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THE ROLE OF THE CEREBELLUM IN MODULATING VOLUNTARY LIMB MOVEMENT COMMANDS

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INTRODUCTION

That the cerebellum plays a role in "fine-tuning" some aspect of limb movement commands has been appreciated for many years. By the middle of the 19th century, it had become clear that cerebellar lesions did not lead to the paralysis associated with the cerebral cortex, but rather a more complex set of motor signs. In human cerebellar patients, the consistent observations include limb movements that are relatively slow, hypermetric, and unusually curved, with poor coordination among joints. In a recent study, the primary cerebellar deficits were attributed specifically to the loss of the ability to compensate for interaction torques among limb segments, and more generally, to the inability to control a large number of muscles (2). Cerebellar dysfunction has also been implicated in a loss of the ability to time finger opening appropriately when throwing a ball (17). Alternatively, it has been proposed that the cerebellum is responsible for "setting the gain" of a variety of reflex loops (11). For example, eye movements controlled by the vestibuloocular reflex become hypermetric when the flocculus is lesioned (15).

Within the cerebellar cortex, the role of the Purkinje cell (PC) output has also been a topic of debate. Most of these cells *burst* during movement, despite their inhibitory influence on the cerebellar nuclei, an observation that is not adequately understood (7). The discharge of these cells has variously been described in terms of its relation to the *speed* of limb movement (12), the *direction* of limb movement (5) and the *combined* direction and speed of movement (4). The results we describe here show significant correlations between PC discharge and limb electromyographic signals (EMG).

In this paper we suggest that these disparate observations can be unified by assuming that the cerebellum produces a predictive signal that is combined with a relatively crude cerebral signal in order to produce an appropriately refined descending command. Consequently, as movements are produced in different environments (e.g. under uncertain loads, speed dependent loads, or spatial anisotropies), its compensatory discharge will take on the particular character of these environments.

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METHODS

Two macaque monkeys (G and F) were trained to press buttons which were arranged in a circle within a vertical plane. The monkeys were required to reach toward and press a center button followed by one of 8 outer buttons. When the sequence was completed correctly, the monkey received a juice reward and was free to return its hand to a touch pad at its side to initiate the next trial.

After training, surgery was performed to implant a head holder, recording chamber, and EMG recording electrodes (13). Thirteen muscles were implanted in monkey F, and seven in monkey G. At the end of the experiments, each monkey received a lethal dose of sodium pentobarbital and was perfused with saline and 10% neutral buffered formalin. Recording sites were identified from the location of pins left in the chamber at the time of perfusion. All procedures were approved by the Institutional Animal Care and Use Committee of Northwestern University.

Data collection and analysis

The neurons reported in this paper were recorded in the Purkinje cell layer within the intermediate zone of lobules III, IV, and V of the cerebellar cortex. They are presumed to be Purkinje cells based on the criteria described by van Kan et al. (18). Briefly, these include the identification of cerebellar cortical layers and cell types by the wave shapes and discharge properties of the known cells in each layer. Recordings were also made from the forelimb area of the primary motor cortex of monkey F, under essentially the same conditions described above.

Neuronal recordings were made using a seven electrode microdrive (Thomas Recording, Giessen, Germany). The microelectrode signals were passed through a microprocessor-based discriminator system (Plexon, Inc., Dallas, Texas). Firing rate was computed from the inverse of the inter-spike intervals and binned at 5 ms. EMG signals were rectified and filtered, and sampled at 200 Hz. Data were typically recorded continuously for 3 minutes, including 21 to 25 repetitions of the basic task. Because we were interested in the modulation of the signals rather the individual action potential events, we applied additional digital low-pass filtering to each of the signals in order to extract the modulation envelope (20 Hz, four poles). Cross-correlations between firing rate and EMG activity were calculated from these signals. In addition, we calculated peri-event time histograms (PETH) of discharge with respect to the onset of the reach toward the center button, and similar ensemble averages of EMG activity. The spontaneous rate of a cell was defined as the mean discharge rate during the middle 500 ms while the monkey's hand was on the touchpad. The magnitude of each cell's task-related discharge was characterized by its depth of modulation (DOM), which was defined as the largest deviation from its spontaneous rate at any latency within the PETH.

RESULTS

Forty-seven Purkinje cells were recorded from monkey F, and 121 from monkey G. Figure 1 displays a raster plot and PETH for each of four different neurons, along with ensemble averages of EMG signals. All of the plots were aligned to the onset of the first reach. To the left of each EMG signal is shown the cross-correlation between unit discharge and that particular EMG signal. The successful task required two reaches (marked with "R") and two presses ("P"). We have chosen a limited set of muscles from each monkey for this Figure.

