Physiological and behavioral changes produced by cerebellar stimulation in the monkey

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Small surface electrodes were placed bilaterally over the intermediate or lateral cerebellar cortex of cynomolgus monkeys to determine how electrical stimulation of different areas of the cerebellar cortex affected average evoked responses and a sequential forelimb movement. Biphasic electrical stimulation was applied between various electrode combinations, and various intensities and frequencies were established for each combination. Transcortical stimulation between the right and left intermediate cerebellar cortex required the lowest intensity (1.5 μC/sq cm/ph) to elicit an average evoked response in the sensorimotor cortex; stimulation between the electrodes over the contralateral intermediate or lateral cortex required slightly higher levels (2.0 μC/sq cm/ph). No response could be elicited from stimulating the ipsilateral cortex. Likewise, 1 minute of transcortical stimulation was more effective than comparable stimulation of the contralateral intermediate or lateral cortex in altering the waveforms of a somatosensory evoked response. Transcortical stimulation also modified the forelimb movement, whereas contralateral stimulation of the intermediate or lateral cortex had little or no effect. Transcortical stimulation at 2.0 μC/sq cm/ph, with frequencies of 150 Hz or higher, increased the time required to execute the forelimb movement but did not affect the accuracy of the movement. High-speed motion pictures indicated that transcortical stimulation decreased the velocity of forelimb movement and in some cases also affected the limb trajectory. These results indicate that consideration should be given to the area of the cerebellum stimulated and to the mode of stimulation, in the hope of achieving optimum clinical benefit.

KEY WORDS - cerebellar stimulation - neuroprosthesis - cerebral palsy - evoked response

Focal electrical stimulation of the cerebellar cortex of patients with various movement disorders has reduced spasticity and athetosis, and in some patients has improved their activities of daily living. However, it is not clear what anatomical systems, physiological variables, or biochemical changes accompany such stimulation. There is little consensus of opinion about the appropriate number of electrodes or the array configuration, the pertinent parameters of electrical stimulation, or the best area of the cerebellar cortex to be stimulated.

Several kinds of electrodes have been used for cerebellar stimulation. Cooper and his associates first used an array of eight platinum electrodes arranged in two rows of four electrodes, with bipolar stimulation between the rows. Davis, et al., used a four-electrode array: the first and third electrodes were connected to one terminal and the second and fourth electrodes to another terminal, with bipolar stimulation between the terminals. Larson and his associates have implanted much larger arrays involving 16 to 40 electrodes, and applied stimulation between various combinations of electrodes or between the arrays. Different frequencies of cerebellar stimulation have been used; including 20 to 30 Hz, 100 Hz, 150 to 200 Hz, and 200 Hz, but the relative effectiveness of each frequency has not been compared. Likewise, the range of intensity levels has varied widely.

The purpose of this investigation was to determine in the monkey how different parameters of electrical stimulation of various regions of the cerebellar cortex affect neurophysiological and behavioral responses. After this study was started, Sances, et al., reported their findings on the effects of various electrode configurations and current patterns upon evoked potentials in one chimpanzee. They showed that the greatest
effects occurred from stimulation of the posterior to superior cerebellar surfaces. However, these investigators did not examine the effects of bilateral electrode placement or stimulation across the midline, or the behavioral consequences of various patterns of stimulation.

Materials and Methods

Six adult cynomolgus monkeys (Macaca fascicularis) served as experimental animals. In three of the animals, cerebellar-stimulating and bone-screw electrodes were implanted, and the neurophysiological and behavioral effects of cerebellar stimulation were analyzed. The cerebellum was later examined histologically. The other three animals were excluded from the behavioral experiments but underwent the other procedures.

The behavioral task required the monkey to touch three buttons in a left-to-right sequence with the left hand. The apparatus was similar to that used in previous experiments.14 The monkey sat in a primate chair facing a 20 x 25 cm panel containing three round metal buttons (22 mm in diameter). The buttons could not be touched before a "start" light shone, nor out of sequence, nor more than once; but no time restrictions were placed on when to begin the task after the start signal was lit or on the time allowed to complete the sequence. The monkeys were rewarded with small drops of apple juice for each correct trial. A PDP-12 computer provided a printout in milliseconds of the time lapses between the various steps of each correct trial.

