Surmounting Retraining Limits in Musicians’ Dystonia by Transcranial Stimulation

Shinichi Furuya, PhD,1 Michael A. Nitsche, MD,2 Walter Paulus, MD,2 and Eckart Altenmüller, MD1

Objective: Abnormal cortical excitability is evident in various movement disorders that compromise fine motor control. Here we tested whether skilled finger movements can be restored in musicians with focal hand dystonia through behavioral training assisted by transcranial direct current stimulation to the motor cortex of both hemispheres.

Methods: The bilateral motor cortices of 20 pianists (10 with focal dystonia, 10 healthy controls) were electrically stimulated noninvasively during bimanual mirrored finger movements.

Results: We found improvement in the rhythmic accuracy of sequential finger movements with the affected hand during and after cathodal stimulation over the affected cortex and simultaneous anodal stimulation over the unaffected cortex. The improvement was retained 4 days after intervention. Neither a stimulation with the reversed montage of electrodes nor sham stimulation yielded any improvement. Furthermore, the amount of improvement was positively correlated with the severity of the symptoms. Bihemispheric stimulation without concurrent motor training failed to improve fine motor control, underlining the importance of combined retraining and stimulation for restoring the dystonic symptoms. For the healthy pianists, none of the stimulation protocols enhanced movement accuracy.

Interpretation: These results suggest a therapeutic potential of behavioral training assisted by bihemispheric, noninvasive brain stimulation in restoring fine motor control in focal dystonia.

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Subjects and Methods

Participants

Twenty adult pianists participated in the present experiment (10 with FD, 10 without FD). Ten pianists with FD of the right hand (4 females, 24–61 years old, mean = 39.6 years old) were recruited from the outpatient clinic of the Institute of Music Physiology and Musicians’ Medicine at Hannover University of Music, Drama, and Media (Table 1). Each pianist underwent a thorough neurological examination and was diagnosed by one of the authors (E.A.) specializing in movement disorders of musicians. Exclusion criteria were bilateral FD, generalized dystonia, epilepsy, history of any other neurological diseases, and injection of botulinum toxin A within the past 3 months. Ten pianists with no history of neurological disorders were recruited as controls (4 females, 24–37 years old; Table 2). In accordance with the Declaration of Helsinki, the experimental procedures were explained to all participants. Informed consent was obtained from all participants prior to participation in the experiment, and the experimental protocol was approved by the ethics committee at Hanover Medical School.

Experimental Design

The pianists were asked to participate in 5 experimental sessions with different stimulation protocols (Fig 1A). Each experiment for each participant was separated by >2 weeks to minimize any carryover effect of the stimulation (see Fig 1B). The order of the stimulation protocols was balanced across participants, and the experimental design was double-blinded by asking a person different from the experimenter to set stimulation parameters so that the experimenter and participant were unaware of the ongoing stimulation protocol. However, 2 of the protocols were virtually single-blinded (i.e., unihemispheric stimulation with retraining [UniAu] and bihemispheric stimulation without retraining [NoRT]), and their order was not balanced with regard to the other 3 sessions that were performed earlier.

