Normalizing Motor Cortex Representations in Focal Hand Dystonia

Task-specific focal dystonia is thought to have a neurological basis where stereotypical synchronous inputs and maladaptive plasticity play a role. As afferent input is a powerful driver of cortical reorganization, we propose that a period of asynchronous afferent stimulation may reverse maladaptive cortical changes and alleviate symptoms. Using transcranial magnetic stimulation (TMS), 3 hand muscles were mapped in 10 dystonics and 10 healthy controls. Mapping occurred before and after 1 h of nonassociative stimulation (NAS) to first dorsal interosseous (FDI) and abductor pollicis brevis (APB). Participants performed grip lift, handwriting, and cyclic drawing before and after NAS. Prior to NAS, dystonics had larger maps, and the centers of gravity (CoGs) of the FDI and APB maps were closer together. Dystonics demonstrated impairments in grip-lift, handwriting, and cyclic drawing tasks. Following NAS, map size was reduced in all muscles in dystonic participants and FDI and APB CoGs moved further apart. Among dystonics, NAS produced a reduction in movement variability during cyclic drawing. Thus, 1 h of NAS can reduce the magnitude, and increase the separation, of TMS representational maps. We suggest that these changes reflect some normalization of the representational abnormalities seen in focal dystonia and provide initial, limited evidence that such changes are associated with improvements in circle drawing.

Keywords: afferent stimulation, cortical reorganization, motor cortex, musician’s dystonia, writer’s cramp

Introduction

Task-specific focal dystonia is characterized by excessive and inappropriate muscle activation during highly skilled fine motor tasks, resulting in slow, clumsy movements and impaired task performance. The condition affects highly trained, stereotypical movement patterns, such as writing (writer’s cramp) or playing a musical instrument (musician’s dystonia; Byl et al. 2003; Candia et al. 2003). Although excessive, repetitive movement patterns may play a role in musician’s dystonia, those with writer’s cramp do not typically have a history of excessive hand use.

The focal dystonias were initially ascribed to psychiatric illness; however, their neurological basis is now widely accepted (Nadeau et al. 2004). In particular, excessive representational plasticity (Quartarone et al. 2003), abnormal cortical representations (Bara-Jimenez et al. 1998; Byrnes et al. 1998), and reduced intracortical inhibition (Ridding et al. 1995; Stinear and Byblow 2004a, 2004c; Bütefisch et al. 2005) may manifest in dystonic symptoms and deficits in movement prevention and control (Stinear and Byblow 2004b). It has been proposed that synchronous and convergent afferent input arising from repetitive motor tasks may play an important role in driving the maladaptive cortical plasticity seen in focal hand dystonia (FHD). Such a hypothesis arises from work conducted in both animal and human subjects. For example, Byl et al. (1996, 1997) trained primates in a repetitive motor task over 12–25 weeks and noted significant disruption in the organization of the sensory cortex and motor symptoms similar to those seen in FHD. This disruption was characterized by enlargement, overlap, and a loss of differentiation in the cortical hand skin representation. It has also been shown that surgical joining of the skin of adjacent digits, which increases correlated sensory inputs, produces similar organizational changes (Clark et al. 1988). Likewise, in healthy human participants, Hebbian-like pairing of tactile stimuli to the digits induces similar changes in the sensory cortex (Godde et al. 1996). Also, synchronous stimulation of peripheral muscles induces organizational changes in motor representations, characterized by an increase in map size of stimulated muscles and a reduction in map separation, as assessed using transcranial magnetic stimulation (TMS) (Schabrun and Ridding 2007). Similar abnormalities of cortical organization are seen in both motor (Byrnes et al. 1998) and sensory (Butterworth et al. 2003) representations in FHD.

Given that afferent input is known to be a powerful driver of cortical reorganization, we suggest that one strategy to reestablish discrete cortical representations and alleviate dystonic symptoms may be to provide independent input from involved muscles through asynchronous afferent stimulation in which there is no consistent temporal coupling of the evoked afferent inputs. Such a hypothesis is supported by the finding that reducing correlated input from adjacent digits, by surgical separation of syndactyly, produces separation of digital cortical representations (Mogilner et al. 1993).

Therefore, it seems feasible that asynchronous and non-associative, stimulation of hand muscles may temporarily reverse representational changes characteristic of FHD. Therefore, the aim of this study was to examine the effect of an asynchronous (nonassociative) afferent stimulation paradigm on motor cortex representations and symptoms in task-specific FHD.

Materials and Methods

Participants

Ten participants with FHD (5 males; 56 ± 12.6 years; mean ± standard deviation [SD]; Table 1) and 10 age- and sex-matched healthy participants (5 males; 55.9 ± 11.7 years) took part in the study. Dystonic participants were included if they 1) had a confirmed diagnosis of FHD, 2) did not suffer from dystonic symptoms at rest, and 3) had not received Botulinum toxin therapy in the last 6 months. All

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participants gave written, informed consent in line with the Declaration of Helsinki. All procedures were approved by the local Human Research Ethics Committee.

