# Effects of Human Cerebellar Thalamus Disruption on Adaptive Control of Reaching

The Harvard community has made this article openly available. **Please share** how this access benefits you. Your story matters.

<table>
<thead>
<tr>
<th><strong>Citation</strong></th>
<th>Chen, Haiyin, Sherwin E. Hua, Maurice Smith, Frederick A. Lenz, and Reza Shadmehr. 2005. Effects of human cerebellar thalamus disruption on adaptive control of reaching. Cerebral Cortex 16(10): 1462-1473.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Published Version</strong></td>
<td><a href="http://dx.doi.org/10.1093/cercor/bhj087">doi:10.1093/cercor/bhj087</a></td>
</tr>
<tr>
<td><strong>Accessed</strong></td>
<td>June 19, 2017 3:19:12 PM EDT</td>
</tr>
<tr>
<td><strong>Citable Link</strong></td>
<td><a href="http://nrs.harvard.edu/urn-3:HUL.InstRepos:3874484">http://nrs.harvard.edu/urn-3:HUL.InstRepos:3874484</a></td>
</tr>
<tr>
<td><strong>Terms of Use</strong></td>
<td>This article was downloaded from Harvard University's DASH repository, and is made available under the terms and conditions applicable to Other Posted Material, as set forth at <a href="http://nrs.harvard.edu/urn-3:HUL.InstRepos:dash.current.terms-of-use#LAA">http://nrs.harvard.edu/urn-3:HUL.InstRepos:dash.current.terms-of-use#LAA</a></td>
</tr>
</tbody>
</table>

*(Article begins on next page)*
Lesion or degeneration of the cerebellum can profoundly impair adaptive control of reaching in humans. Computational models have proposed that internal models that help control movements form in the cerebellum and influence planned motor output through the cerebello-thalamo-cortical pathway. However, lesion studies of the cerebellar thalamus have not consistently found impairment in reaching or adaptation of reaching. To elucidate the role of the cerebellar thalamus in humans, we studied a group of essential tremor (ET) patients with deep brain stimulation (DBS) electrodes placed in the cerebellar thalamus. The stimulation can be turned on or off remotely and is thought to reduce tremor by blocking the spread of the pathological output from the cerebellum. We studied the effect of thalamic DBS on the ability to adapt arm movements to novel force fields. Although thalamic DBS resulted in a dramatic and significant reduction of tremor in ET, it also impaired motor adaptation: the larger the stimulation voltage, the greater the reduction in rates of adaptation. We next examined ET patients that had undergone unilateral thalamotomy in the cerebellar thalamus and found that adaptation with the contralateral arm was impaired compared with the ipsilateral arm. Therefore, although both lesion and electrical stimulation of the cerebellar thalamus are highly effective in reducing tremor, they significantly impair the ability of the brain to form internal models of action. Adaptive control of reaching appears to depend on the integrity of the cerebello-thalamo-cortical pathway.

**Keywords:** DBS, essential tremor, internal models, motor control, motor learning, thalamotomy, Vim

**Introduction**

Our limbs have inertial dynamics that dictate a complex relationship between joint motions and joint torques. In order to reliably produce a simple movement, such as flexion of the elbow, the brain must activate not only elbow flexors but also shoulder flexors that counter the shoulder extension torque produced by acceleration of the elbow. To decelerate the elbow flexion and stop at the target, activation and precise timing of elbow extensors are required. Otherwise, the limb will overshoot the target and oscillate (Vilis and Hore, 1980). Current theories suggest that because of time delays in sensory feedback, the brain implicitly accounts for this physics when it composes motor commands (Shadmehr and Mussa-Ivaldi, 1994). To perform a voluntary movement, the brain appears to perform 2 kinds of computations: 1) given a desired change in the proprioceptively or visually defined sensory state of the limb, it predicts the motor commands that are likely to produce the desired change, and 2) given a planned motor command, it predicts the sensory consequences of that command. These sensorimotor and motor-sensory maps are collectively called “internal models” of action (Wolpert and Ghahramani, 2000).

A fundamental characteristic of internal models is that when they are embedded into a control system, they reduce the reliance of the controller on sensory feedback. As a result, the accuracy of action is thought to be linked to the accuracy of internal models. For example, when internal models of reaching are inaccurate, simulations of reaching show ataxic symptoms (Schweighofer and others, 1998) like those recorded in cerebellar patients (Bastian and others, 1996). Indeed, neuropsychological studies suggest that the cerebellum is crucially involved in the formation of internal models of reaching. For example, patients with lesions in the posterior cerebellum were unable to adapt to changes in visuomotor alignments imposed by prism goggles (Weiner and others, 1983; Martin and others, 1996). Patients with global cerebellar degeneration were profoundly impaired in adapting to the novel dynamics of a force field (Maschke and others, 2004; Smith and Shadmehr, 2005). In contrast, patients with Huntington disease or Parkinson disease showed normal adaptation of reaching in force fields (Krebs and others, 2001; Smith and Shadmehr, 2005) and normal adaptation with prisms (Fernandez-Ruiz and others, 2003).

The dentate nucleus of the cerebellum projects to the ventrolateral thalamus, which in turn projects to the motor areas of the frontal lobe (Sakai and others, 2002). In nonhuman primates, neural correlates of internal models of reaching have been recorded in the frontal motor areas, including the primary motor cortex (Li and others, 2001; Paz and others, 2003), supplementary motor area (Padoa-Schioppa and others, 2004), and premotor cortex (Padoa-Schioppa and others, 2002). In light of results in human patient studies, it seems likely that aspects of the internal models of reaching form in the cerebellum and influence descending motor commands via cerebello-thalamo-cortical pathways.

Current evidence, however, has not led to any consensus about the role of this pathway in motor learning. Martin and others (1996) reported that 2 out of the 3 patients with lesions in the cerebellar thalamus learned to compensate for prism goggles normally, whereas the other patient did not pass criteria for either baseline performance or adaptation. On the other hand, animal lesion research has demonstrated that cerebellar thalamic nucleus is important for the acquisition of certain motor skills. Fabre and Buser (1979) reported that bilateral lesion of the ventrolateral thalami in cats impaired learning of a reaching task that involved pointing to moving targets. Jeljeli and others (2003) showed that lesion of the ventral thalamic nuclei in rats caused pronounced deficits in their ability to learn to walk on a rotating beam. The inconsistency between human and animal research could be the result of a real interspecies...
difference in the role thalamus plays in adaptation. For example, the cerebellar nuclei project to the thalamus as well as the spinal motor neurons through brain stem nuclei. It is plausible that in humans, the cerebellum’s contribution to adaptive control of reaching movements is primarily conveyed via brain stem pathways. However, it is difficult to make any conclusion based on the studies so far because of the paucity of available data and inconsistency across patients.