Each experimental session consisted of pretest, training, and post-test. During training, in 4 of 5 protocols (i.e., all except for NoRT), participants were asked to perform bimanual mirrored finger movements that consist of successive strokes on 4 adjacent keys (right, G-F-E-D; left, C-D-E-F) with the little, ring, middle, and index fingers in synchrony with a metronome (3 strokes per beat, 100 beats per minute, interstroke interval = 200 milliseconds) as evenly as possible. This movement
rate is fast enough to elicit neural crosstalk between the hemispheres.\(^3\) The whole training session consisted of 8 subsessions, each of which consisted of the bimanual playing for 150 seconds and subsequent rest for 30 seconds (3 minutes × 8 sessions). A sequence was played so that a key was not released until the next key was depressed at the loudness of 70 MIDI velocity (mezzo-forte). A pilot study with 3 other patients confirmed no occurrence of muscular fatigue throughout the training session, which lasted for 24 minutes. The 4 stimulation protocols were referred to as CaAu, CuAa, sham, and NoRT. The training session, each participant did not perform bimanual training, but instead received tDCS under resting conditions. The remaining protocol (UniAu) involved bimanual mirrored finger movements with unihemispheric anodal stimulation over the unaffected hemisphere to probe the effect of transcortical inhibition and neural crosstalk by selectively activating the contralateral ("healthy") motor cortex. One electrode was placed over the right motor cortex, and the return electrode was positioned over the left orbit. tDCS was induced through sponge electrodes (surface = 35cm\(^2\)) and delivered by a battery-driven constant-current stimulator (Eldith, neuroConn, Ilmenau, Germany). This method has already been used in numerous studies and is regarded as safe.\(^{26}\)

During the pretest and post-test sessions, each participant played the trained sequence of keystrokes for 8 seconds with right and left hands in synchrony with a metronome (interkey-stroke interval = 200 milliseconds) as accurately as possible. To evaluate a transfer effect of the training on an untrained motor skill, each patient also struck a single key repetitively with the affected finger for 6 seconds as fast and accurately as possible, while keeping the remaining digits immobilized by depressing the adjacent keys.\(^{27}\) Patients suffering from dystonic movements in multiple fingers were asked to perform this tapping task with each of the affected fingers.

**Data Acquisition and Analysis**

We recorded the time of each keystroke in pretest, training, and post-test conditions. The standard deviation of the interkey-stroke intervals across strokes was computed as an index of rhythmic variability of sequential keystrokes. High evenness of keystrokes with only very little rhythmic variability indicates a high degree of fine motor control. For the untrained task (repetitive tapping by the affected finger), the variability of keystrokes of the participants who had multiple fingers affected was evaluated by averaging rhythmic variability of the keystrokes across the affected fingers.
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Statistics
To assess rhythmic variability at the pretest and post-test, and the difference for both the patient and control groups, a 2-way analysis of variance (ANOVA) with mixed design using stimulation protocol as the within-factor (CaAu, CuAa, sham, UniAu, and NoRT) and group as the between-factor (healthy pianists and pianists with FD) was designed. We excluded age-related effects by regression analysis, which yielded no significant regression between age and each of the variables (p > 0.05). Tukey post hoc tests with multiple comparison correction were performed in the case of significant results of the ANOVA. To determine factors associated with individual differences of stimulation effects on rhythmic variability of keystrokes, a correlation analysis was performed with severity of the symptom (i.e., initial rhythmic variability of keystrokes at the pretest), actual age of pianists and patients, and time period indicating the elapsed time between diagnosis of FD and participation in the study. For the training session, a 2-way repeated-measures ANOVA with session and stimulation protocol as between-factors was also performed for the patient group. To evaluate the effect of training, we subtracted rhythmic variability of the initial 5 seconds of the first training session (baseline performance) from the variability of keystrokes averaged within each of 8 training sessions of the affected right hand by the patients. This value was used as a dependent variable for the repeated-measures ANOVA, to assess improvements in motor performance over the training sessions. In addition, rhythmic variability during the 5-second baseline was assessed by 2-way ANOVA, to confirm that there was no difference across stimulation protocols.

Results
First, a 2-way mixed-design ANOVA using group and protocol as independent variables was performed, to confirm that the initial baseline performance prior to the training did not differ across the protocols. Neither main effect of protocol nor interaction effect of protocol and group was significant for rhythmic variability of the keystrokes during both the pretest of the trained sequential strokes and the baseline of the training (Table 3). Similarly, rhythmic variability of the single-finger tapping in the pretest yielded no main effect of protocol for the affected finger of the right hand in the patient group ($F_{4,36} = 2.47, p = 0.06$) and for all right fingers in the healthy group ($F_{4,36} = 0.79, p = 0.54$).

