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Roles of Cerebellar Cortex and Nuclei in Motor Learning: Contradictions or Clues?

Minireview

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The cerebellum, with its relatively simple and regular synaptic organization, has yielded much about its contribution to brain function and its internal information processing. A central theme that has emerged is the cerebellum's role in the adaptation or learning of movements. Ideas about cerebellar-mediated motor learning began in the 1960s, most notably with the seminal theory proposed by Marr (1969). The basic tenets of this theory are supported by numerous studies. In particular, analysis of two forms of motor learning, adaptation of the vestibulo-ocular reflex (VOR) and Pavlovian eyelid conditioning (EC), has revealed much about cerebellar contributions to motor learning and the cerebellar information processing involved.

The cerebellum is comprised of two anatomical components, the cerebellar cortex and nuclei. Despite much progress, their relative contributions to motor learning remain a fundamentally important issue that is largely unresolved and hotly debated. Here I will address this issue by briefly outlining major experimental findings and ideas that fuel this debate. I will then present a working hypothesis that addresses major points of contention, largely by suggesting that the relative contributions of the cerebellar cortex and nuclei are not constant but instead may depend on the amount and type of training that the animal has experienced.

The Synaptic Organization of the Cerebellum and Its Relation to Motor Learning

Characteristics of cerebellar anatomy and physiology are central to ideas about its role in motor learning (Figure 1). Cells of the deep nuclei provide the sole output of the cerebellum. These outputs are influenced by two input types, the climbing fibers and mossy fibers, which display quite different characteristics. Although climbing fibers make excitatory synapses in the nuclei, their primary projection involves powerful and spatially distributed synapses onto a few Purkinje cells. Each Purkinje cell receives input from only one climbing fiber, which produces an all or none response in the Purkinje cell, involving a transient and cell-wide increase in intracellular calcium (Tank et al., 1988). Mossy fibers make excitatory synapses in the nuclei and branch profusely to make excitatory synapses with a large number of granule and Golgi cells in the cortex. The sole outputs of the cerebellar cortex are the inhibitory Purkinje cell synapses in the cerebellar nuclei. Thus, cerebellar output is influenced by direct excitatory inputs from mossy and climbing fibers, as modulated by the inhibitory input from the cerebellar cortex.

What are the relative contributions of these pathways to motor learning? We can anticipate different contributions from relative differences in size and complexity (Eccles et al., 1967). Human cerebellar nuclei contain around 5×10^5 neurons, whereas the cerebellar cortex contains at least five orders of magnitude more, including 5×10^{10} granule cells. There are corresponding differences in complexity as well (Figure 1). Whereas the nuclei are virtually a relay, mossy fiber throughput in the cortex involves divergent input onto the enormous population of granule cells, whose activity is also influenced by the inhibitory Golgi cells. One numeric fact illustrates these dramatic differences in computing power; each nucleus cell receives around 10^4 mossy fiber synapses (mf→nuc) and is influenced by 10^8 granule cell synapses onto Purkinje cells (gr→Pkj).

Early ideas about cerebellar-mediated motor learning were based on these notable anatomical characteristics. In 1969, Marr proposed a theory suggesting how plasticity in the cerebellar cortex at the gr→Pkj synapses could mediate motor learning. Three basic components of this theory were: (i) the mossy fiber/granule cell system encodes the contexts in which movements occur, with the abundance of granule cells providing a rich representation; (ii) climbing fibers signal that the movement controlled by its Purkinje cell should change, and (iii) these climbing fiber inputs induce plasticity at coactive gr→Pkj synapses, improving subsequent movement performance in the context encoded by that pattern of granule cell activity. Albus (1971) noted that this learning was analogous to Pavlovian conditioning, in which (for EC) a tone paired with a reinforcing puff of air in the eye promotes the acquisition of a learned eyelid response. Thus, Albus' analogy suggests that the tone is conveyed to the cerebellum via mossy fibers, the air puff via climbing fibers, and the learned response is mediated by plasticity at the gr→Pkj synapses.