Programable stimulation of the cerebellar thalamus provides a unique opportunity to explore the role of thalamus in human motor adaptation. We studied patients with essential tremor (ET) who had deep brain stimulators (DBS) stereotactically placed in the posterior aspect of their ventrolateral thalamus (VLp), also known as the ventral intermediate nucleus (Vim). ET is characterized by a 4- to 12-Hz "postural tremor" (present during voluntary maintenance of steady posture) that affects both limbs. In advanced stages, this postural tremor is often accompanied with an intention tremor that intensifies as the hand approaches a target (Ellble and Koller, 1990). There is growing evidence supporting the hypothesis that the pacemaker for ET is in the inferior olive-cerebellar circuits (for review, see Deuschl and Bergman, 2002). The anomalous oscillation is believed to be then transmitted by the cerebello-thalamo-cortical pathway and manifest as tremor. In ET patients, pathological rhythmic discharges at tremor frequency are seen in all 3 major nuclei of the ventrolateral thalamus: the cerebellar recipient (Vim), the pallidal recipient, and the principal somatosensory nucleus, with Vim having the highest concentration of such tremor-related neurons (Hua and Lenz, 2005). It has been shown that Vim DBS is highly effective for relief of ET (Koller and others, 2000). The success is made possible by accurate and individual localization of the region within Vim that is associated with limb tremor. The locus of Vim DBS implant is determined by the combination of finding Vim’s stereotactic coordinates from MRI, neurophysiological mapping of the nucleus, and intraoperative confirmation of tremor relief with micro- or macrostimulation of the region identified (Garonzik and others, 2002).

The mechanism by which DBS produces its therapeutic effect is still being elucidated. Mathematical modeling of the response of thalamocortical neurons to DBS suggests that with typical settings of the stimulator, axons of thalamic relay neurons within a 2-mm region around the stimulating electrode are driven to fire at the stimulus frequency, whereas cell bodies and the intrinsic activities of these neurons are inhibited (McIntyre and others, 2004). Indeed, positron emission tomography (PET) imaging studies have shown that DBS leads to increased activation, hence blood flow, in the cortical regions that Vim projects to (Ceballos-Baumann and others, 2001; Perlmuter and others, 2002; Haslinger and others, 2003). Thalamic DBS also tends to drive local inhibitory interneurons in the Vim and may potentially drive the cerebellar nuclei antidromically (the dentate, interpositus, and fastigial nuclei all project to VLp [Macchi and Jones, 1997]). The combined effect of thalamic DBS is thought to prevent the tremor-generating signal in the cerebellar nuclei from reaching the cerebral cortex. However, if cerebellar nuclei also convey to the cerebral cortex information related to internal models of reaching, then Vim stimulation might impair adaptive control of reaching.

We found evidence in support of this conjecture. In a reaching task known to induce adaptation, we observed that when DBS was turned on, patients tended to adapt slower than when no stimulation was given. To explore the possibility that this stimulation related adaptation impairment might have been primarily a result of indirect stimulation of cortical motor regions by thalamic DBS (Haslinger and others, 2003), we considered another group of ET patients, those with prior Vim thalamotomy. We found that although tremor was generally small or absent in the arm contralateral to the thalamotomy, adaptation was better with the arm ipsilateral to the thalamotomy. Together, these findings corroborate with our hypothesis that adaptation of reaching requires the integrity of the cerebellar thalamus.

Materials and Methods

Subjects

Twenty ET patients were recruited from the Johns Hopkins Neurosurgery clinic (FAL). Fifteen ET patients had either unilateral (11 patients) or bilateral (4 patients) Vim DBS implants (mean age: 65 years, range: 42-80 years). Thus, a total of 19 unique DBS sides were tested (mean time since procedure: 16 months, range: 1 day to 5 years, see Table 1), and they are considered as separate DBS cases in the data analysis. The other 5 patients had unilateral Vim thalamotomy (mean age: 66 years, range: 51-71 years; mean time since procedure: 7 years, range: 4-12 years). Of these 5 patients, 4 had left Vim thalamotomy and 1 had right Vim thalamotomy. Of these 20 ET patients, 4 were left-handed and 16 right-handed.

Twenty-six healthy adults were recruited to serve as control subjects for the 2 patient groups. Nineteen served as controls for the DBS patient group (mean age: 58 years, range: 49-84 years) and 7 as controls for the thalamotomy patient group (mean age: 58 years, range: 50-71 years). Of these 26 subjects, 3 were left-handed and 23 right-handed. No difference in performance or adaptation level was found between the left- and right-handed control subjects. Subjects gave written consent for the experiments, and the experimental procedures were approved by Johns Hopkins Institutional Review Board.

Experimental Design

We examined adaptive control of reaching in force fields. The task that we used has been previously described (Shadmehr and Brashers-Krug, 1997). Briefly, the subject held onto the handle of a robotic arm and reached to targets that were displayed on a video monitor. A sling was used to support the subject’s arm and restrict movements to the horizontal plane. Each reach was called a "trial." On odd-number trials, the targets appeared at 10 cm from the center of the screen at 1 of 4 angles: 0°, 90°, 180°, or 270° (measured clockwise from the horizontal axis). On even-number trials, the target appeared back at the center of the screen. At the start of each trial, the subject held the cursor at a crosshair (1 cm wide) indicating trial origin for 0.5 s. The crosshair then disappeared and a square box (1 cm wide) representing the target was displayed. At the end of each reach, the subject received color and sound feedback on the speed and duration of his/her reach. A pleasant “burst” sound was played if the trial was completed within 0.5 ± 0.07 s, and the peak movement speed was between 0.20 and 0.55 m/s. Criteria for movement completion and proximity to trial origin and target were relaxed to accommodate for patient’s tremor. At trial start, the target box would be given if the cursor had been held within 1.5 cm from the center of the crosshair for 0.5 s. Movements were considered complete either after movement speed had fallen below 0.05 m/s or after the cursor had been within 1.5 cm from the target center for 1 s.

Trials were organized into sets of 96 targets. A single session consisted of 4 “null” sets, followed by 4 “adaptation” sets, followed by 3 “washout” sets. During the null sets, the robot arm was passive and the motors were turned off. During the adaptation sets, the robotic arm applied a viscous curl force field at the handle to perturb the subject’s movements. The force applied at the hand, \( \mathbf{F}(t) \), was proportional in magnitude and perpendicular in direction to the movement velocity of the hand \( \mathbf{v}(t) \):

\[
\mathbf{F}(t) = C \mathbf{v}(t) \tag{1}
\]

where \( C = [0 \ 13] \) N/s/m for the clockwise curl field and \( C = [0 \ -13; \ 13] \) N/s/m for the counterclockwise curl field. Also given within the
frequency, polarity at each of the 4 contacts, and polarity at the battery

Programing of the DBS was performed by a trained physician. The adjustable parameters for DBS are stimulation voltage, pulse width, frequency, polarity at each of the 4 contacts, and polarity at the battery