Surgery was performed under sterile conditions and halothane anesthesia. An array of eight stainless steel bone-screw electrodes were placed symmetrically over the cranium to record cortical evoked potentials. The cerebellar electrode arrays were placed bilaterally in the paravermal groove and then slid anteriorly to the caudal portions of Lobule IV13 in four animals. In two animals, they were placed over the lateral cortex of Lobules V and VI, approximately 12 mm from the midline. The electrode leads were attached to the dura as it was closed by suture. The leads were then brought subcutaneously to the top of the skull and attached to a connector.

Cerebellar stimulating electrodes were made proportionally smaller than those used in human patients, and consisted of 1.57 x 2.51 mm (3.96 sq mm) platinum discs embedded in a thin Silastic membrane. In three monkeys, an array of two-electrode contacts on a 3 x 5 mm Silastic pad (Model XI 341-1)* was implanted bilaterally. In the remaining monkeys, a four-contact array (Model XE 350-0-1)* mounted on a 3.5 x 15 mm pad was implanted bilaterally. The interelectrode distance was 1.0 mm in both array models. In the two-electrode array, each electrode could be stimulated independently; in the four-electrode array, the first and third electrodes were connected, and the second and fourth electrodes had a common lead.

The 100 to 250 cerebral potentials were averaged on line with a PDP-12 computer; the resulting waveform was photographed, and the amplitude and latencies were printed on the teletype. All cerebellar stimulation consisted of biphasic square waves delivered from an isolation unit that provided a constant stimulus current. The average sensory evoked responses were elicited from monophasic pulses delivered through large conductive rubber electrodes attached to the distal part of the tail.

The effects of cerebellar stimulation on the execution of sequential movements were determined by introducing brief trains of stimulation during various phases of the movement. A testing session consisted of blocks of 50 correct trials, that were alternated with blocks of no stimulation and blocks during which a parameter of stimulation occurred during various parts of sequential movement. Comparisons were made between preoperative and postoperative performance and between trials without cerebellar stimulation (control) and trials during various parameters of stimulation. High-speed motion pictures were taken during some of the test situations, and were used to reconstruct the trajectory of the limb.

When the neurophysiological and behavioral studies were completed, the monkeys were sacrificed, and standard histological procedures were used to process the cerebellum.

Results

Neurophysiological Studies

Average evoked responses to cerebellar stimulation could be obtained only from the skull electrodes over the sensorimotor cortex. The latency, waveform, and amplitude of the evoked response to cerebellar stimulation were fairly consistent from animal to animal. The lowest threshold to elicit an evoked response was obtained from biphasic stimulation between the right and left four-electrode arrays (transcortical stimulation) located over the intermediate cortex (Fig. 1). Stimulation at 1.5 microC/sq cm/ph within 20 presentations produced a biphasic positive-negative wave, with an average peak latency of 10.29 msec. At higher intensities (2.3 microC/sq cm/ph), the positive-negative wave increased in amplitude and there was a later positive wave with latencies of 25 to 28 msec, which was susceptible to movement artifacts.

Contralateral stimulation, in which the stimulation was confined between electrodes on one side of the cerebellum, required more charge per phase to evoke a

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![Diagram](attachment:image.png)

**FIG. 1.** Average evoked responses from the right sensorimotor cortex elicited by biphasic stimulation of different areas of the cerebellum at various intensities in Monkey 7471. Each tracing is an average of 100 presentations at 1/sec. Transcortical stimulation (between the right and left intermediate cerebellar cortex) required a lower charge per phase to elicit the response than did contralateral stimulation (between electrodes only on the left intermediate cortex). Ipsilateral stimulation (between electrodes on the right cerebellum) failed to produce an evoked response.

A response comparable to that caused by transcortical stimulation (Fig. 1). A larger amplitude of the negative wave and a third positive wave could be achieved by contralateral stimulation at higher stimulus intensities. The average peak latencies were the same. Ipsilateral stimulation failed to elicit an evoked response.

Slightly greater charge densities (2.0 to 2.3 μC/sq cm/ph) were needed for transcortical stimulation between the hemispheric electrodes than were required for transcortical stimulation of the intermediate cortex. Contralateral stimulation of the hemispheres needed even higher charges per phase (2.5 μC/sq cm/ph) to produce a threshold response.