Figure 2A illustrates the group mean of the standard deviation of the interkeystroke intervals across strokes (i.e., rhythmic variability of keystrokes) after the training session (i.e., post-test) with each of the 5 stimulation protocols while FD patients and healthy individuals played a trained sequence with the affected hand. For the patient group, rhythmic variability for the CaAu protocol was smaller than for the other protocols. By contrast, none of the stimulation protocols elicited any discernible change in the healthy group. The 2-way mixed design ANOVA yielded a significant interaction effect of group and stimulation protocol ($F_{4,72} = 2.97, p = 0.02$). Post hoc tests confirmed significant differences between the CaAu and each of the CuAa, sham, and NoRT protocols in the patient group. In addition, a group difference was significant for the protocols except only for the CaAu. The findings indicate that CaAu stimulation elicited an improvement in rhythmic accuracy of keystrokes with the affected hand of the FD patients. Similarly, the group mean of the amount of change in rhythmic variability of keystrokes after the training test (i.e., post-test − pretest) for the CaAu, CuAa, sham, UniAu, and NoRT conditions was $-8.5 \pm 12.9$ milliseconds, $3.2 \pm 6.7$ milliseconds, $0.9 \pm 5.2$ milliseconds, $0.3 \pm 2.5$ milliseconds, and $0.6 \pm 3.6$ milliseconds for the patient group, and $-0.7 \pm 2.3$ milliseconds, $-1.5 \pm 3.0$ milliseconds, $-1.4 \pm 2.2$ milliseconds, $-0.2 \pm 2.9$ milliseconds, and $-0.3 \pm 1.6$ milliseconds for the healthy group, respectively. A 2-way mixed design ANOVA confirmed an interaction effect of group and protocol ($F_{4,72} = 3.89, p = 0.01$), and post hoc tests identified a significant difference between the CaAu and each of the other 4 protocols ($p < 0.01$ for CuAa and sham, $p < 0.05$ for UniAu and NoRT). None of any other protocol pairs yielded a significant difference.

By contrast, for the unaffected hand, rhythmic variability of the keystrokes in the post-test did not differ across the stimulation protocols (group × protocol: $F_{4,72} = 0.34, p = 0.85$ by 2-way mixed-design ANOVA; no group difference for any protocols in post hoc tests). The group mean of rhythmic accuracy of keystrokes in the post-test for the CaAu, CuAa, sham, UniAu, and NoRT protocols was $12.2 \pm 3.0$, $11.3 \pm 2.7$, $11.9 \pm 3.6$, $11.1 \pm 3.0$, and $11.1 \pm 2.8$ in the patient group, and $11.0 \pm 2.7$, $11.2 \pm 3.2$, $10.7 \pm 3.2$, $11.0 \pm 3.2$, and $10.6 \pm 2.5$ in the healthy group, respectively. Figure 2B displays the relation between the amount of change in rhythmic variability of the keystrokes while the FD patients were playing the trained sequence with the affected hand and rhythmic variability of the keystrokes in the pretest (i.e., severity of the symptom) for the CaAu stimulation condition. A significant negative correlation was evident between these factors ($r = -0.92, p = 1.4 \times 10^{-6}$). By contrast, none of the other 4 conditions yielded any significant negative correlation ($r = 0.76$ and $p = 0.01$ for CuAa, $r = -0.38$ and $p = 0.28$ for sham, $r = -0.54$ and $p = 0.11$ for UniAu, $r = -0.53$ and $p = 0.12$ for NoRT). This finding indicates greater effects of the CaAu stimulation on rhythmic accuracy of keystrokes for patients with more severe symptoms of FD. In the healthy group, these variables...
TABLE 3. Rhythmic Variability of the Keystrokes at Pretest, Post-Test, and Testing Baseline