Table 1
DBS subjects information

<table>
<thead>
<tr>
<th>Case ID</th>
<th>DBS setting</th>
<th>Time of experiment relative to surgery</th>
<th>Electrode contacts</th>
<th>Voltage (V)</th>
<th>Pulse width (μs)</th>
<th>Frequency (Hz)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1R</td>
<td>0 0 0 0 0 +</td>
<td>3 months 10 days 5 months 10 days -0.028</td>
<td>0 1 2 3 Case</td>
<td>2 270</td>
<td>185</td>
<td></td>
</tr>
<tr>
<td>1R</td>
<td>0 0 0 0 0 +</td>
<td>23 months 23 months -0.205</td>
<td></td>
<td>1.8 270</td>
<td>185</td>
<td></td>
</tr>
<tr>
<td>1R</td>
<td>0 0 0 0 0 +</td>
<td>23.5 months 23.5 months -0.112</td>
<td></td>
<td>1.8 270</td>
<td>185</td>
<td></td>
</tr>
<tr>
<td>2R</td>
<td>0 0 0 0 0 +</td>
<td>6 months 6 months -0.300</td>
<td></td>
<td>6.7 120</td>
<td>185</td>
<td></td>
</tr>
<tr>
<td>3R</td>
<td>0 0 0 0 0 +</td>
<td>11 months 11 months -0.354</td>
<td></td>
<td>4.9 120</td>
<td>185</td>
<td></td>
</tr>
<tr>
<td>4R</td>
<td>0 0 0 0 0 +</td>
<td>37 months 37 months -0.074</td>
<td></td>
<td>4.3 60</td>
<td>185</td>
<td></td>
</tr>
<tr>
<td>5R</td>
<td>0 0 0 0 0 +</td>
<td>-1 day'a 2 days -0.342</td>
<td></td>
<td>4.1 210</td>
<td>185</td>
<td></td>
</tr>
<tr>
<td>5R</td>
<td>0 0 0 0 0 +</td>
<td>-1 day'a 9 days -0.192</td>
<td></td>
<td>3 210</td>
<td>185</td>
<td></td>
</tr>
<tr>
<td>5R</td>
<td>0 0 0 0 0 +</td>
<td>-1 day'a 5 months -0.043</td>
<td></td>
<td>3.8 210</td>
<td>185</td>
<td></td>
</tr>
<tr>
<td>5R</td>
<td>0 0 0 0 0 +</td>
<td>16 months 16 months -0.046</td>
<td></td>
<td>2.8 210</td>
<td>185</td>
<td></td>
</tr>
<tr>
<td>5L</td>
<td>0 0 0 0 0 +</td>
<td>-1 day'b 10 days 0.149</td>
<td></td>
<td>2.5 210</td>
<td>185</td>
<td></td>
</tr>
<tr>
<td>5L</td>
<td>0 0 0 0 0 +</td>
<td>12 months 12 months -0.313</td>
<td></td>
<td>4.5 60</td>
<td>145</td>
<td></td>
</tr>
<tr>
<td>6R</td>
<td>0 0 0 0 0 +</td>
<td>-1 day'b 5 days 0.028</td>
<td></td>
<td>1.8 120</td>
<td>185</td>
<td></td>
</tr>
<tr>
<td>7R</td>
<td>0 0 0 0 0 +</td>
<td>9 months 1 day -0.187</td>
<td></td>
<td>3.2 150</td>
<td>185</td>
<td></td>
</tr>
<tr>
<td>7R</td>
<td>0 0 0 0 0 +</td>
<td>1.3 months 1.3 months -0.054</td>
<td></td>
<td>2.5 60</td>
<td>185</td>
<td></td>
</tr>
<tr>
<td>8R</td>
<td>0 0 0 0 0 +</td>
<td>1.5 months 1.5 months -0.049</td>
<td></td>
<td>4 60</td>
<td>185</td>
<td></td>
</tr>
<tr>
<td>9R</td>
<td>0 0 0 0 0 +</td>
<td>1.7 months 1 month -0.043</td>
<td></td>
<td>2 60</td>
<td>185</td>
<td></td>
</tr>
<tr>
<td>9L</td>
<td>0 0 0 0 0 +</td>
<td>30 months 29.5 months 0.003</td>
<td></td>
<td>3.5 90</td>
<td>185</td>
<td></td>
</tr>
<tr>
<td>10R</td>
<td>0 0 0 0 0 +</td>
<td>4.3 months 4.3 months 0.126</td>
<td></td>
<td>3.5 150</td>
<td>185</td>
<td></td>
</tr>
<tr>
<td>10R</td>
<td>0 0 0 0 0 +</td>
<td>6 months 6 months 0.100</td>
<td></td>
<td>2.9 210</td>
<td>185</td>
<td></td>
</tr>
<tr>
<td>11R</td>
<td>0 0 0 0 0 +</td>
<td>28 months 28 months 0.129</td>
<td></td>
<td>3.2 90</td>
<td>185</td>
<td></td>
</tr>
<tr>
<td>12L</td>
<td>0 0 0 0 0 +</td>
<td>33 months 33 months -0.006</td>
<td></td>
<td>3.5 90</td>
<td>185</td>
<td></td>
</tr>
<tr>
<td>12L</td>
<td>0 0 0 0 0 +</td>
<td>34 months 34 months -0.106</td>
<td></td>
<td>2.1 90</td>
<td>185</td>
<td></td>
</tr>
<tr>
<td>13R</td>
<td>0 0 0 0 0 +</td>
<td>24 months 24 months -0.156</td>
<td></td>
<td>3.6 120</td>
<td>185</td>
<td></td>
</tr>
<tr>
<td>14R</td>
<td>0 0 0 0 0 +</td>
<td>61 months 61 months 0.103</td>
<td></td>
<td>3.3 60</td>
<td>185</td>
<td></td>
</tr>
<tr>
<td>15R</td>
<td>0 0 0 0 0 +</td>
<td>8 months 8 months -0.121</td>
<td></td>
<td>3 60</td>
<td>185</td>
<td></td>
</tr>
</tbody>
</table>

adaptation sets are "catch trials" (probability of 1/6, randomly placed) where the force field was unexpectedly removed for the duration of the trial. During the washout sets, the robot motors were turned off with the intention of washing out the effect of motor adaptation induced by the force field. In total, subjects performed 11 sets of trials or 1056 reaching movements in each session. A complete study consisted of 2 sessions.

DBS Patient Group and DBS Control Group

Fifteen ET patients with DBS implants were trained in the curl fields under 2 conditions: DBS turned on versus DBS turned off. The hand contralateral to the implant was used in each condition. For patients with bilateral implants, the effect of DBS was studied separately for each implant. The implant ipsilateral to the hand performing the reaching task was always turned off in order to eliminate possible interference. Subjects were randomly assigned to have DBS off during the first session or off during the second session. In 10 DBS sides/cases, DBS was turned on during the first session and off during the second session. In 9 DBS sides/cases, the DBS order was off first, on second. In 3 cases among this later group, the patients performed the first session 1 day before their surgeries (see Table 1). To be consistent, when discussing results for the entire DBS patient group, we use the descriptor "no stimulation" in place of "DBS off". Because we found an effect of stimulation voltage in the group data, we asked 4 DBS patients (patients 1, 5, 10, 12) to return and repeat the study more than once, each time at a different DBS voltage setting. Only data from each patient’s first study are included for group analyses of motor learning. Patient 15 did not complete the washout sets in session 2 and was excluded from the state space analysis (see Supplementary Material online).

For both the patient and the control groups, the counterclockwise field was given in the first session and the clockwise field in the second.