Increasing the pulse width, which resulted in a higher charge/phase, produced greater amplitude but did not change the latency of any peak. Increasing the frequency of cerebellar stimulation of 1 to 30 Hz did not alter either the amplitude or the latency of the response. Because of equipment limitations, we could not test at higher frequencies.

Modification of waveforms or peak latencies of somatosensory evoked responses by 1 minute of cerebellar stimulation is a procedure that has been used to establish threshold intensity. The typical average somatosensory response consisted of a large positive wave with a 12-msec latency, followed by a negative, a small positive, a negative, and finally large positive waves (Fig. 2). One minute of transcortical cerebellar stimulation produced a depression of the later components of the somatosensory evoked responses that were elicited during the first 90 seconds after stimulation (Fig. 2). The stimulation had little effect on either the latency or the shape of the initial positive wave. The threshold of transcortical stimulation to modify the somatosensory evoked response was 2.0 μC/sq cm/ph, which was slightly higher than that required to produce the cortical evoked response. Examination of a succession of somatosensory evoked responses taken every 2 to 3 minutes showed no other consistent major change in the waveform. Except in about 60% of the responses obtained after 3 to 4 minutes, the later waveform showed an increased amplitude, which has been described as a rebound phenomenon. A study of the effects of the various parameters of electrical stimulation on the somatosensory potential showed them to be similar to those obtained for cerebellar-produced evoked potentials.
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FIG. 2. Effects of 1 minute of cerebellar stimulation upon somatosensory evoked potentials. The somatosensory evoked potentials were elicited by supramaximal electrical stimulation of the tail (prestimulation). Serial evoked potentials were collected after 1 minute of either contralateral or transcortical cerebellar stimulation. Transcortical stimulation suppressed the late components of the waveform obtained during the first 90 seconds after cerebellar stimulation; contralateral stimulation was less effective.

Behavioral Studies

The effects of cerebellar stimulation on performance were directly related to the location of stimulating electrodes and the mode of stimulation. The greatest effect occurred with transcortical stimulation of the intermediate cortex (Monkeys 7471 and 7561) at 20 μC/sq cm/ph or higher, which increased the duration of movement between buttons. The standard deviation of the interbutton movement for trials with no stimulation or with stimulation at or below 1.8 μC/sq cm/ph did not overlap with the standard deviation for trials where stimulation was 2.0 μC/sq cm/ph or higher, and at 150 Hz or above. Cerebellar stimulation at all parameters tested had no effect on the initiation of the performance, number of errors, trials per day, or duration of button contact. Stimulation at even higher intensities of the contralateral or ipsilateral intermediate zone of the lateral cortex had no effect, and transcortical stimulation of the lateral cortex was also ineffective.

Figure 3 illustrates the increased duration of the movement between buttons after transcortical stimulation of the intermediate cortex in one monkey (Monkey 7471). A 200-msec train of stimulation triggered by contact with Button 1 increased the length of time the monkey took to move from Button 1 to Button 2, but did not affect the duration of contact with the first or second button. Increasing the intensity of stimulation increased the duration of the movement. When transcortical stimulation was applied during other phases of the movement, only the subsequent movement between buttons was affected. When stimulation was applied throughout the whole trial, from the start signal to the reward, the phases involving the first limb movement and the interbutton movements increased in duration, but no other behavioral changes occurred.

When the stimulation intensity was 2.0 μC/sq cm/ph, the interbutton duration increased at 150 to 200 Hz at train durations of 150 msec or longer in both monkeys during transcortical stimulation of the intermediate cortex (Table 1). In these cases, no overlap of the standard deviation occurred with the standard deviation for the unstimulated condition. At stimulation intensities of 2.3 μC/sq cm/ph or higher, duration of movement between buttons also increased with stimulation at 100 Hz for 150 msec or longer.