Clinical Rating of FHD
Dystonic symptoms were assessed using the Arm Dystonia Disability Scale (ADDS; Fahn 1989) and the Writer’s Cramp Rating Scale (WCRS; Wissel et al. 1996). The ADDS provides a measure of functional hand impairment on a range of everyday tasks. An ADDS score of 100% indicates the absence of any motor impairment, whereas a score of 80% denotes the presence of social restrictions but no limitation in activities. Scores below 90% indicate significant impairment in daily activities, including writing, personal hygiene, and feeding. The WCRS measures the degree of dystonic posturing and speed during handwriting. A score of 0 indicates normal posture, and a score of 30 indicates severe impairment. Participants were videotaped as they wrote the sentence “Sheila collects shells” 10 times in their normal handwriting across a sheet of blank paper. Secondly, following the procedure of Zeuner et al. (2007), participants were asked to draw superimposed circles approximately 2 cm in diameter for a period of 10 s. On the first attempt, participants were instructed to draw as quickly as possible and on the second attempt to use minimal pen pressure. Both tasks were repeated following the intervention. The 3 subjects with musician’s dystonia all reported mild (2) to moderate (1) difficulties with handwriting on the ADDS scale. Handwriting and cyclic drawing tasks were recorded using a pressure sensitive digitizing tablet and an inking digitizing pen connected to a personal computer (Wacom Intuos A4 oversized, Wacom Europe, Germany). Data were sampled at 166 Hz with a spatial resolution of 0.05 mm.

Grip-Lift Task
Participants washed their hands thoroughly with soap and water and were comfortably seated at a table. Participants lifted a 350-g manipulandum based on that originally described by Westling and Johansson (1984). The device was comprised of 2 lightweight load cells situated 35 mm apart and an accelerometer. Participants were instructed to lift the manipulandum to the height indicated (10 cm), hold it steady for 3 s, and then replace it on the table. The lift was performed primarily by flexing the elbow. Each participant performed 5 consecutive lifts, 5 s apart. Measures of the horizontal grip force (GF) exerted by the index finger and thumb, the vertical load force (LF), and the onset of the lift were obtained. All GF, LF, and acceleration signals were low-pass filtered at 100 Hz, sampled at 400 Hz, and stored on a computer for off-line analysis.

Nonassociative Stimulation
The NAS protocol has been described previously (Ridding and Uy 2003; Schabrun and Ridding 2007) and consisted of asynchronous electrical stimuli (square wave stimuli of 1-ms duration) applied to the motor points of FDI and APB for a period of 1 h, using a constant current stimulator (Digitimer D17A, Digitimer Ltd, Welwyn Garden City, UK). There was no consistent temporal coupling between the 2 stimulated muscles with the time between each pair of stimuli randomized in the range 0.15–2.85 s (i.e., mean frequency of 1.5 Hz). Stimulation was never applied to the 2 muscles at the same time. Stimulation intensity was set to evoke a just visible contraction in each stimulated muscle. Stimulation was not considered painful by any of the participants.

Experimental Procedure
Participants first completed the handwriting tasks and then the grip-lift task. TMS was then used to map the corticomotor representations of the 3 muscles, before a 1-h period of NAS was applied. Participants were verbally reminded to focus on their stimulated hand every 5 min (Ridding and Uy 2003; Schabrun and Ridding 2007). Following the period

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**Table 1**

<table>
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<th>Subject</th>
<th>Age (year)</th>
<th>Gender</th>
<th>Handedness</th>
<th>Diagnosis</th>
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Note: WC, writer’s Cramp; MD, musician’s dystonia; RH, Right Handed; LH, Left Handed; ADDS, max score 100%; WCRS, max score 30.
of NAS, participants sat quietly for a further 5 min, before cortical mapping was repeated for each of the 3 muscles. Finally, the grip-lift and handwriting tasks were repeated. The rMT was assessed for FDI and APB prior to TMS mapping and again following the NAS intervention.

Data and Statistical Analysis

Neurophysiological Data

Background EMG data were rectified and averaged in each subject for the 100 ms preceding the TMS pulse before and after NAS. A 3-way analysis of variance (ANOVA) with between-subject factor GROUP (Dystonic, Control) and within-subject factors MUSCLE (FDI, APB, ADM) and TIME (Pre, Post) was performed. This analysis ensured that changes in map volume were not due to voluntary activity during the mapping procedure.

The number of active sites and map volume were calculated for each muscle (FDI, APB, ADM) before and after NAS. A scalp site was considered active if the mean peak-to-peak amplitude of the MEPs evoked at that site was greater than 0.05 mV. Map volume was calculated by summing the mean MEP amplitude at all the active sites for each muscle. In addition, we calculated the distance between the CoGs of the 3 muscle maps. The CoG is the amplitude-weighted center of the map (Wassermann et al. 1992; Wilson et al. 1993; Uy et al. 2002).