The examples in Figures 1A and 1B were typical of the majority of Purkinje cells from both monkeys, in that their rate *increased* during the task. There was a burst of activity that began prior to each reach and continued until approximately the time

the first button was being pressed. Among those cells whose discharge changed by more than 4 standard deviations from their spontaneous rate, the majority (60% for both monkeys) primarily increased their discharge during the task. Figure 1C shows a neuron that paused during the reach, but had a slight increase in activity during the button hold period. A more striking example of such a bi-phasic discharge is shown in Figure 1D.

There was no difference in the onset latencies for neurons that burst and those that paused for either monkey, although the latencies for the two monkeys were different (*t*-test, Monkey G: 64 ms vs 48 ms, $p = 0.36$; Monkey F: 111 ms vs 128 ms, $p = 0.41$).

Relation between Purkinje cell and EMG activity.

The cross-correlations shown to the left of each muscle signal in Figure 1 quantify the similarity of each pair of signals. The cross-correlation potentially ranges between ± 1 for perfect negative and positive correlations, and is a function of tau, or the time shift between the signals. Occasionally, as in the FDS correlation in Figure 1A, which had a peak at 435 ms, the peak correlation occurred at a lag that would not be considered a reasonable causal latency between neuron and muscle activity. Hence, rather than considering the correlation strength of the peak, we used the maximum correlation within a narrow window from 0 to 100 ms as an indication of the extent to which the neuron and muscle were related. Subsequent references to correlation strength refer to this particular measure.

The example in Figure 1A was reasonably well related to at least two different proximal limb muscles, triceps and pectoralis. However, although aspects of this neuron's discharge were related to features in both muscles, neither muscle was a "copy" of the neuron's discharge. Understanding the role of these PCs which burst and are correlated with similar increases in muscle activity is problematic, in that the output of the PC is inhibitory.

If the bursting activity were intended to inactivate unwanted muscles, one would expect to find negative correlations. Figure 1B shows one of these cases. The neuron burst prior to the reach, but its strongest muscle-related correlations were negative, a result of the burst of unit activity which coincided with the large decrease in FPB activity at the *end* of the first button press. A similar effect may be present just *prior* to the first press, but since the muscle activity was already low, it is much less obvious.

The example in Figure 1C had a completely different discharge profile from those in Figures 1A and 1B. In this case, the negative correlations were the result of the initial *pause* in discharge which coincided with an initial *burst* of muscle activity, and the subsequent ramp increase in discharge which closely mirrored the muscle's decline in activity. Although these correlations were stronger than the previous examples (and among the strongest negative correlations we measured) it should be noted that there were non-linearities in the relation between neuron and EMG that would have reduced their magnitude. For example, although the muscle remained above its quiescent level throughout the button hold periods, the unit discharge fol-