Programing the DBS

Programing of the DBS was performed by a trained physician. The adjustable parameters for DBS are stimulation voltage, pulse width, frequency, polarity at each of the 4 contacts, and polarity at the battery case. The optimal parameter combination for each patient was carefully searched based on reports and observations of stimulation response by both the patient and the physician. Tasks used to evaluate the response include postural hold (arm extension or drinking from a cup), pointing (finger-to-nose pointing), drawing (spiral and line drawing), and writing. The final DBS setting selected was the one that achieved maximum effectiveness on tremor reduction while inducing little, no, or only transient side effects of stimulation such as paresthesia and dysarthria. In some patients, multiple parameter combinations achieved similar therapeutic results. We conducted multiple experiments in 4 such DBS patients, each time under a different stimulation parameter combination to assess the effect of stimulation parameter on motor learning (see Table 1).

Thalamotomy Patient Group and Thalamotomy Control Group

We recruited 5 ET patients with Vim thalamotomy (see Table 3) and tested them in 2 sessions in a procedure similar to that of DBS patients. In the morning session, thalamotomy patients trained with the arm ipsilateral to the thalamotomy in the counterclockwise curl field. In the afternoon, they trained with the arm contralateral to the thalamotomy in a clockwise field. Control subjects for the thalamotomy patient group trained with their nondominant arms in the counterclockwise field during the first session and their dominant arms in the clockwise field during the second session.

Performance Measures

For each trial, we measured general movement performance with 4 parameters: path length, movement duration, peak speed, and movement error in terms of angular deviation (defined below) 300 ms after movement onset.

Movement onsets can be easily detected with a speed threshold when the speed profiles of the movements are relatively smooth and single peaked. For ET patients, however, postural tremor can often prevent the hand from holding still at trial origin and add oscillatory irregularities to the movements. Thus a simple speed threshold can lead to false detection of movement onset. We took a number of steps to accurately
detect movement onset. The trajectory of each trial was broken down to movement segments that exceeded 0.03 m/s, and only those segments longer than 300 ms were selected. To select the correct movement segment, the starting point of the segment had to be no farther than 1 cm from the origin and the net displacement toward the target for the segment had to be at least 4.5 cm. This precluded erroneous inclusion of looping trajectories resulting from postural tremor while patients attempt to hold still at origin, as well as in trials in which sudden dips in speed occurred on route to target.

To analyze motor adaptation, we focused on the movement error made in the first 300 ms of each reach. We defined angular error as the angle of trajectory deviation from the target direction at a fixed time after movement onset, with the convention that counterclockwise errors were positive. Another frequently used measure of error is displacement in the direction perpendicular to target direction. Results from analysis performed with perpendicular displacement at 250 or 300 ms and angular error at 250 or 300 ms were consistent. We chose to use angular error at 300 ms for this paper.

During the adaptation and washout trials, we measured movement error with respect to errors recorded at the end of the null sets—after subjects had completed nearly 300 practice trials. That is, a baseline movement error for each direction was estimated from the last null set by taking the median angular error of all trials made in that direction. All subsequent analyses on motor adaptation were based on these median-corrected angular error measurements.

Learning Index

To reduce motor errors while unfamiliar forces are applied at the hand, the motor system could adopt either one of 2 strategies: cocontract the muscles to increase the stiffness of the arm or predictively compensate for the force fields by developing an internal model. Both strategies lead to the reduction of trajectory deviations during field trials; however, they result in very different catch trial behaviors. Cocontraction would keep errors small in catch trials just as it does field trial. Internal model, on the other hand, would cause catch trial trajectories to become more deviated in the opposite direction as it evolves to better compensate the external forces (Shadmehr and Mussa-Ivaldi, 1994). Hence, the measure that quantifies learning must capture changes of trajectory errors in both field and catch trials. A learning index (Donchin and others, 2002; Smith and Shadmehr, 2005) is calculated for each set as follows:

\[
\text{Learning index} = \frac{y_{\text{catch}}}{y_{\text{field}} - y_{\text{null}}}.
\]


Table 2

<table>
<thead>
<tr>
<th>Performance measure</th>
<th>DBS patients</th>
<th>Controls</th>
<th>Change from controls (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group size</td>
<td>19</td>
<td>19</td>
<td>—</td>
</tr>
<tr>
<td>Peak speed (m/s)</td>
<td>0.29 (0.05)</td>
<td>0.31 (0.04)</td>
<td>–8 (24*)</td>
</tr>
<tr>
<td>Path length (cm)</td>
<td>10.70 (1.34)</td>
<td>10.06 (0.7)</td>
<td>5* (91****)</td>
</tr>
<tr>
<td>Movement duration (s)</td>
<td>1.55 (0.33)</td>
<td>1.11 (0.17)</td>
<td>39** (95**)</td>
</tr>
<tr>
<td>Arm compliance (%)</td>
<td>16.55</td>
<td>15.19</td>
<td>9</td>
</tr>
</tbody>
</table>

Note: With the exception of arm compliance, performance measures in the table are computed using trials from the last null set (before adaptation sets began) of each experimental session. The across-trial mean and standard deviation of each performance measure are averaged across sessions for each subject and then compared between the DBS patient group (n = 19) and the control group (n = 19). The group means of the 2 statistics for each measure are displayed in separate rows with the mean standard deviation shown in parentheses. The columns, from left to right, show mean values for the patient group, mean values for the control group and percent change of the patient group mean from the control group mean. Arm compliance is measured as the average difference between catch trial and field trial angular errors (at 300 ms) during the last 2 adaptation sets, hence given in units of degree. Standard deviation was not calculated for arm compliance as arm compliance was derived per set rather than per trial. ae: raw angular errors, before corrections for bias. Asterisks indicate significance of the patient group mean difference from controls using 2-sided t-test. *p < 0.05, **p < 0.01, ***p < 0.001, ****p < 0.0001.
Amplitude. (Power in the range of 3-10 Hz (tremor frequency range) was used to quantify tremor subjects (averaged over the 2 sessions). Dotted vertical line marks 3 Hz. The fraction of stimulation condition were plotted along with the group average PSD for the control peak was absent. (The PSD exhibited a peak centered at 5 Hz. With stimulation, this tremor-associated the first null set of each experimental session for a DBS patient. With no stimulation, the patients' implant surgery dates. DBS is very effective in treating this tremor (Vaillancourt and others, 2003). Indeed, our patients displayed clear benefits from the DBS during routine neurological examination consisting of tasks such as postural hold (arm extension or drinking from a cup), pointing (finger-to-nose pointing), drawing (spiral and line drawing), and writing. Because we were interested in quantifying the effect of thalamic stimulation on learning control of reaching, we assessed the effect of stimulation on tremor during the same task.

Figure 1 provides information on stimulation settings and the times at which experiments were conducted relative to the patients' implant surgery dates.

**Stimulation Reduced Tremor in the Initial Null Set**

Oscillations of the hand at 4–12 Hz are a typical feature of ET when the arm is held up against gravity. DBS is very effective in treating this tremor (Vaillancourt and others, 2003). Indeed, our patients had tremor during the initial null set, but then decreased substantially with time and practice. The initial tremor may in part have been due to nervousness associated with exposure to a novel task, as ET can be aggravated by stress (Gengo and others, 1986). With practice and familiarity, patients may have been able to assume a more relaxed posture and mental state.