Forms of Motor Learning Mediated by the Cerebellum

Simple forms of motor learning such as analysis of VOR adaptation and EC has provided particularly specific evidence for cerebellar involvement in motor learning (Gilbert and Thach, 1977). The VOR keeps images stable on the retina during head movements by generating eye movements that are equal in magnitude and opposite in direction to the head movement (Figure 2). Visual acuity requires this reflex to be precisely calibrated, and abundant evidence indicates that the VOR adapts when changing conditions produce errors (image motion across the retina). In EC, paired presentation of a conditioned stimulus, such as a tone, with a reinforcing stimulus, such as an air puff in the eye, promotes the acquisition of a learned eyelid response elicited by the tone (Figure 2). VOR adaptation and EC are similar in that each requires paired presentation of two stimuli, one that conveys movement context (head turn or tone), and one that is a reinforcing or error signal (image motion or air puff). Learning in both systems can also be bidirectional; VOR gain can increase or decrease and eyelid responses can be acquired and extinguished.

Evidence suggests that EC and VOR adaptation both engage the cerebellum in the manner suggested by Albus (Raymond et al., 1996). VOR studies have shown that mossy fibers convey context (head movement), climbing fibers convey error signals (image motion), and adaptation requires the cerebellar cortex (du Lac et al., 1995).

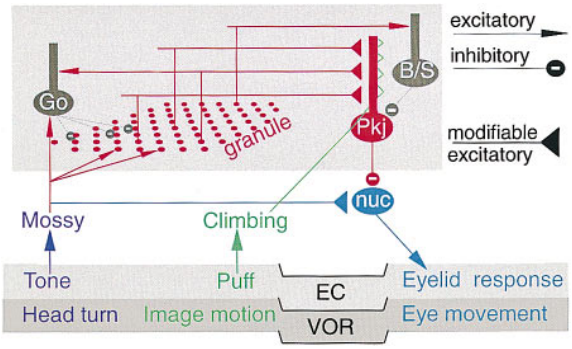

Figure 1. The Circuitry of the Cerebellum and Its Relation to Motor Learning

Mossy fibers influence nucleus cells via both a direct pathway and an indirect pathway through the cortex (outlined in gray). Climbing fibers project to a limited number of Purkinje cells, the climbing fiber collaterals to nucleus are not shown. The stimuli that produce VOR adaptation and EC activate mossy and climbing fibers, and cerebellar output drives the expression of the movement in each case. Pkj, Purkinje cell; Go, Golgi cells; B/S, basket and stellate cells; and nuc, nucleus cells.

Moreover, gr→Pkj synapses undergo long-term depression (LTD) when coactivated with a climbing fiber input to the Purkinje cell (Linden and Connor, 1995). For EC, evidence suggests that mossy fibers convey the tone, climbing fibers convey the reinforcing air puff, and output of the cerebellar interpositus nucleus is required for conditioned response expression (Thompson and Krupa, 1994).

Both VOR adaptation and EC provide the ability to address the specific input–output properties of the cerebellum. This advantage arises primarily from the correspondence between the stimuli used in training and the activation of cerebellar mossy and climbing fibers, and the extensive characterization of the behavioral properties of both forms of learning. These factors provide a window on how the synaptic organization of the cerebellum processes inputs to produce its changing outputs. This window has been used in large part to ask which synapses in the cerebellum undergo plasticity during motor learning.

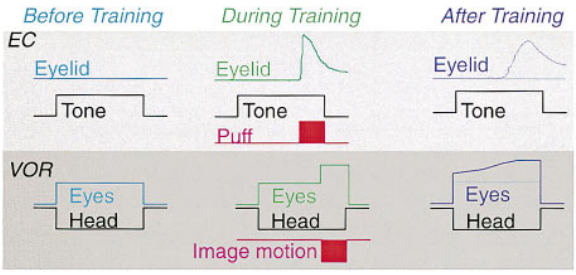

Figure 2. Behavioral Properties of EC (Top) and VOR (Bottom)

In EC, paired presentation of a tone and puff of air in the eye (middle column) promotes the acquisition of a conditioned eyelid response such that the tone elicits eyelid closure (right), whereas before training it did not (left). In VOR, pairing head movement with image motion changes the amplitude of the VOR such that the error (image motion) decreases.