Correlations between the CoG and the within-subject factors of TIME (Pre, Post) and MUSCLE PAIR (FDI-APB, ADMAFPB, FDI-ADM) were performed using a Pearson’s product-moment correlation with significance corrected using Bonferroni.

Variables Muscle | Dystonic group | Control group
| | Pre NAS | Post NAS | Pre NAS | Post NAS |
| SDS | 0.020 (0.003) | 0.019 (0.003) | 0.014 (0.007) | 0.002 (0.003) |
| Resting motor threshold (% stimulator output) | | | | |
| FDI | 49.5 (4.3) | 49.4 (4.3) | 47.1 (2.9) | 47.0 (2.7) |
| APB | 49.5 (4.3) | 49.6 (4.3) | 47.3 (3.2) | 47.4 (3.0) |
| ADM | 49.1 (4.2) | 49.1 (4.3) | 47.3 (3.2) | 47.1 (2.6) |
| Mean MEP amplitude (hot spot) | | | | |
| FDI | 1.2 (0.31) | 0.91 (0.31) | 0.93 (0.31) | 0.92 (0.32) |
| APB | 0.54 (0.09) | 0.46 (0.06) | 1.0 (0.34) | 1.0 (0.41) |
| ADM | 29.9 (2.6) | 21.5 (1.5) | 20 (3.2) | 21.5 (3.5) |
| Active sites | | | | |
| FDI | 27.6 (3.2) | 21.3 (2.9)* | 19.6 (3.2) | 19.9 (2.9) |
| APB | 25.8 (3.6) | 21.4 (2.6)* | 18.2 (3.2) | 17.7 (1.8) |
| ADM | 15.7 (4.7) | 10.6 (3.5)* | 6.7 (1.6) | 6.3 (1.5) |
| Volume (mV) | | | | |
| FDI | 15.7 (3.6) | 7.9 (1.5)* | 7.0 (2.2) | 10.5 (3.2) |
| APB | 8.6 (3.2) | 6.8 (2.4)* | 3.4 (1.2) | 6.1 (1.6) |
| ADM | 0.24 (0.022) | 0.40 (0.02)* | 0.29 (0.02) | 0.33 (0.02) |
| Distance between CoGs (cm) | | | | |
| FDI-APB | 0.39 (0.016) | 0.44 (0.029) | 0.54 (0.05) | 0.42 (0.04) |
| APB-ADM | 0.31 (0.024) | 0.34 (0.025) | 0.39 (0.03) | 0.35 (0.04) |

Handwriting and Cyclic Drawing Data

Kinematic variables were analyzed using the MovAlyzeR 4.1 software package (NeuroScript, Arizona, USA). The mean stroke frequency (MSF; mean number of up and down strokes per second) provides a measure of the automaticity and fluency of the movement (Zeuner et al. 2007). Mean pen pressure and the coefficient of variation (CV) of the positive velocity peaks were also calculated according to the procedure described by Zeuner et al. (2007). The CV of positive velocity peaks provides a measure of the variability of consecutive movements (Zeuner et al. 2007). A 2-way mixed ANOVA was performed for each of the above measures, the between-subjects factor was GROUP (Dystonic, Control) and the within-subjects factor TIME (Pre, Post). All post hoc analyses were performed using Bonferroni corrected t-tests for pairwise comparisons. A P < 0.05 was considered statistically significant.

Grip-Lift Data

Four variables were extracted from each trial of the grip-lift task: 1) preload duration (time between the onset of GF and the onset of positive LF), 2) the maximum grip force (GFmax), 3) maximum correlation coefficient, and 4) Timeshiftmax. To determine the maximum correlation and the Timeshiftmax the rate of change of GF (dGF/dt) in the lift phase was correlated with the rate of change of LF (dLF/dt), by shifting one signal with respect to the other in 2 ms increments (Duque et al. 2003; Schabrun et al. 2008). This procedure determines the delay (Timeshiftmax) between the rate of change of GF and the rate of change of LF at the point where the correlation is maximal and is thought to reflect anticipatory or reactive scaling of GF (Duque et al. 2003; Schabrun et al. 2008). Post hoc analyses were performed using Bonferroni corrected t-tests (P < 0.05).

Statistical analysis was performed using a 3-way ANOVA for each of the above variables with between-subjects factor GROUP (Dystonic, Control) and within-subjects factors TIME (Pre, Post) and LIFT NUMBER (1-5).

Results

Neurophysiological Data

Mean ± standard error of the mean (SEM) values for all mapping data are given in Table 2.

There was no main effect of GROUP (F1,119 = 0.79; P = 0.37), MUSCLE (F2,119 = 2.2; P = 0.11), or TIME (F1,119 = 0.54; P = 0.46),
on background EMG data. In addition, there was no GROUP × MUSCLE interaction ($F_{2, 119} = 1.2; P = 0.31$).