The trajectory of the forelimb was analyzed in one monkey with and without transcortical stimulation with high-speed motion pictures taken from above the monkey (Fig. 4). The film was then projected and the location of the hand plotted for each frame (every 42 msec). The distance of the trajectory was measured with a planimeter, and various components of the movement were identified. With transcortical stimulation of the intermediate cortex at 2.3 μC/sq cm/ph at 150 Hz for 200 msec and triggered by first-button con-
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Fig. 3. Effects of various intensities of intermediate transcortical stimulation on different phases of the forelimb movement. Histograms for each intensity show the mean time of the first button contact (B1); between the first and second button (F1); second button contact (B2); and between the second and third button contact (F2). Cerebellar stimulation is indicated by a shaded bar below each histogram. Transcortical cerebellar stimulation at or above 2.0 μC/sq cm/ph increased the time required to move from one button to the next, but did not affect button contact time.

tact, the trajectory of most trials corresponded to that of the unstimulated condition, but an increased number of frames was needed to follow the movement between the first and second button; this, of course, indicated a decrease in the velocity of movement (Fig. 4B). There were no other changes in other phases of the performance, such as the time of contact with the button, or movement between the second and third button. However, approximately 15% of the trials showed a definite alteration in the normal trajectory for the movement between the first and second button; this could also account for the increased interbutton duration (Fig. 4C). In these trials, the length of the trajectory always exceeded the greatest length of the trajectory during nonstimulation. Single-frame analysis showed that in some places the animal moved very quickly, but in others it came to an almost complete stop, usually during the transition from flexion to extension. Typically, the flexion/extension phases of movement were similar in both duration and length.

TABLE 1
Interbutton duration (msec) for transcortical stimulation of three monkeys at two intensities and various frequencies and train durations*

<table>
<thead>
<tr>
<th>Intensity (μC/sq cm/ph)</th>
<th>Train Duration (msec)</th>
<th>Animal No.</th>
<th>Frequencies (Hz)</th>
<th>0</th>
<th>10</th>
<th>50</th>
<th>100</th>
<th>150</th>
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<td>2.3</td>
<td>200</td>
<td>7471</td>
<td>352 ± 39</td>
<td>381 ± 38</td>
<td>361 ± 57</td>
<td>501 ± 59</td>
<td>531 ± 52</td>
<td>565 ± 64</td>
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<td></td>
<td></td>
<td>7561</td>
<td>237 ± 51</td>
<td>324 ± 32</td>
<td>330 ± 33</td>
<td>459 ± 61</td>
<td>467 ± 24</td>
<td>448 ± 43</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>7510</td>
<td>158 ± 21</td>
<td>175 ± 15</td>
<td>164 ± 31</td>
<td>167 ± 28</td>
<td>177 ± 53</td>
<td>183 ± 63</td>
<td></td>
</tr>
<tr>
<td>150</td>
<td>7471</td>
<td>347 ± 35</td>
<td>345 ± 59</td>
<td>383 ± 66</td>
<td>559 ± 74</td>
<td>528 ± 47</td>
<td>511 ± 20</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>7561</td>
<td>275 ± 31</td>
<td>269 ± 46</td>
<td>273 ± 29</td>
<td>451 ± 38</td>
<td>492 ± 47</td>
<td>487 ± 45</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>7510</td>
<td>152 ± 28</td>
<td>171 ± 20</td>
<td>153 ± 37</td>
<td>152 ± 55</td>
<td>142 ± 28</td>
<td>160 ± 25</td>
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<td>7471</td>
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<td>401 ± 53</td>
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<tr>
<td></td>
<td></td>
<td>7561</td>
<td>280 ± 27</td>
<td>324 ± 38</td>
<td>326 ± 51</td>
<td>366 ± 47</td>
<td>476 ± 55</td>
<td>568 ± 17</td>
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<td></td>
<td></td>
<td>7510</td>
<td>147 ± 34</td>
<td>153 ± 25</td>
<td>171 ± 25</td>
<td>152 ± 28</td>
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<tr>
<td>150</td>
<td>7471</td>
<td>305 ± 48</td>
<td>396 ± 23</td>
<td>313 ± 29</td>
<td>412 ± 101</td>
<td>559 ± 41</td>
<td>521 ± 73</td>
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<td>7561</td>
<td>313 ± 18</td>
<td>285 ± 74</td>
<td>286 ± 22</td>
<td>255 ± 73</td>
<td>448 ± 44</td>
<td>475 ± 29</td>
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<td></td>
<td>7510</td>
<td>140 ± 20</td>
<td>162 ± 21</td>
<td>165 ± 38</td>
<td>145 ± 29</td>
<td>188 ± 43</td>
<td>168 ± 20</td>
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*Values are mean ± standard deviation. Monkeys 7471 and 7561 were stimulated in the intermediate cortex, and Monkey 7510 in the lateral cortex.
FIG. 4. A–C: Examples of the trajectory of the left hand during the execution of the task, as reconstructed from single-frame motion pictures taken from above the monkey (Monkey 7471); each dot corresponds to the position of the hand in a single frame. The locations of the first (B1), second (B2), and third (B3) buttons are indicated; F1 refers to the trajectory between B1 and B2; and F2 represents the trajectory between B2 and B3. Two representative trials are shown during nonstimulation (A), 200 msec of transcortical cerebellar stimulation, in which a decrease in velocity occurred but no change in the trajectory (B), and 200 msec of transcortical cerebellar stimulation in which both the trajectory and velocity changed (C). Interbutton trajectories that exceeded the longest control trial (greater than 35 cm) accounted for about 15% of the trials during cerebellar stimulation. D–E: Histograms of the median interbutton duration and distance for the flexion or extension phases of movement. The extension phase in trials with abnormal trajectories were slower than the flexion phase.
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of trajectory (Fig. 4D and E). However, in trials with abnormal trajectory, there was also increased duration of the extension movement.