Plasticity in the Cerebellar Cortex Versus Nuclei: Contradictions or Clues?

Interestingly, both fields have experienced parallel controversies regarding the relative contributions of plasticity in the cerebellar cortex and nuclei. Marr's theory predicts that lesions of the cerebellar cortex should abolish previously acquired learning and prevent all subsequent learning. Although lesions of the cerebellar cortex prevent VOR adaptation, these lesions have variable effects on previously acquired adaptation. Also, recording studies have fueled debates about the importance of plasticity at gr→Pkj synapses in the cortex and at mf→nuc synapses in the cerebellar nuclei. (e.g., Lisberger, 1988; du Lac et al., 1995). This pattern of results has made the role of plasticity at gr→Pkj versus mf→nuc synapses open to lively debates (Ito, 1993; Lisberger and Sejnowski, 1993).

For EC, these issues have been no less contentious. Although there is general agreement that lesions of the cerebellar interpositus nucleus prevent conditioned response expression, the effects reported for cerebellar cortex lesions have varied considerably from reports of complete abolition to complete sparing of the learned responses. In contrast to VOR results, early EC studies reported that cortex lesions slow but do not prevent acquisition (Thompson and Krupa, 1994).

Recent studies, however, suggest that at least some of these contradictions in EC stem from anatomical considerations. Perrett et al. (1993) found that cerebellar cortex lesions spare conditioned eyelid responses but abolish their timing. In intact animals, responses are timed to peak near the onset of the air puff, whereas the postlesion responses displayed a fixed, short latency. Unexpectedly, this effect occurred only when the lesions included the anterior lobe, a region of cortex not previously implicated in EC. When the same animals were tested for their ability to acquire new eyelid responses or to extinguish the previously learned responses, the results paralleled those obtained for VOR adaptation–no further learning was possible (Perrett and Mauk, 1995).

Reversible lesions have also provided apparently contradictory data. The inability of local anesthetic infusions into the interpositus nucleus to block EC was interpreted as evidence that the nuclei are not involved in conditioning (Welsh and Harvey, 1991). In contrast, local inactivation of the interpositus nucleus by the GABA agonist muscimol prevents acquisition of eyelid responses, which was interpreted as evidence that the interpositus nucleus is essential for EC (Krupa and Thompson, 1993).

Thus, for both EC and VOR, there exists apparent support for plasticity at gr→Pkj synapses in the cortex and for either a critical role, or no role at all, for plasticity at mf→nuc synapses.

Rules for Plasticity in Cerebellar Cortex and Nuclei: A Working Hypothesis

Do these data really contain so many contradictions, or do they provide clues pointing to mechanisms that explain these various results as being only apparently contradictory? I suggest that a model involving specifically stated rules for plasticity at both gr→Pkj and mf→nuc synapses supports the latter possibility. This working hypothesis is comprised of three propositions. 1) *Granule cells produce both stimulus and temporal representations.* The conversion of mossy fiber inputs

to granule cell activity not only produces a fine-grained discrimination of similar contexts (as Marr suggested) but also permits discrimination of different times during a mossy fiber input. In VOR for example, mossy fibers encode horizontal head movement in one direction. In the cortex, this relatively coarse representation might lead to a more specific and fine-grained representation (Figure 4). Different subsets of granule cells might be active depending on specific characteristics of the head movement such as its velocity (stimulus discrimination) and depending on the time since its onset (temporal discrimination). Results from computer simulations of the cerebellar cortex are consistent with this proposition (Buonomano and Mauk, 1994).