Figure 2 provides examples of reaching movements of a DBS patient during early and late null sets with and without stimulation. Figure 2A shows that with no stimulation, the patient’s movements in the first null set exhibited significant tremor both while the hand was waiting at the origin and while the hand was moving. In the later null sets during the same no-stimulation session (Fig. 2B), the patient’s tremor was mostly confined to the waiting period and its magnitude was greatly reduced so that the total movement time was shortened almost by half. Surprisingly, tremor in late null set with no stimulation was comparable with tremor with DBS turned on (Fig. 2C,D). Indeed, across all patients, we found that by the last null set tremor magnitude (in terms of fraction of power in the 3- to 10-Hz range) in the no-stimulation condition had been reduced from the first null set by an average of 32%. This compares with the 44% tremor reduction by DBS (from the first null set of the no-stimulation condition to the first null set in the DBS-on condition). Therefore, regardless of the stimulation condition, tremor had substantially decreased by the last null set of each experimental session.

Once the tremor had subsided, did DBS affect other aspects of reaching? We focused on trials made in the last null set of each session and used 4 parameters to characterize movement trajectories: path length, angular errors at 300 ms after movement onset, peak speed, and movement duration. The mean and standard deviation values of these parameters were used to compare both across stimulation condition and subject group. Surprisingly, we found that with stimulation there was no significant within-subject change in the mean value of any of the 4 kinematic parameters. DBS also did not change patient’s arm compliance. In fact, performance with DBS turned on showed a significant increase in standard deviations of path length (24%, 2-sided paired t-test, \(P = 0.0085\)) and peak speed (8%, \(P = 0.013\)). Thus, although DBS effectively suppressed tremor, it did not improve the average movement kinematics and actually resulted in increased trial-to-trial variability of the movements. As compared with control subjects, ET patients had increased mean path length (6%) and movement duration (39%) (Table 2). Performance by patients also showed significantly increased intertrial variability in all parameters.

**Stimulation Impaired Reaching Adaptation to Force Fields**

Adapting to altered dynamics of reaching requires changes in motor commands that initiate the reach (Thoroughman and...
Shadmehr, 1999). These changes are due to feedforward mechanisms because in catch trials where the dynamics are unexpectedly removed, the limb overcompensates, resulting in aftereffects. Figure 3A shows the average size of the aftereffects achieved by a control subject and a DBS patient toward the end of trainings in the adaptation sets. For the control subject, aftereffects from the 2 experimental sessions were comparable, indicating similar amounts of adaptation. The DBS patient, however, showed significantly larger aftereffects in the no-stimulation session than in the DBS session.

Figure 3B shows for the same DBS subject the time course of angular errors (trajectory deviation at 300 ms into the movement) during each experimental session. For a system that learns to predict the dynamics of the task, we would expect to see decreasing field trial errors along with increasing catch trial errors (aftereffects). This patient exhibited the expected error pattern both with and without thalamic stimulation. However, training without stimulation led to significantly larger aftereffects (as seen in Fig. 3A) and smaller force-field errors than training with stimulation. We used the ratio of catch trial errors to the difference between catch and field errors as a learning index (Donchin and others, 2002; Smith and Shadmehr, 2005). As errors in catch trials increase and errors in field trials decrease this index increases from 0 to 1, with unity value reflecting complete adaptation. Figure 3C plots the distribution of this index for each subject group. Without stimulation, patients were impaired in adaptation with respect to controls. However, stimulation further degraded this performance. Figure 3D quantifies this effect by averaging performance in the last 2 training sets. When no stimulation was applied, ET patients showed on average an 8% reduction in learning index compared with controls ($P = 0.025$). However, with stimulation, the patients showed an additional 13% reduction in the learning index ($P = 0.024$ when comparing DBS on and no stimulation; 20% reduction comparing DBS on with control, $P = 0.0007$).

Acquisition of internal models involves error-dependent trial-to-trial changes in motor commands. For adaptation to take place, error experienced in a given movement to a given target needs to influence subsequent motor commands for that movement direction; this corrective influence may “spill over” to other movement directions as well, resulting in generalization of adaptation. We can quantify this pattern of direction-dependent trial-to-trial adaptation via an error generalization function (Thoroughman and Shadmehr, 2000; Donchin and others, 2003; Smith and Shadmehr, 2005). The rate of adaptation also depends on the strength of motor memory retention. It is possible that patients do not adapt as well because the trace of motor memory somehow decays faster. In Supplementary Material, we characterized these properties of adaptation for our subject populations with an autoregressive linear state space model that has been previously applied to study both healthy subjects and movement disorder patients (Thoroughman and Shadmehr, 2000; Donchin and others, 2003; Smith and Shadmehr, 2005). Our goal was to use the model to identify components of the adaptive computation that were affected by either ET itself or stimulation, which led to the overall reduction in learning we observed with learning index. We found that neither ET nor thalamic stimulation significantly affected the general shape of the error generalization function or motor memory retention. Rather, they significantly reduced the strength of generalization in several key movement directions relative to the direction in which error was experienced. In particular, at the movement direction where error was experienced, ET patients without stimulation showed over 30% reduction in error sensitivity compared with controls. Thalamic stimulation led to an additional 37% reduction in this sensitivity to errors.

**Adaptation Impairment Was Correlated with Stimulation Voltage**

Thalamic stimulation does not simply switch off a subcortical-cortical neuronal relay. Rather, variation of stimulation parameters (voltage amplitude, frequency, pulse duration, and electrode selection) produces a complex pattern of activity in the thalamocortical circuitry. A recent study found that although increased stimulation voltage was consistently associated with increased tremor relief, pulse duration had only a small effect...
and frequency change had no significant effect (O'Suilleabhain and others, 2003). If the degree of tremor reduction depends on parameter settings, then do deficits in motor learning also depend on parameters of stimulation? Figure 4A,B illustrate the performance of 2 patients with 2 different stimulation voltage settings. With the DBS off, both subjects demonstrated motor adaptation (the exact levels of adaptation vary from patient to patient). When DBS was turned on, performance of the subject with higher voltage (Fig. 4A) was significantly reduced, whereas performance of subject with lower voltage (Fig. 4B) remained similar to that of the off state. Figure 4C plots the relationship between the magnitude of within-subject percent change in the learning index and the stimulation voltage. We found a significant correlation (Pearson's correlation, $r = -0.67$, $P = 0.0018$; Spearman rank correlation, $r = -0.62$, $P = 0.0044$) between stimulation voltage and the degree of impairment in motor adaptation. The voltage sensitivity was somewhat stronger when the electrode configuration was in bipolar mode (stimulating with respect to 1 of the 4 electrodes, Fig. 4C) than in unipolar mode (stimulating with respect to the battery case, Fig. 4D).