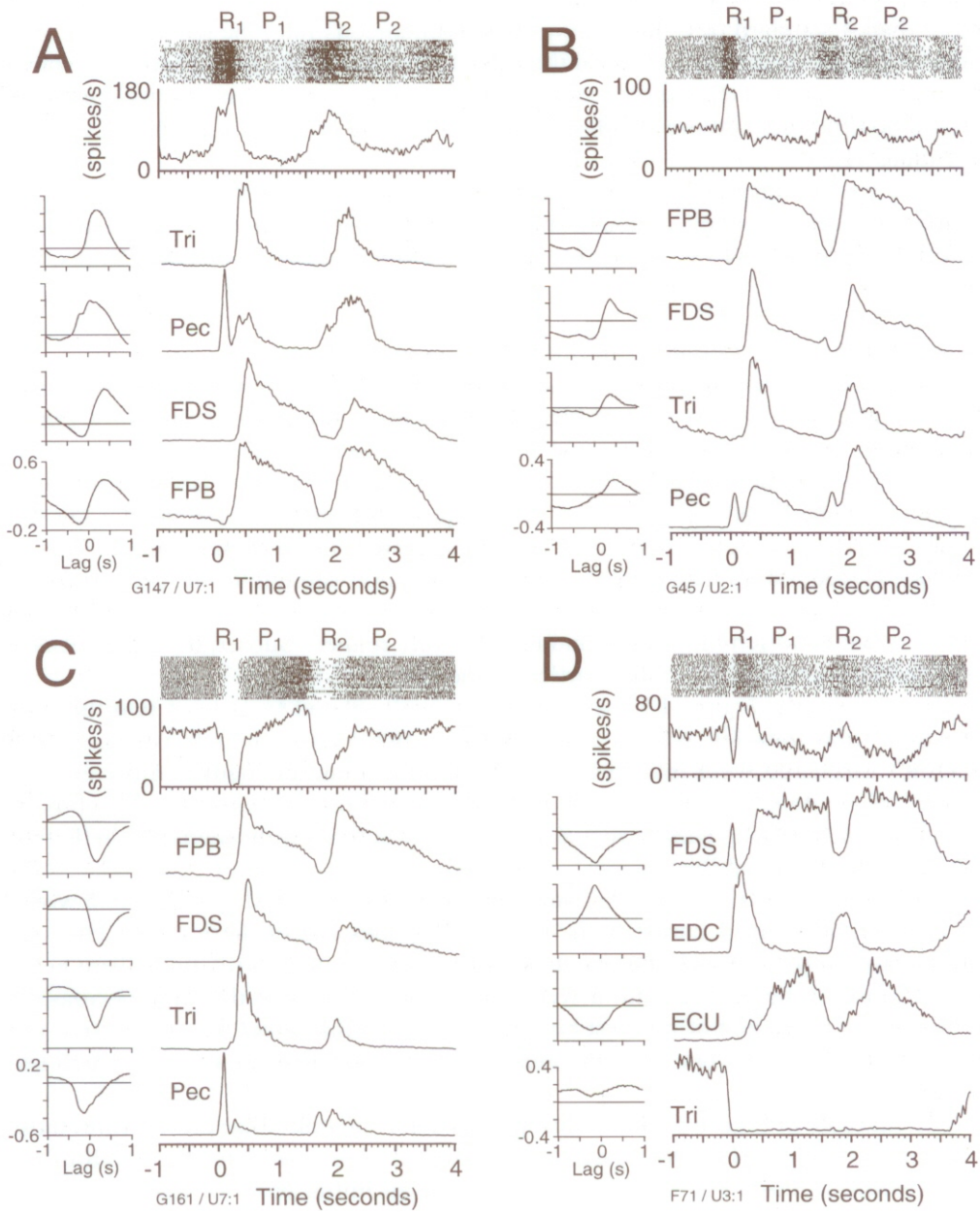

Fig. 1. - *Summary plots of PC simple spike discharge, EMG activity, and the cross-correlations between these signals.*

To the right of each panel, raster plots, spike histogramms, and EMG ensemble averages are all aligned to the onset of the initial reach to the center button (R_1). In a single trial, the monkey reached toward (R_1/R_2) and pressed (P_1/P_2) two buttons sequentially. In the left column of each panel are cross-correlation functions calculated between firing rate and the corresponding EMG signal. The level of zero correlation is marked by a thin line in each graph.

lowing the pause did not remain depressed, but reached levels *above* the spontaneous rate, at least during the first press period.

The final neuron (ID) had a bi-phasic discharge, which appeared to have separate features that related to different well-correlated muscles. Furthermore, since FDS and EDC were nearly exactly out of phase with one another, the two strongest cross-correlations had opposite signs.

Relation between correlation strength and depth of modulation.

While pauses in Purkinje cell simple spike discharge would seem to have an obvious role in *facilitating* movement, the bursts of discharge that more often accompany movement are puzzling. In order to summarize results like those shown above for a larger number of cells, we plotted the strength of cross-correlation in the 0-100 ms window against the cell's task-related DOM. Because each cell yielded a cross-correlation with more than one muscle, we used the single muscle with the greatest magnitude correlation to characterize a given cell.

These results are summarized by the open circles in Figure 2. The first quadrant contains cells like that of Figure 1A, namely positive correlation and DOM. The majority (62%) of cases for both monkeys fell within this quadrant. The next most common quadrant was the third, having negative correlations and DOMs (20%; Figure 1C). The two monkeys differed somewhat with respect to quadrant IV, the quadrant in which muscles *inhibited* by bursting PCs would be found. Sixteen percent of the cases from monkey G fell within this quadrant, but only 6% from monkey F. Beyond the fewer numbers, the magnitude of these correlations was considerably smaller than those in quadrant III, even for monkey G. Finally, there were very few cases having positive correlations and negative DOMs (quadrant II).

The filled circles of this Figure indicate the results for the same analysis done for 135 neurons recorded from the forelimb area of the primary motor cortex from monkey F. These recordings were made under conditions which were essentially identical to those of the PC recordings. Considering only the most strongly correlated muscle for each significantly modulated neuron, the positive correlations were significantly stronger for M1 neurons than PCs (0.39 vs 0.28; $p < 0.0001$). However, if one considers only the negative correlations, there was no difference (-0.20 vs -0.19; $p = 0.64$). We also compared the latency of the M1 discharge to that of the PCs. The PCs tended to modulate at a greater latency before movement than did M1 neurons, but the difference was not significant (PC: 116 ms; M1: 105 ms; $p = .56$). Similar results were found if only those PCs which paused were included (128 ms; $p = .55$).

