameter duration and coefficient of variation of duration (CoVar) in the *mezzoforte* (MF) and *pianissimo* (PP) performance condition. Separate analyses were performed on the data obtained before or after the proprioceptive training. Furthermore, the data obtained in healthy musicians before and in musician's dystonia after proprioceptive training were compared. The F and p values for the two-way interaction (middle sets of columns) and the main effect of HM/MD as between-group factor (right sets of columns) are given.