In contrast, we did not observe a correlation between learning impairment and pulse width of DBS (frequency of stimulation was identical in all but one of our patients). The partial correlation between percent change in learning index and stimulation voltage, controlling for stimulation frequency, pulse width, stimulation mode (bipolar or unipolar), number of cathodes activated, number of all activated contacts, time of the study relative to each patient’s implant surgery, and time lag between the DBS-on session and no-stimulation session (see Table 1), was $r = -0.75$ ($P = 0.005, df = 10, 2$ tailed). This indicates that in our study, voltage was the only parameter in the above 8 factors that plays a significant role in motor adaptation impairment. We further performed stepwise regression to examine the effect of interaction between stimulation voltage and pulse width, which is related to total current output from the DBS and found no significant improvement of fit between learning index reduction and voltage.

Although each of the linear regressions in Figure 4C, D, and E reveals strong correlation between percent reduction in learning index and stimulation voltage, the intercepts of the regressions are 39%, 31%, and 57% for the combined, unipolar stimulation, and bipolar stimulation groups, respectively, predicting a facilitation of adaptation at 0 V stimulation. However, when DBS is programed to stimulate at 0 V, we should not expect any change in the level of adaptation between DBS on and no stimulation. The intersession learning index change for control subjects was $-1 \pm 11\%$ (mean and standard deviation), rendering it unlikely that there exists some forward interference or facilitation of performance from session 1 to session 2. We speculate that the relationship between adaptation impairment and voltage may be better characterized by a nonlinear function. One possibility is a sigmoid-type function that gradually decreases from 0% reduction near 0 V, then decreases more steeply beyond 3 V, and finally saturates somewhere beyond 7 V. It is also possible that the relationship between adaptation reduction and voltage is nonmonotonic. At low stimulation voltage, patients may adapt better than the no-stimulation condition given that the abnormal tremor signal is a source of noise that can be disruptive to normal neuronal processing. Our finding that, on average, ET patients adapt less than control subjects (Fig. 3) when no stimulation is given lends support to this hypothesis. Given limited patient population, it is difficult to conclude the true relationship between adaptation reduction and voltage. It is clear, however, that at stimulation voltage beyond 4 V, adaptation is greatly reduced.
Vim Thalamotomy Impaired Reach Adaptation in Force Fields

Was the impairment of adaptation due to the fact that Vim thalamic stimulation indirectly stimulated motor regions of the cerebral cortex? To explore this question, we recruited 5 ET patients who had undergone unilateral Vim thalamotomy (Table 3) and tested them in the same paradigm as the DBS patients. The important difference was that in one session the patient used the arm ipsilateral to the thalamotomy and in the other session the contralateral arm.

Because ET is generally a bilateral disease, one expects to find significant tremor in the arm ipsilateral to the thalamotomy as compared with the contralateral arm. Figure 5A plots our measure of tremor during reaches in the null field for a representative patient and for the entire group. For the patient, the hand ipsilateral to the thalamotomy exhibited a clear peak in PSD at 5 Hz, whereas no such peak was evident in the contralateral hand. As expected, the fraction of power in the 3- to 10-Hz range was lower on average when the patients used the arm contralateral to the thalamotomy than the arm ipsilateral to the thalamotomy (Fig. 5B). In terms of movement kinematics, thalamotomy did not significantly affect either the mean or the standard deviation of peak speed, path length, movement duration, or angular error of movements made in the last null set. Additionally, thalamotomy had no significant effect on arm compliance measured during adaptation sets. Compared with control subjects, thalamotomy patients showed significant reduction in peak speed (23%) and increase in movement duration (24%) (Table 4). Patients also showed reduction of standard deviation for peak speed (24%), though numerically it was not different from that of the control subjects for DBS patients (Table 2); thus, this reduction in intertrial peak speed variability may be an artifact of the small sample size. To test this, we compared the data of all ET patients (n = 24: 5 thalamotomy subjects and 19 DBS cases) with the data of all control subjects (n = 26) (Table 4). We found that ET patients showed significantly increased intertrial variability in path length (65%), movement duration (85%), and angular errors (44%) but not in peak speed. ET patients, on average, moved significantly slower than control subjects—they achieved 12% smaller peak speed, and their movement path lengths and durations were 5% and 35% longer, respectively. Our measures of movement kinematics indicated that ET patients moved slower than healthy control subjects and their trajectories tended to be more variable across trials.

Figure 5C plots the learning index for all the thalamotomy patients. Switching from contralateral to ipsilateral arm produced a significant improvement in performance (1-sided paired t-test of the learning index over the last 2 training sets, comparing ipsilateral with contralateral arm P = 0.038). Therefore, the thalamotomy patients as a group were significantly better in learning the task when they used the arm that exhibited more tremor (i.e., the arm ipsilateral to the thalamotomy).

Discussion

We tested the hypothesis that the cerebello-thalamo-cortical pathway plays a crucial role in adaptation of reaching movements by studying ET patients in whom this pathway was disrupted by Vim DBS or thalamotomy. We found that although both DBS and thalamotomy effectively reduced tremor...
during posture and reaching, they significantly impaired the rates of adaptation. In addition, we observed a significant correlation across the patients between stimulation voltage and the amount of adaptation impairment induced by stimulation. Patients with larger stimulation voltage tended to show greater adaptation impairment. The cerebellum has long been associated with motor adaptation. A number of psychophysical patient studies have found that damage to the cerebellum can profoundly impair the ability to adapt to novel kinematics or dynamics of reaching (Weiner and others, 1983; Martin and others, 1996; Maschke and others, 2004; Smith and Shadmehr, 2005). It is thought that the cerebellum has the ability to rapidly form internal models and “correct” the motor commands that are planned by the cortical motor areas by supplying information that predicts and compensates for constraints of the task (Conrad and others, 1974; Vilis and Hore, 1980). Alternatively, the cerebellum may compute signals that are crucial for forming an internal model (such as motor errors) and convey these signals to the cortical motor areas where motor memories form.

In humans, the cerebellum directs most of its output to the cerebellar thalamus and only a small number of fibers to the red nucleus (Nolte and Angevine, 2000); thus, from the anatomical standpoint, the cerebello-thalamo-cortical pathway should play a significant role in human motor adaptation, particularly reaching adaptation. However, until now, there has been very little empirical evidence directly supporting the importance of the cerebellar thalamus in human reaching adaptation (Martin and others, 1996). In the present study, we found evidence for this hypothesis using a within-subject design. We found that reversible disruption of the cerebellar thalamus produced adaptation deficits.

**Figure 5.** Effect of thalamotomy on tremor and motor adaptation. (A) Left: normalized average PSD for all trials in the first null set of each session for a thalamotomy patient. PSD for the untreated arm, ipsilateral to the thalamotomy, has a tremor-associated peak at 5 Hz. In the treated arm, contralateral to thalamotomy, this peak is greatly reduced. Right: group averages of normalized PSD for the patients’ ipsilateral arms and contralateral arms, as well as the control subjects’ (average of the 2 arms). Dotted vertical line marks 3 Hz, as in Figure 1A. (B) Group average of fractional power in the tremor frequency range (3–10 Hz) for the control subjects and the ipsilateral and the contralateral arms of the patients. Error bars are standard errors. (C) Performance of each thalamotomy patient quantified by learning index. Solid line indicates performance of the ipsilateral arm and dotted line that of the contralateral arm. (D) Average between-arm change in learning index for the patient group (ipsilateral – contralateral) and the control group (session 1 – session 2). Only learning indices from the last 2 adaptation sets are used. Thalamotomy patients show a significant decrease in adaptation in the contralateral arm ($P \leq 0.039$).