DISCUSSION

We recorded the discharge of 168 Purkinje cells during the execution of a simple reaching task. As others have described before, the majority of these cells burst during movement, although a significant minority pause (5, 7). Pausing PCs would appear to have an obvious role, given their inhibitory influence on the cerebellar

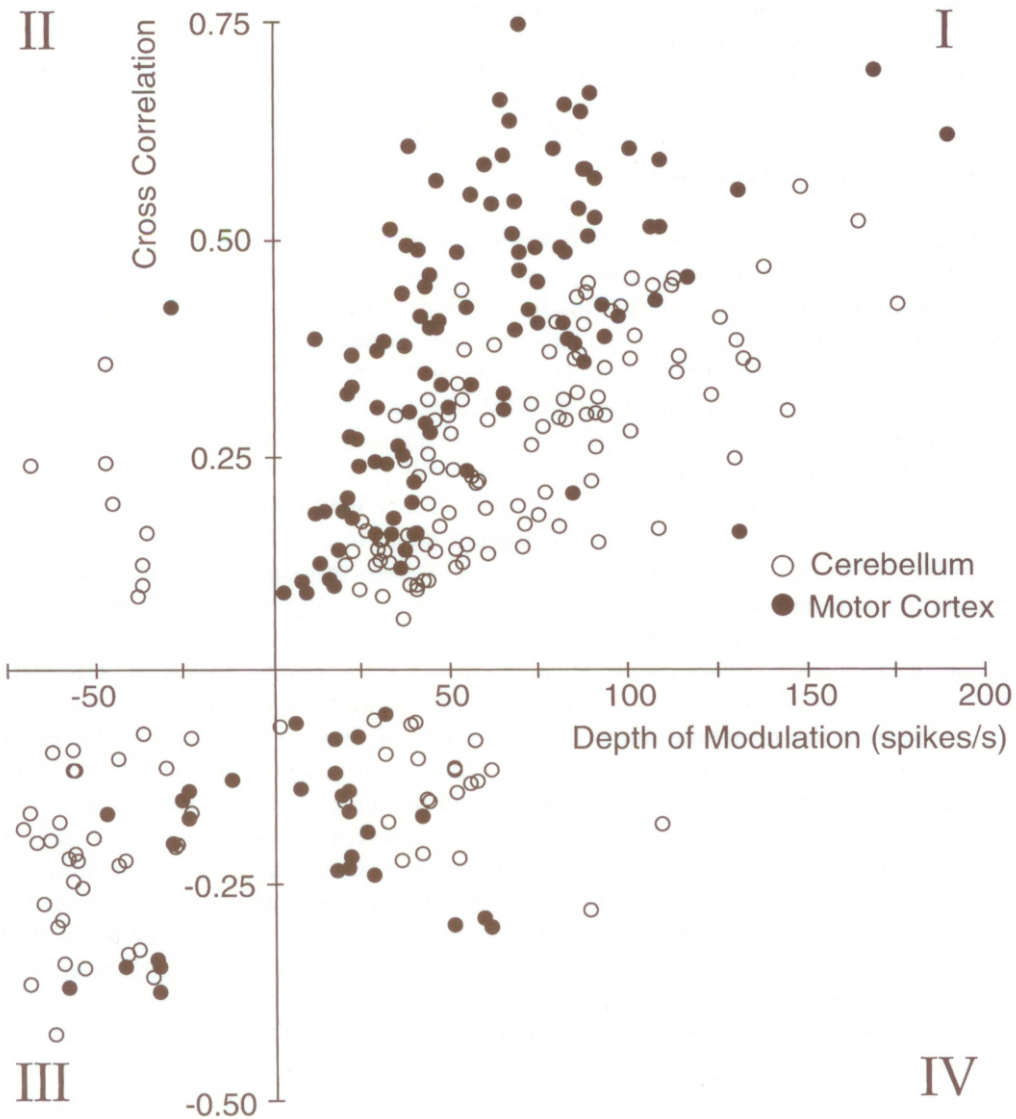

Fig. 2. - *Summary of cross-correlation and DOM results for PCs (open circles) and M1 neurons (filled circles).*
The DOM is the largest magnitude deviation from spontaneous rate during any phase of the task as measured from PETHs like those of Figure 1. Cross-correlation strength is for the single most strongly correlated muscle.

nucleus and ultimately the motor cortex. The resulting disinhibition would allow increased cerebellar nuclear and cerebral cortical activity, leading to the onset of movement. Less obvious, is the role of the bursting neurons. If they function to inactivate unwanted muscles, one would anticipate that their discharge would be nega-

tively correlated with the inactivated muscles. In fact, we found relatively few neurons with this type of profile (quadrant IV of Figure 2). However, the interpretation of this observation is complicated by the fact that an inhibitory influence exerted on a quiescent muscle is difficult to detect.