<table>
<thead>
<tr>
<th>Hand</th>
<th>Time Point</th>
<th>Group</th>
<th>Protocol</th>
<th>CaAu (sd)</th>
<th>CuAa (sd)</th>
<th>sham (sd)</th>
<th>UniAu (sd)</th>
<th>NoRT (sd)</th>
<th>ANOVA Results</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Protocol</td>
<td>F(1,18)</td>
<td>p</td>
<td>F(4,72)</td>
<td>p</td>
<td>F(4,72)</td>
<td>p</td>
</tr>
<tr>
<td>Affect[ed</td>
<td>pretest</td>
<td>Patient</td>
<td>CaAu</td>
<td>20.7 (12.8)</td>
<td>102.2</td>
<td>0.01</td>
<td>0.57</td>
<td>0.69</td>
<td>1.04</td>
</tr>
<tr>
<td>hand</td>
<td></td>
<td>Control</td>
<td>CaAu</td>
<td>11.4 (3.8)</td>
<td>8.37</td>
<td>0.01</td>
<td>2.93</td>
<td>0.03</td>
<td>2.97</td>
</tr>
<tr>
<td></td>
<td>posttest</td>
<td>Patient</td>
<td>CaAu</td>
<td>12.2 (5.0)</td>
<td>8.37</td>
<td>0.01</td>
<td>2.93</td>
<td>0.03</td>
<td>2.97</td>
</tr>
<tr>
<td>Unaffected</td>
<td>pretest</td>
<td>Patient</td>
<td>CaAu</td>
<td>13.0 (9.4)</td>
<td>0.82</td>
<td>0.38</td>
<td>1.82</td>
<td>0.14</td>
<td>2.29</td>
</tr>
<tr>
<td>hand</td>
<td></td>
<td>Control</td>
<td>CaAu</td>
<td>10.8 (2.7)</td>
<td>0.82</td>
<td>0.38</td>
<td>1.82</td>
<td>0.14</td>
<td>2.29</td>
</tr>
<tr>
<td></td>
<td>posttest</td>
<td>Patient</td>
<td>CaAu</td>
<td>12.2 (3.0)</td>
<td>0.35</td>
<td>0.56</td>
<td>0.34</td>
<td>0.85</td>
<td>0.34</td>
</tr>
<tr>
<td>baseline</td>
<td></td>
<td>Control</td>
<td>CaAu</td>
<td>11.0 (2.7)</td>
<td>0.35</td>
<td>0.56</td>
<td>0.34</td>
<td>0.85</td>
<td>0.34</td>
</tr>
<tr>
<td>training</td>
<td></td>
<td>Patient</td>
<td>CaAu</td>
<td>35.9 (24.3)</td>
<td>21.46</td>
<td>2.1×10^-4</td>
<td>1.11</td>
<td>0.36</td>
<td>1.46</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Control</td>
<td>CaAu</td>
<td>11.6 (3.7)</td>
<td>21.46</td>
<td>2.1×10^-4</td>
<td>1.11</td>
<td>0.36</td>
<td>1.46</td>
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</tbody>
</table>

A number in parenthesis indicates the standard deviation within a group.
A bold number indicates p<0.05.
baseline: movement variability at the affected hand during the first 5 seconds of the training session
A group difference was significant at both the pretest with the affected hand and baseline, but not at the pretest with the unaffected hand.
CaAu: cathodal over the affected cortex and anodal over the unaffected cortex, CuAa: the reverted montage of CaAu,
UniAu: unilateral anodal over the unaffected cortex, NoRT: CaAu stimulation without retraining.