**Table 4**

<table>
<thead>
<tr>
<th>Performance measure</th>
<th>Thalamotomy patients</th>
<th>Thalamotomy controls</th>
<th>Change from controls (%)</th>
<th>All ET patients</th>
<th>All controls</th>
<th>Change from controls (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group size</td>
<td>5</td>
<td>7</td>
<td>—</td>
<td>24</td>
<td>26</td>
<td>—</td>
</tr>
<tr>
<td>Peak speed (m/s)</td>
<td>0.26 (0.04)</td>
<td>0.34 (0.06)</td>
<td>−23.4∗∗∗ (∗∗∗)</td>
<td>0.28 (0.05)</td>
<td>0.32 (0.05)</td>
<td>−12*** (10)</td>
</tr>
<tr>
<td>Path length (cm)</td>
<td>10.43 (1.40)</td>
<td>10.49 (1.13)</td>
<td>−0.5 (22.7)</td>
<td>10.65 (1.35)</td>
<td>10.18 (0.82)</td>
<td>5∗∗∗ (65∗∗∗)</td>
</tr>
<tr>
<td>Movement duration (s)</td>
<td>1.52 (0.36)</td>
<td>1.23 (0.22)</td>
<td>24.1* (65.0)</td>
<td>1.54 (0.34)</td>
<td>1.14 (0.18)</td>
<td>35∗∗∗∗ (85∗∗∗)</td>
</tr>
<tr>
<td>ae at 300 ms (°)</td>
<td>0.23 (6.14)</td>
<td>−0.08 (5.18)</td>
<td>−388 (12.9)</td>
<td>0.52 (6.70)</td>
<td>−0.15 (4.64)</td>
<td>−441 (44∗∗∗∗)</td>
</tr>
<tr>
<td>Arm compliance (°)</td>
<td>16.83</td>
<td>16.66</td>
<td>1.0</td>
<td>16.61</td>
<td>15.59</td>
<td>7</td>
</tr>
</tbody>
</table>

Note: This table follows the same convention as Table 2. All ET patients—combining DBS and thalamotomy patients; all controls—combining the respective control subject groups.

* $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$, **** $P < 0.0001$, ***** $P < 0.00001$. 
Additionally, we showed that during the no-stimulation condition ET patients with DBS implants had an intermediate amount of adaptation impairment between stimulator-on and healthy controls. This suggests an underlying adaptation deficit associated with ET, a finding that is consistent with the current understanding that ET results from abnormal oscillatory activities in the inferior olive–cerebellum neural network (Elble, 2000; Deuschl and Bergman, 2002). Animal models of ET have shown enhancement of olivary rhythmicity with injection of β-carboline drugs, which produces a tremor that resembles ET (Elble, 1998). Clinically, it has been observed that ET can disappear after lesions of the cerebellum (Dupuis and others, 1989), the pons (Urushitani and others, 1996; Nagaratnam and Kasabail, 1997), or the thalamus (Duncan and others, 1988). PET studies of ET have shown hyperactivity in the cerebellum (Jenkins and others, 1993), the inferior olive, as well as the thalamus (Hallett and Dubinsky, 1993). These works, along with the well-established surgical success of Vim DBS and thalamotomy for the suppression of ET, support the theory that tremor-related oscillations originate in the olivocerebellar circuits and propagate to the motor cortex by the cerebello-thalamic-cortical pathway. Taken together, it seems that in the untreated state of ET, functional disturbance of the cerebello-thalamic-cortical pathway caused by tremor-related oscillations compromises the relay and processing of information pertaining to reach adaptation. Thalamic lesion or stimulation disrupts the transmission of this oscillation and relieves ET but can further impair motor adaptation.

What is the nature of the information contained in the cerebellar outflow to the thalamus? One possibility is that the cerebellum forms internal models that compensate for specific dynamics of the task (forces produced by the robot) and correct the motor cortical commands. That is, the site of plasticity is in the cerebellum. Alternatively, the cerebellum may be involved in generating certain critical components of the internal model to be used by cortical motor areas. In particular, the cerebellum is well situated for computing motor errors. The intermediate zone of the cerebellar cortex receive afferents about the limbs from both the motor cortex and the spinal cord, allowing it to compare the desired motor output with the results of motor action. Both hypotheses on the cerebellum’s role in internal model formation can explain the gross impairments in movement control and motor adaptation seen in cerebellar patients (Martin and others, 1996; Smith and Shadmehr, 2005). However, because motor error is a crucial training signal for adaptation of internal models, these two possible functional roles of the cerebellum cannot be distinguished with the current experiments.

Recently, Diedrichsen and others (2005) showed with a functional magnetic resonance imaging study that when reaching motor errors were generated by force field, visual rotation, or target jump and resulted in similar patterns of online feedback correction, the cerebellum became activated regardless of the nature of the error and whether the error led to adaptation. This suggests that the cerebellum may be involved in error correction even when no new internal model is forming and supports the possibility that internal models form in motor cortical regions but depend on information supplied by the cerebellum through the thalamus. On the other hand, it has been shown that patients with cerebellar degeneration show somewhat preserved online error feedback correction when given force perturbations (Smith and others, 2000), whereas they are profoundly impaired in tasks that involve trial-to-trial error-driven learning (Smith and Shadmehr, 2005). These studies on cerebellar degeneration patients suggest that their ability to generate motor errors and to compensate accordingly is not completely abolished; rather, it is the ability to use these errors to drive adaptive changes to motor command that is abolished. Thus, although it is clear that the cerebellum plays a critical role in motor plasticity, we do not yet understand the relative contributions of the cerebellum, the thalamus, and the motor cortices in reaching motor control and adaptation.

How does thalamic stimulation affect the brain? High-frequency stimulation produces a complex pattern of excitation and inhibition, and its influence can reach beyond the stimulating nucleus. That is, thalamic stimulation is likely to affect downstream and upstream neurons via orthodromic and antidromic stimulation of the nearby axons (Perlmutter and others, 2002; Anderson and others, 2003; Hashimoto and others, 2003; Haslinger and others, 2003; McIntyre and others, 2004). Indeed, imaging studies have demonstrated increased activity in the thalamus, M1, and supplementary motor area in resting ET patients with DBS on versus off (Perlmutter and others, 2002; Haslinger and others, 2003). Although no significant changes were found in the cerebellar nuclei, it is possible that thalamic stimulation might artifically generate action potentials in the cerebellar thalamic axons, which could travel antidromically to the cerebellar nuclei without causing large changes in synaptic activity. Thus, thalamic stimulation is likely to disrupt neuronal activity in 3 locations: the motor cortex, the thalamus, and the cerebellar nuclei.

Given this, an alternate interpretation for our DBS study is that adaptation impairment associated with thalamic stimulation was not due to the disruption of the cerebellar thalamus. Rather, it was a result of indirect stimulation of the motor cortical regions via the thalamocortical neurons in Vim. However, we found that thalamotomy and stimulation affected adaptation similarly. Therefore, this suggests that impaired adaptation cannot be exclusively attributed to indirect stimulation of the motor cortex or the cerebellar nuclei.