If the burst neurons were primarily involved in withdrawing activation to end the movement, one would predict that their modulation as a group would occur later than the pause neurons. This was not the case for either monkey, and suggests that this is not a good explanation for the different types of discharge. If the pausing neurons were responsible for initiating movement, one might expect their discharge to precede that of the primary motor cortex. Although this was the case, the difference was not significant even at the 10% level. Similar results have been described previously (6, 16).

An alternative explanation for the typical PC discharge is that it serves to regulate the ongoing cerebellar nuclear and M1 discharge. It has been suggested that the excitatory connections which link the cerebral cortex and the cerebellar nuclei in both directions act as a substrate for positive feedback, providing both a driving force and a means of rapidly distributing a motor command signal throughout the network of hundreds of thousands of pre-motor neurons (8, 9). The inhibitory influence of the bursting Purkinje cells might then be necessary to restrain the loop discharge, thereby sculpting it into the appropriate spatio-temporal pattern.

Several modeling studies have suggested that the cerebellar cortex may be quite effective in predicting the movement of a visual target (10) or other aspects of an evolving movement (1). Under these conditions, PC modulation could be nearly synchronous with the evolving cerebral command signal, making it unlikely for there to be significant, systematic time lags between M1 and PC signals. If bursts of PC activity were in phase with the motor command signals, they would serve to reduce the magnitude of the overall signal. However, within the frequency range of the in-phase *envelopes* of the signals, the bursting PCs would be *positively* correlated with the coincident bursts of EMG activity. The smaller number of PCs which pause during movement would serve to *increase* the magnitude of the EMG bursts with which they were correlated.

It is important to recognize the different information provided by the long time span cross-correlations described here, and the effects of individual action potentials. Regardless of the quadrant characterizing the response of any given PC, if it were possible to calculate the cell's spike-triggered average effect on EMG activity, it would presumably mainly reflect an inhibitory effect, analogous to the post-spike suppression which can sometimes be demonstrated from M1 (3). However, the greater number of intervening synapses makes this prospect unlikely.

The strong correlations between M1 neuronal discharge and muscle activity suggest that corticospinal neurons may produce muscle-coded command signals (14). If the role of PCs is ultimately to shape a relatively crude cerebral signal in a manner appropriate to produce a refined descending command signal, their dynamics would not be exactly like those of the muscles. Rather the dynamics of such a corrective signal would be influenced by the various intrinsic and extrinsic factors affecting the

movement but not accounted for by the unrefined cerebral signal. That the PC/EMG cross-correlations are weaker than M1/EMG cross-correlations may reflect this fact.

SUMMARY

We recorded the activity of cerebellar Purkinje cells (PCs), primary motor cortical (M1) neurons, and limb EMG signals while monkeys executed a sequential reaching and button pressing task. PC simple spike discharge generally correlated well with the activity of one or more forelimb muscles. Surprisingly, given the inhibitory projection of PCs, only about one quarter of the correlations were negative. The largest group of neurons burst during movement and were positively correlated with EMG signals, while another significant group burst and were negatively correlated. Among the PCs that paused during movement most were negatively correlated with EMG. The strength of these various correlations was somewhat weaker, on average, than equivalent correlations between M1 neurons and EMG signals. On the other hand, there were no significant differences in the timing of the onset of movement related discharge among these groups of PCs, or between the PCs and M1 neurons. PC discharge was modulated largely in phase, or directly out of phase, with muscle activity. The nearly synchronous activation of PCs and muscles yielded positive correlations, despite the fact that the synaptic effect of the PC discharge is inhibitory. The apparent function of this inhibition is to restrain activity in the limb premotor network, shaping it into a spatiotemporal pattern that is appropriate for controlling the many muscles that participate in this task. The observed timing suggests that the cerebellar cortex learns to modulate PC discharge predictively. Through the cerebellar nucleus, this PC signal is combined with an underlying cerebral cortical signal. In this manner the cerebellum refines the descending command as compared with the relatively crude version generated when the cerebellum is damaged.

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