There was a main effect of GROUP on the number of active sites ($F_{1, 108} = 8.7; P = 0.004$) and map volume ($F_{1, 108} = 6.6; P = 0.01$). There was also an interaction between GROUP and TIME for the number of active sites ($F_{1, 108} = 4.2; P = 0.043$) and map volume ($F_{1, 108} = 4.5; P = 0.037$). The number of active sites ($t = 2.9; P = 0.004$) and map volume ($t = 2.6; P = 0.01$) were greater in the dystonic group at baseline than in the control group in all 3 muscles. Following NAS, there was a reduction in both the number of active sites ($t = 2.7; P = 0.008$; Fig. 1a) and map volume ($t = 2.2; P = 0.029$; Fig. 1b) among dystonic participants. In contrast, no change was observed in either the number of active sites ($t = 0.18; P = 0.86$) or map volume ($t = 0.78; P = 0.43$) following NAS in the control group. There was no effect of MUSCLE and no MUSCLE × TIME interaction for either variable (active sites, both $F_{2, 108} < 0.6; P > 0.54$; map volume, both $F_{2, 108} < 2.4; P > 0.091$). Data from a representative dystonic subject are shown in Figure 2a and data from a representative control subject in Figure 2b.

There was a GROUP × TIME × MUSCLE PAIR interaction ($F_{2, 108} = 3.9; P = 0.049$) on the distance between map CoGs. In

![Figure 1](https://academic.oup.com/cercor/article-abstract/19/9/1968/278460)

**Figure 1.** (a) Mean SEM number of active sites for each muscle before and after NAS in dystonic and control groups. There was a decrease in the number of active sites in all 3 muscles following NAS in the dystonic group; *$P < 0.05$. (b) Mean (standard error) map volume of each muscle before and after NAS in dystonic and control groups. There was a significant decrease in volume in all 3 muscles in the dystonic group after NAS; *$P < 0.05$.

![Figure 2](https://academic.oup.com/cercor/article-abstract/19/9/1968/278460)

**Figure 2.** (a) Illustration of the cortical representation obtained for FDI (top) and APB (bottom) before and after NAS in one representative dystonic subject. Coordinates are referenced to the vertex (0,0). The average MEP amplitude evoked at each scalp site is indicated by the gray scale (mV). The CoG of each map is indicated by the circle (FDI, white; APB, black). The CoG of each APB map has also been superimposed over each FDI map to demonstrate the CoG shift following NAS. A decrease in the number of active sites and map volume was observed for FDI and APB following NAS ($P < 0.05$). Additionally, the CoGs of the 2 muscles were further apart after NAS (pre, 0.26 cm; post, 0.37 cm). (b) Illustration of the cortical representation obtained for FDI (top) and APB (bottom) before and after NAS in one representative control subject. Same conventions as in Figure 1a. There was no change in either map area or volume and no change in the distance between the 2 CoG locations after NAS (pre, 0.23 cm; post, 0.20 cm).
dystonic participants, there was greater separation of the CoGs for the FDI-APB muscle pair following NAS. There was no change in the degree of separation for the FDI-ADM (\( t = 2.7; P = 0.02 \)) or ADM-APB (\( t = 3.8; P < 0.001 \); Figs 2a and 3) muscle pairs. In the control participants, no changes were noted in the degree of separation of CoGs for any muscle pair following the intervention (all; \( t < 0.44; P > 0.1 \); Fig. 2b). Examination of the raw data suggested that the increase in separation between the CoGs of FDI and APB was not associated with any consistent directional shift of individual muscles CoGs across the dystonic participants.

There were no effects of GROUP (\( F_{1,108} = 1.2; P = 0.26 \)), MUSCLE (\( F_{2,108} = 0.003; P = 0.99 \)), or TIME (\( F_{1,108} < 0.001; P = 0.99 \)) on rMT, and there were no interactions between these factors (both \( F_{2,108} < 0.002; P > 0.99 \); see Table 2). The average MEP amplitude at the hot spot was similar for each of the 3 muscles prior to NAS (Table 2). A 3-way ANOVA with factors GROUP (Dystonic, Control), TIME (Pre, Post), and MUSCLE (FDI, ADM, APB) revealed no significant difference between groups (\( F_{1,119} = 0.1; P = 0.75 \)), muscles (\( F_{2,119} = 1.1; P = 0.34 \)), or across time (\( F_{1,119} = 0.4; P = 0.5 \)). In addition, there was no GROUP \( \times \) TIME interaction (\( F_{1,119} = 0.1; P = 0.7 \)).

**Behavioral Data**

Mean \( \pm \) SEM values for all handwriting and grip-lift data are given in Table 3.