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linear regression analysis. Negative values indicate a decrease in the data of one patient. A line was drawn based on the result of all pianists with FD in the CaAu protocol. Each point indicates rhythmic variability of keystrokes following training (measured in affected hand between pretest and post-test conditions (y-axis) and difference in rhythmic variability of keystrokes with the sessions of training during CaAu of keystrokes with the affected hand of pianists with FD over 8 milliseconds). (C) Group mean of changes in rhythmic variability

\[ \Delta V = \frac{V_{\text{post}} - V_{\text{pre}}}{V_{\text{pre}}} \]

\* and NoRT protocols, respectively. One-way repeated-measures ANOVA yielded no main effect of stimulation \((F_{5,63} = 0.34, p = 0.85)\), which indicates a lack of transfer effects of the training on performance of the untrained tapping.

\[ V = \frac{V_{\text{post}} - V_{\text{pre}}}{V_{\text{pre}}} \]

\[ \Delta V = \frac{V_{\text{post}} - V_{\text{pre}}}{V_{\text{pre}}} \]

\[ V_{\text{pre}} = \frac{V_{\text{st}} - V_{\text{tr}}}{V_{\text{tr}}} \]

\[ V_{\text{st}} = \frac{V_{\text{tr}} - V_{\text{st}}}{V_{\text{tr}}} \]

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Discussion

FD is a disease extremely difficult to treat. In musicians, it frequently leads to early termination of their professional career. Retraining techniques either by repetitive movement training following the principles of induced beneficial brain plasticity by sensory–motor retuning of the affected hand, or by behavioral therapies including the slow-down technique and awareness training, remain promising therapeutic attempts. Here, we report that combining motor training with tDCS seems to be required to produce improvement on the task selected for training. This progress seems to require a combined use of bihemispheric tDCS with bimanual mirrored finger movements to elicit improvement of rhythmic accuracy of a trained sequence of finger movements. It occurs exclusively when stimulating the affected motor cortex with the cathodal and the unaffected motor cortex with the anodal electrode. So far, none of the previous studies has restored loss of inhibition at the affected motor cortex and fine motor control in FD patients using unihemispheric cathodal tDCS with the return electrode at the contralateral forehead position, even if this stimulation was combined with a retraining procedure. Bihemispheric tDCS possesses 2 possible advantages over unihemispheric stimulation. First, it is assumed to directly increase interhemispheric inhibition into the affected cortex via the corpus callosum, and thereby might facilitate its intracortical inhibitory mechanisms. This concept was recently supported by bihemispheric tDCS with the reversed montage for stroke patients, which is assumed to decrease interhemispheric inhibition to the affected cortex. Second, bihemispheric stimulation might augment the fraction of motor commands transmitted from the unaffected to the affected cortex via the corpus callosum, and thereby normalize abnormal motor programs. This concept is supported by a lack of improvement in the fine motor control both of untrained single finger tapping following the stimulation with retraining and of trained sequential finger movements following the stimulation without retraining, making it likely that the current training specifically restored control of the trained motor skill of pianists with FD. Attention could also modulate the stimulation effect so as to suppress cortical excitation and to enhance the capacity of plastic alterations. We acknowledge that a limitation of this study is the lack of a cortical excitability or activity assessment before and after stimulation, which would have helped to clarify mechanisms of action at the physiological level. In future studies, we will include such an assessment, which was not possible in the present design for logistical reasons. We also would like to point out that although the experimental results of our study are clear, future studies need to show if and to what extent these results translate into meaningful therapeutic improvements when combined with prolonged repeated training protocols. Nevertheless, we think that the current tDCS protocol offers qualitatively new options to improve rehabilitative efforts in occupational dystonia. Another limitation is that effects of neither unihemispheric cathodal stimulation over the affected cortex during retraining nor bihemispheric stimulation before or after retraining were evaluated due to limited feasibility in the patients.

Authorship

S.F. participated in the design of the study, carried out the experiments, analyzed data, performed the statistical analysis, and drafted the manuscript. M.A.N. participated in the design and coordination of the study and helped to interpret the data and draft the manuscript. W.P. participated in the design and coordination of the study and helped to interpret the data and draft the manuscript. E.A. participated in the design and coordination of the study, recruited and diagnosed the patients, and helped to draft the manuscript. All authors read and approved the final manuscript.

Potential Conflicts of Interest

Nothing to report.

References