Our finding that DBS impairs motor adaptation is consistent with recent reports showing that stimulation of the subthalamic nucleus in Parkinson disease impairs performance in certain cognitive or declarative memory tasks. Halbig and others (2004) compared the DBS-on and -off conditions and found that stimulation impaired recall in a declarative memory task. Hershey and others (2004) found that subthalamic stimulation in Parkinson disease impaired performance in a task that required spatial working memory. It seems that stimulation, whether in the subthalamic nuclei or in the cerebellar thalamus, has the potential to produce certain side effects in addition to its known therapeutic actions.

Previously known side effects associated with Vim DBS and thalamotomy in ET patients include paresthesia, dystartria, persistent and transient arm ataxia, and gait disturbance (Mohajer and others, 1990; Shahzadi and others, 1995; Schuurman and others, 2000; Dowsey-Limousin, 2002). For patients who have DBS, these side effects can often be reversed by turning the stimulator off. Still, many patients who experience side effects choose to leave the stimulator on during the day because the benefit of tremor suppression far outweighs the side effects. Comparative studies of the effects of thalamic DBS and thalamotomy on ET and 2 other movement disorders—associated severe tremor (Parkinson disease, multiple sclerosis) have shown that although the 2 surgical therapies are equally
effective for tremor suppression, DBS tends to give fewer side
effects and greater improvement in function as measured
by patient's ability to perform daily life activities, self-assessment
of surgical outcome, and neuropsychological evaluations
(Schuurman and others, 2000). For patients with bilateral
drug-resistant tremor, bilateral thalamotomy is no longer used
in clinical practice, whereas bilateral thalamic stimulation is
a viable therapy. In the present study, we found that although
thalamotomy produced motor adaptation deficits, DBS impaired
adaptation in a voltage-dependent fashion. This means that at
low stimulation voltage, DBS has the potential to eliminate
tremor without affecting motor adaptation, further suggesting
that DBS may be advantageous over thalamotomy.

Supplementary Material
Supplementary material can be found at: http://www.cercor.
oxfordjournals.org/

Notes
This work was supported by a grant from the National Institutes
of Health (NIH) (NS037422). HC was supported by a National Research
Service Award fellowship from the NIH. SEH was supported by a
postdoctoral grant from the Parkinson's Disease Foundation and the
American Parkinson Foundation and a grant from the American
Parkinson's Disease Association. MAS was supported by a grant from
the Hereditary Disease Society of America. We thank Drs H. Chris
Lawson and Stephen Grill for their help with patient recruitment for
the study. We also thank Drs Steve Wise and Amy Bastian for their
helpful comments on the manuscript.

Address correspondence to Haiyin Chen, Department of Biomedical
Engineering, Johns Hopkins School of Medicine, 419 Traylor Building,
720 Rutland Avenue, Baltimore, MD 21205, USA. Email: haiyin@jhu.edu.

References
Anderson ME, Postupna N, Rufio M. 2003. Effects of high-frequency
stimulation in the internal globus pallidus on the activity of thalamic

Bastian AJ, Martin TA, Keating JG, Thach WT. 1996. Cerebellar ataxia:
abnormal control of interaction torques across multiple joints.
J Neurophysiol 76:492-509.

Ceballos-Baumann AO, Boecker H, Fogel W, Alesch F, Bartenstein P,
Conrad B, Diederich N, von Falkenhayn I, Moringlane JR, Schwaiger
M, Tonnier VM. 2001. Thalamic stimulation for essential tremor
activates motor and deactivates vestibular cortex. Neurology
56:1347-1354.

Conrad B, Matsunami K, Meyer-Lohmann J, Wiesendanger M, Brooks VB.
1974. Cortical load compensation during voluntary elbow move-


in motor control: theory and experiments in human motor control. J
Neurosci 23:9032-9045.

tremor. Mov Disord 17(Suppl 3):S208-S211.

adjacent to the thalamus. J Neurol Neurosurg Psychiatry 51:591-592.

disappearance of essential tremor after cerebellar stroke. Mov Disord

University Press.


Fabre M, Buser P. 1979. [Visually guided movement in the cat: difference
in the effects of a bilateral lesion of the thalamic nucleus ventralis
lateralis performed either before or after training]. C R Seances Acad

Fernandez-Ruiz J, Diaz R, Hall-Haro C, Vergara P, Mischner J, Nunez L,
tation but reduced after-effect in basal ganglia disorders using a

Garonzik IM, Hua SE, Ohsara S, Lenz FA. 2002. Intraoperative microelec-
trode and semi-microelectrode recording during the physiological
localization of the thalamic nucleus ventral intermediate. Mov Disord
17(Suppl 3):S135-S144.

Gengo FM, Kalonaros GC, McHugh WB. 1986. Attenuation of response to
mental stress in patients with essential tremor treated with metoprolol.
Arch Neurol 43:687-689.

Halgren TD, Gruber D, Kenjo UA, Scherer P, Schneider GH, Trottenberg T,
modulates declarative and nondeclarative memory. Neuroreport
15:539-543.

Hallett M, Dubinsky RM. 1993. Glucose metabolism in the brain of

Hashimoto T, Elder CM, Okun MS, Patrick SK, Vitek JL. 2003. Stimulation
of the subthalamic nucleus changes the firing pattern of pallidal

Haslinger B, Boecker H, Bucel C, Vesper J, Tonnier VM, Pfister R,
Alesch F, Moringlane JR, Krauss JK, Conrad B, Schwaiger M,
Ceballos-Baumann AO. 2003. Differential modulation of subcortical
target and cortex during deep brain stimulation. Neuroimage
18:517-524.

Hershey T, Revilla FJ, Wernle A, Gibson PS, Dowling JL, Perlmuter JS.
2004. Stimulation of STN impairs aspects of cognitive control in PD.
Neurology 62:1110-1114.

Hua SE, Lenz FA. 2005. Posture-related oscillations in human cerebellar
thalamus in essential tremor are enabled by voluntary motor circuits.

Jelleli M, Strazielle C, Caston J, Lalonde R. 2003. Effects of ventrolateral-
ventromedial thalamic lesions on motor coordination and spatial

Jenkins IH, Bain PG, Colebatch JG, Thompson PD, Findley LJ, Frackowiak
RS, Marsden CD, Brooks DJ. 1993. A positron emission tomography
study of essential tremor: evidence for overactivity of cerebellar

stimulation of the Vim nucleus of the thalamus for the treatment of

Procedural motor learning in Parkinson's disease. Exp Brain Res
141:245-257.

performance and motor learning in the primary motor cortex of
monkeys adapting to an external force field. Neuron 30:593-607.

Macchi G, Jones EG. 1997. Toward an agreement on terminology of

Throwing while looking through prisms. I. Focal olivocerebellar

cerebellar ataxia progressively impairs force adaptation during

of deep brain stimulation: model-based analysis of activation and
localization of the thalamic nucleus ventral intermediate. Mov Disord
17(Suppl 3):S135-S144.

results of stereotaxy in the treatment of essential tremor. Stereotac-
tic Funct Neurosurg 54/55:125-129.