Under both cyclic drawing conditions (quick drawing and light pen pressure), there was a main effect of TIME (both \( F_{1,36} > 8.4; P < 0.006 \)) and a GROUP \( \times \) TIME interaction (both \( F_{1,36} > 8.5; P < 0.006 \)) for the CV of positive velocity peaks. Following NAS, the CV of positive velocity peaks was lower in dystonic participants (both \( t > 4.1; P < 0.001 \)), whereas there was no change among control participants (both \( t < 0.01; P > 0.98 \)). The degree of improvement in the CV of positive velocity peaks among dystonic participants was positively correlated with the increase in the separation of the FDI and APB CoGs (\( r = 0.72; P = 0.018 \); Fig. 4).

For both cyclic drawing conditions, there was an effect of GROUP on MSF (both \( F_{1,108} > 7.5; P < 0.01 \)), CV of positive velocity peaks (both \( F_{1,108} > 15.7; P < 0.001 \), and pen pressure (both \( F_{1,108} > 4.3; P < 0.044 \)). Dystonic participants demonstrated lower stroke frequency (both \( t > 7.5; P < 0.01 \)), higher CV of positive velocity peaks (both \( t > 3.2; P < 0.008 \), and greater pen pressure (both \( t > 4.3; P < 0.044 \)) under both drawing conditions when compared with control participants.

There was an effect of GROUP on MSF (\( F_{1,36} = 4.6; P = 0.039 \)) and the CV of positive velocity peaks (\( F_{1,36} = 4.3; P = 0.045 \)) during the handwriting task. Stroke frequency at baseline was lower in dystonic participants (2.8 \( \pm \) 1.2 Hz; mean \( \pm \) SD) than control participants (4.1 \( \pm \) 2.1 Hz; \( t = 2.1; P = 0.039 \)). The CV of positive velocity peaks was greater in dystonic participants (0.51 \( \pm \) 0.2; mean \( \pm \) SD) than control participants (0.37 \( \pm \) 0.09; \( t = 2.1; P = 0.045 \)). There was no GROUP effect on pen pressure (\( F_{1,36} = 0.42; P = 0.52 \)). There was no effect of TIME (all \( F_{1,36} < 1.69; P > 0.2 \)) and no GROUP \( \times \) TIME interactions for MSF, pen pressure, or the CV of positive velocity peaks (all \( F_{1,36} < 0.24; P > 0.6 \)), indicating that the NAS protocol did not affect handwriting in dystonic or control participants.

There were significant effects of GROUP on preload duration (\( F_{1,180} = 8.5; P = 0.004 \)) and \( G^F_{\text{max}} \) (\( F_{1,180} = 16.0; P < 0.001 \)) during the grip-lift task. Preload duration was longer in dystonic participants (317.5 \( \pm \) 297.1 ms; mean \( \pm \) SD) than control participants (169.5 \( \pm \) 174.3 ms; \( t = 2.9; P = 0.004 \)). Dystonic participants also applied a higher GF during object lifting (13.1 \( \pm \) 3.9 N) when compared with control participants (9.2 \( \pm \) 10.7 N; \( t = 4.0; P < 0.001 \)). There was no difference between the dystonic and control groups with respect to the correlation coefficient or Time\( _{\text{shift}}^F \) variables, indicating that anticipatory scaling of GF is preserved in this group of patients. There was no effect of the NAS intervention on any of the grip-lift variables (all \( F_{1,180} < 1.8; P > 0.17 \)).

**Discussion**

The main findings of this study can be summarized as follows. First, representative motor maps in the dystonic group were larger at baseline than those obtained from the control group. Second, representational maps in the dystonic group contracted following a 1-h period of NAS, becoming smaller in both area and volume. In addition, the CoGs for the 2 stimulated muscles (FDI, APB) were further apart in the dystonic group following NAS (\( *P < 0.05 \)).

At baseline, maps obtained for all 3 muscles were considerably larger in both area and volume, and the FDI and APB CoGs were significantly closer together, in dystonic participants than in control subjects. As trials containing background EMG...
activity were discarded, the increase in map area and volume in dystonic participants is unlikely to be due to difficulties with muscle relaxation. Furthermore, these findings are consistent with previous reports in both the animal (Byl et al. 1996, 1997) and human literature (Byrnes et al. 1998; Elbert et al. 1998). Although the exact mechanism of altered cortical representations in focal dystonia remains unclear, it appears that repetitive, simultaneous afferent inputs arising from prolonged motor practice plays a key role in the development of the maladaptive reorganization of the sensorimotor cortex. Indeed, it is well known that use-dependent plasticity of the sensorimotor cortex is heavily influenced by the pattern of afferent input (Brons and Woody 1980; Sanes et al. 1990). In particular, synchronous or tightly temporally coupled afferent inputs have been shown to be a particularly powerful driver of cortical reorganization. For example, Godde et al. (1996) applied synchronous afferent stimulation to digits in the rat and reported enlargement and overlap of cortical representations. Furthermore, muscles which cocontract during a motor task, and thus produce convergent patterns of afferent input, have greater overlap of their cortical representations (Nudo et al. 1996). Conversely, surgical separation of syndactyly in humans, which reduces convergent and associative afferent input, results in separation of digital cortical representations (Mogilner et al. 1993). Therefore, it may be that the abnormal sensorimotor representations seen in FHD are due to an abnormally increased response to repeated patterns of stereotypical and convergent afferent inputs. This hypothesis receives some support by the finding of abnormally increased representational plasticity in FHD (Quartarone et al. 2003).