**Discussion**

The results of the present study demonstrated the importance of mode of stimulation and electrode location. Transcortical stimulation between electrode arrays located bilaterally over the intermediate cortex required the lowest intensity to produce a physiological response, and was the only procedure that modified the behavioral response. Different electrical fields would exist where the anode and the cathode electrodes are alternated on the same array in comparison with the situation where one array contains only the positive electrodes. Biphasic transcortical stimulation should produce a relatively uniform current field around each electrode array, and the current field should be less affected by encapsulation, surrounding cerebrospinal fluid, or tissue damage. An evaluation of the effect on somatosensory evoked potentials of stimulating between various electrodes located on one side of the chimpanzee cerebellum showed that the greatest depression of the potential occurred when stimulation was applied between two different electrode arrays. In addition, in animal models of epilepsy, transcortical stimulation was more effective in decreasing seizure activity than was stimulation restricted to the contralateral cerebellar cortex.

Although cerebellar stimulation can modify spontaneous or elicited neural activity in the deep nuclei, brain stem, thalamus, and cerebral cortex, it has not been established how stimulation of the cerebellar surface can affect distant neuronal systems. Probably most of the neuronal substrate adjacent to or underlying the electrodes is affected by the stimulation. Initially, it was assumed that cerebellar stimulation would activate Purkinje cells, and thereby inhibit the deep cerebellar or vestibular nuclei. Just the opposite effect occurred in an experimental study, where stimulation produced a marked suppression of the Purkinje cells up to 6.5 mm from the electrode. Furthermore, stimulating with surface electrodes caused antidromic activation of afferent fibers, which could modulate the deep cerebellar nuclei and reticular formation.

Even though the anatomical systems have not been identified, electrical stimulation of discrete areas of the cerebellum can alter spinal cord reflexes and single-muscle activity. Single-muscle contractions can be elicited by microstimulation of the restiform body, brachium pontis, deep cerebellar nuclei, or red nucleus. Microstimulation of the medial accessory olivary nucleus, which projects to the intermediate zone of the anterior lobe, produced augmentation in some muscles that were active during spontaneous walking. These experimental studies support the theory that “tonic” activity within specific muscle groups can be altered by electrical stimulation of different fiber systems, particularly the climbing fibers. Such a bias of muscle activity during cerebellar stimulation could account for the decreased forelimb velocity and the absence of any effect on the accuracy of the movement.

It is not known whether the type of movement produced by stimulation in the normal monkey also occurs in patients with severe spasticity. In monkeys made spastic by motor cortex lesions, stimulation of only the ipsilateral cerebellar hemisphere at 100 Hz reduced muscle tone, as demonstrated by resistance to passive displacement by the upper limb. In patients with cerebral palsy, cerebellar stimulation at 20 to 30 Hz reduced rigidity and coactivation of leg muscles immediately in one patient and after several months in another patient, although two patients showed no change. In the present study, however, stimulation of the ipsilateral hemisphere or any area at frequencies below 100 Hz had no effect on the movement in a normal monkey. Thus, electrical stimulation of the cerebellum may produce different effects, depending on the neurophysiological and anatomical substrate of each patient. A particular form of cerebellar stimulation may be appropriate for one specific patient, but inadequate or inappropriate for another. The problem is to determine which cerebellar areas with what stimulation parameters can produce selected muscular responses via identified pathways.

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**References**


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