A novel finding in the present study is that 1 h of asynchronous electrical stimulation delivered to the motor points of FDI and APB is sufficient to produce a normalization of TMS representational maps in those with focal dystonia. Following NAS, there was a decrease in MEP amplitudes in all 3 muscles and a separation of the CoGs for stimulated muscles (FDI and APB). No significant shift in CoGs occurred in muscle pairs containing the unstimulated ADM muscle. The decrease in the number of active sites and map volume for the nonstimulated ADM muscle is likely due to the innervation of multiple hand muscles by single corticomotorneuronal cells (Cheney and Fetz 1980; Lemon et al. 1991). Thus, changes in the excitability of individual corticomotorneuronal cells projecting to FDI and APB muscles may also induce a change in the excitability of the unstimulated ADM muscle. Indeed, other studies using peripheral stimulation have reported similar “overflow” of excitability changes to adjacent nonstimulated muscles (Ridding et al. 2001; Schabrun and Ridding 2007).

A question to arise is whether the observed separation in the CoGs of the stimulated muscles is due to the period of NAS or other technical or nonspecific time effects. As the MEP amplitude evoked following NAS was smaller than baseline MEPs in the maps of the FHD patients, it could be argued that this would produce changes in CoG measurements. However, we think this unlikely as we have previously demonstrated that simply changing the amplitude of MEPs in representational TMS maps does not produce significant CoG shifts (Ridding et al. 2001). The CoG is a reliable and stable measure of the point of greatest excitability within representational maps (Miranda et al. 1997; Thickbroom et al. 1999; Uy et al. 2002). Furthermore, the distance between the CoGs of various muscles appears to be a consistent and stable measure over time (Schabrun and Ridding 2007). Therefore, we consider it unlikely that the increase in the separation of the CoG of the stimulated muscles is due to nonspecific time effects.
Additionally, the fact that such a shift was not seen in the control group argues against this possibility.

Motor cortex maps produced with TMS provide information on the surface topography of the corticomotor projection for each stimulated muscle (Byrnes et al. 1998). Changes induced in the spatial territory of the corticomotor projection are therefore reflected as a shift in the CoG. Thus, in the present study, an increase in the distance between the CoGs of stimulated muscles likely reflects a separation in the spatial territory of the corticomotor projection to each of the stimulated muscles.

Several studies have examined the effect of afferent stimulation in FHD. Tinazzi et al. (2006) reported that MEP amplitudes are reduced in normal subjects after a single session of transcutaneous electrical nerve stimulation (TENS) but were unchanged in patients with FHD. However, if repeated sessions of TENS were applied, FHD subjects showed MEP suppression which was associated with an improvement in handwriting. These findings are similar to the current findings and indicate that a reduction in cortical excitability in FHD may be important for functional improvements and symptom alleviation. Several studies have also examined the effect of afferent stimulation on sensorimotor reorganization in FHD. In normal subjects, muscle vibration has a differential effect on cortical excitability with short interval intracortical inhibition being reduced in the projection to the vibrated muscles but increased for adjacent nonvibrated (Rosenkranz and Rothwell 2003). In FHD, the topographic specificity of this effect is disturbed (Rosenkranz et al. 2005). Rosenkranz et al. (2008) demonstrated that a period of vibratory proprioceptive training could normalize the response to muscle vibration in participants with musician’s dystonia but not those with writer’s cramp. This finding suggests that there may be some differences in the pathophysiology of writer’s cramp and musician’s dystonia. In the present study, the small number of subjects with musician’s dystonia studied makes it difficult to comment with any certainty that afferent input arising from the hand may be less important for the development of pathological changes in writer’s cramp subjects than in those with musician’s dystonia. However, inspection of the data revealed no obvious differences in either baseline maps or response to NAS between participants with writer’s cramp and musician’s dystonia (a summary of the dystonia subgroup data is given in Table 4). Finally, sensorimotor reorganization has also been demonstrated following a period of motor training known as sensorimotor retuning (SMR). SMR involves splitting of the fingers to produce isolated movement patterns in the dystonic hand and, using the technique of magnetoencephalography, has been shown to promote more ordered and discrete cortical representations in those with FHD (Candia et al. 2003, 2005). These studies, coupled with the results reported here, indicate that modulation of afferent input is likely to be of significant importance in the successful treatment of FHD.

A question arises as to whether there is a particular importance associated with the application of asynchronous afferent input to 2 muscles or whether providing a similar amount of stimulation to only one muscle would produce comparable neurophysiological changes. Although not examined here, previous studies have demonstrated that changes in cortical organization can be seen following the application of afferent stimulation to only one muscle (Ridding et al. 2000, 2001). However, such changes occurred only after a prolonged period of stimulation. These findings suggest that stimulation applied to only one muscle is unlikely to produce effects similar to those reported here. In addition, at least in normal subjects, such stimulation produces representational map enlargement, in contrast to the map reduction seen in the FHD subjects in the present study. Therefore, it seems unlikely that isolated peripheral stimulation would be effective in producing the organizational changes reported here.

Investigation of the mechanisms by which NAS normalizes cortical representations in FHD was not an aim of the present study. However, it is known that cortical representations are thought to be maintained and adjusted by intracortical inhibitory circuits, primarily through the modulation of the inhibitory neurotransmitter γ-aminobutyric acid (GABA) (Sanes et al. 1988; Ridding et al. 1995; Liepert et al. 1998). In healthy humans, GABAergic intracortical inhibition is decreased in muscles required for the execution of a voluntary motor task (Ridding et al. 1995) and increased in adjacent muscle groups that need to be maintained relaxed (Liepert et al. 1998; Stinear and Byblow 2003; Zoghi et al. 2003). This process is likely important for the fractionation of motor outputs from the primary motor cortex, creating isolated movements in the absence of muscle overflow and cocontraction. Interestingly, intracortical inhibitory networks are impaired or poorly modulated in FHD (Ridding et al. 1995; Stinear and Byblow 2004a, 2004c; Bütefisch et al. 2005). Therefore, it may be that a period of NAS exerts its effect on cortical representation by increasing GABAergic inhibition and “decoupling” overlapping muscle representations as was evident in the CoG separation observed.

NAS did not produce analogous changes in healthy subjects. This is consistent with previous reports (Schabrun and Ridding 2007). There was no change in map area, volume, or the CoG in these subjects, suggesting that in healthy individuals, asynchronous afferent input does not lead to rapid change in cortical representations. Therefore, it is possible that the rapid, aberrant plasticity seen in dystonic subjects is in part driven by excessive sensitivity in the sensorimotor cortex to afferent inputs. Such a mechanism receives support from several sources. First, Quartarone et al. (2003) demonstrated that in subjects with FHD, paired associative stimulation produces an abnormal increase in corticospinal excitability, which was not confined to stimulated muscles. These findings provide support for the role of excessive plasticity in FHD. Secondly, the genetic contribution to the dystonias is increasingly recognized (Defazio et al. 2007), indicating that repetitive, stereotyped afferent inputs may lead to late-onset dystonia, such as FHD, more rapidly in genetically susceptible individuals.

### Table 4

<table>
<thead>
<tr>
<th>Variable</th>
<th>Muscle</th>
<th>Writers cramp</th>
<th>Musician’s dystonia</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre NAS</td>
<td>Post NAS</td>
<td>Pre NAS</td>
</tr>
<tr>
<td>CoGs (cm)</td>
<td>FDI-APB</td>
<td>0.31 (0.05)</td>
<td>0.69 (0.14)</td>
</tr>
<tr>
<td></td>
<td>ADM-FDI</td>
<td>0.21 (0.05)</td>
<td>0.40 (0.04)</td>
</tr>
<tr>
<td>Distance</td>
<td>FDI-APB</td>
<td>0.22 (0.04)</td>
<td>0.38 (0.08)</td>
</tr>
<tr>
<td></td>
<td>ADM-FDI</td>
<td>0.62 (0.35)</td>
<td>5.4 (1.10)</td>
</tr>
<tr>
<td>Volume (mV)</td>
<td>FDI</td>
<td>19.1 (11.2)</td>
<td>6.9 (0.9)</td>
</tr>
<tr>
<td></td>
<td>APB</td>
<td>29.2 (4.5)</td>
<td>23.5 (3.5)</td>
</tr>
<tr>
<td></td>
<td>ADM</td>
<td>21.5 (3.4)</td>
<td>18.2 (2.9)</td>
</tr>
<tr>
<td>Active sites</td>
<td>FDI</td>
<td>29.1 (3.5)</td>
<td>20.7 (1.8)</td>
</tr>
<tr>
<td></td>
<td>APB</td>
<td>29.2 (4.5)</td>
<td>23.5 (3.5)</td>
</tr>
<tr>
<td></td>
<td>ADM</td>
<td>21.5 (3.4)</td>
<td>18.2 (2.9)</td>
</tr>
</tbody>
</table>
In the present study, we examined several behavioral tasks that have been shown to be abnormal in writer's cramp and musician's dystonia. Abnormalities in the grip-lift task have been demonstrated in both writer's cramp and musician's dystonia patients (Nowak et al. 2005). In addition, all 3 subjects with musician's dystonia reported mild ($n = 2$) to moderate ($n = 1$) difficulties with writing on the ADDS scale, making the inclusion of a handwriting task relevant for all subjects. Dys tonic participants displayed significant impairments in grip-lift, handwriting, and cyclic drawing tasks when compared with the healthy control group. In the grip-lift task, they demonstrated preloads that were double those seen in healthy controls, and peak GF levels that were elevated by 4 N on average, signifying an increased safety margin during the lift. Several previous studies have demonstrated similar increases in peak GF in those with focal dystonia (Odergren et al. 1996; Serrien et al. 2005; Nowak et al. 2005). However, it is noteworthy that in both the present study and the previous literature, anticipatory scaling of fingertip forces is maintained in dystonic subjects. This suggests that the underlying pathophysiology does not interfere with the generation or execution of the internal, feedforward model (Odergren et al. 1996; Nowak et al. 2005).

Previous studies have hypothesized that increased GF levels in those with dystonia are the result of impaired sensorimotor integration (Odergren et al. 1996; Serrien et al. 2005). However, it has also been shown that visual feedback training is successful in reducing GF levels in subjects with writer’s cramp (Schenk and Mai 2001). This suggests that excessive GF may be a learned, compensatory strategy rather than a pathophysiological deficit in sensorimotor integration (Nowak et al. 2005). If the impairments noted during the grip-lift task are the result of a prelearned strategy, it is perhaps not surprising that single, short period of NAS produced no significant change in these variables.

Dystonic participants performed both the handwriting and cyclic drawing tasks with significantly lower mean stroke frequencies than control participants. In fact, MSF consistently fell below 3 Hz, indicating significant impairment in movement fluency and automaticity (Zeuner et al. 2007). Pen pressure was also significantly increased in dystonic participants. However, this increase was only present during cyclic drawing and not during the handwriting task. These results are similar to those obtained by Zeuner et al. (2007) and confirm that cyclic drawing is a more sensitive measure of motor dysfunction than handwriting in focal dystonia. Dystonic participants showed greater variability in movement profiles during both the handwriting and cyclic drawing tasks than their healthy counterparts. Interestingly, the only behavioral variable that significantly improved in the FHD patients following NAS was the coefficient of variability in the movement velocity. As there was no sham condition in the present study, it is difficult to completely rule out placebo effects. However, we suggest that the reported changes are unlikely due to placebo or non-specific time effects for several reasons. First, although the change was only seen in one variable (CV of positive velocity peaks), the magnitude of the change was large and highly significant ($p < 0.001$). Second, as there were no significant changes in the control group, this suggests that these measures are reliable across time. Finally, there was a significant correlation between the separation of motor cortical representations of the stimulated muscles and improvements in the CV of positive velocity peaks. This suggests that the improvements in performance were related to normalization in representational maps.

The baseline CV value for FHD subjects was slightly higher than that reported previously by Zeuner et al. (2007) for circle drawing. As our testing protocol was identical, as far as we can tell, to that employed by Zeuner et al. (2007), we suggest that this difference in velocity variability likely reflects differences in subject characteristics between the 2 studies. Following the intervention, the CV of positive velocity peaks for FHD subjects were remarkably similar to those obtained for controls (Table 3).

The question arises as to why changes in other functional measures were not seen. We suggest that improvements in the CV of positive velocity peaks were seen because this is a highly sensitive measure, especially when investigated during cyclic drawing tasks performed with minimal pen pressure (Zeuner et al. 2007). In contrast to the improvement in this variable, there was no significant improvement in the WCRS scores following NAS. We suggest that this may reflect the relatively low sensitivity of this functional scale to small differences in hand function due to its relatively broad and nonspecific nature. To produce additional clinical and functional gains, it is likely that repeated or extended sessions of NAS would be necessary. Although not examined here, previous research has demonstrated that effects on cortical organization seen following a single session of afferent stimulation are maintained for 30–60 min (McKay et al. 2002). However, repeated sessions of afferent stimulation have been shown to produce longer lasting effects (McKay et al. 2002). This finding opens up the possibility that repeated sessions of NAS may be effective in producing longer lasting reversal of the cortical abnormalities seen in FHD, which may be necessary for more robust functional effects to develop. However, if the primary cause of abnormal cortical organization in FHD is excessive plasticity, it is unlikely that the approach described here will lead to any permanent normalization of cortical representations.

Conclusion

In conclusion, NAS resulted in a decrease in the volume and area of representational motor maps as well as a separation in the CoG of the cortical representations for stimulated muscles. NAS also produces a decrease in the variability of movement profiles during a sensitive cyclic drawing task. These results provide initial evidence that specific patterns of nonassociative afferent input are capable of, at least temporarily, reversing the characteristic representational changes seen in FHD. Importantly, the present findings also indicate that such representational changes may be associated with improvements in hand function. Therefore, these findings may be important for the development of novel therapeutic strategies for the treatment of task-specific focal dystonia.

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References