2) *Plasticity at gr→Pkj synapses is controlled by climbing fibers.* gr→Pkj synapses undergo LTD when active during a climbing fiber input (Linden and Connor, 1995) and increase in strength (long-term potentiation) (LTP) when active without a climbing fiber input (Sakurai, 1987; Salin et al., 1996).

3) *Plasticity at mf→nuc synapses is controlled by Purkinje cells.* mf→nuc synapses undergo LTD when active during robust inhibitory input from Purkinje cells and undergo LTP when active during a *transient* release from Purkinje cell inhibition. In contrast to gr→Pkj plasticity, this proposition is completely gratuitous since almost nothing is known about mf→nuc plasticity.

These propositions simply elaborate Marr's theory with three added features. Plasticity is bidirectional, plasticity at mf→nuc synapses is induced under the control of Purkinje cells (see Miles and Lisberger, 1981), and granule cell activity provides both temporal and stimulus coding. This hypothesis satisfies the constraints that (i) a lesion of the cerebellar cortex may abolish some but not all of the memory for previous learning, since one but not both sites of plasticity remain; and (ii) that no further learning occurs after a cerebellar cortex lesion, since an input critical for plasticity at the remaining site of plasticity is missing. Although these propositions are relatively simple, together they suggest that many apparent contradictions are instead clues to the ways that the relative contributions of the cerebellar cortex and nuclei can vary depending on the amount and type of training.

The Relative Distribution of Plasticity Can Depend on the Amount of Training

These propositions predict that the relative contribution of plasticity in the cerebellar cortex and nuclei should vary with the amount of training. Under the propositions, plasticity at gr→Pkj synapses is controlled by the patterns of mossy fiber and climbing fiber inputs, whereas plasticity at the mf→nuc synapses is controlled by Purkinje cells. Thus, motor learning would first involve the induction of plasticity at gr→Pkj synapses, thereby (i) altering Purkinje cell activity and motor performance during subsequent executions of that movement and (ii) inducing plasticity at mf→nuc synapses, further changing the movement.

This predicted sequence can be illustrated for EC by considering a simplified example with only one gr→Pkj and one mf→nuc synapse, each activated by the tone (Figure 3). Paired presentation of the tone (mossy fiber) and air puff (climbing fiber) would induce LTD at the gr→Pkj synapse. During subsequent tone presentations, Purkinje cell activity decreases, the nucleus cell would be disinhibited, and a conditioned eyelid response would be elicited (compare Figures 3A and 3B). The hypothesis predicts that with further training the mf→nuc synapse would undergo LTP due to the decreased Purkinje cell input during the tone. Thus, learning first occurs in the cortex and is then transferred to the nucleus (Figure 3C). The opposite series of events is predicted during extinction. Presenting the tone without the air puff induces LTP at gr→Pkj synapses. The corresponding return of Purkinje cell inhibition of the nucleus cell would both decrease the eyelid response and induce LTD at the mf→nuc synapses.

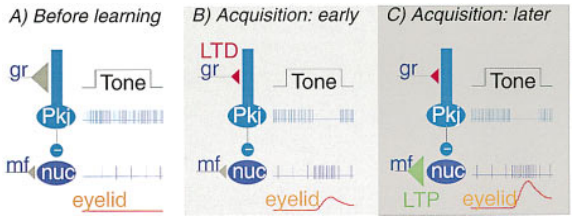

Figure 3. Plasticity at gr→Pkj and mf→nuc Synapses Proposed to Mediate Cerebellar Motor Learning

The strengths of the synapses are depicted by the size of the symbol; synapses that have undergone LTP or LTD are shown respectively as green or red. The left panel represents conditions prior to training, the center panel shows changes early in training, and the right panel shows changes that may occur later in training.

This example illustrates that these two plasticity rules predict that each gr→Pkj synapse acts to make the strength of the mf→nuc synapses consistent with the response that it (the gr→Pkj synapse) encodes. Relatively weak gr→Pkj synapses, which encode a strong eyelid response or high gain of the VOR, act to make the mf→nuc synapses stronger such that they also encode a robust response. Relatively strong gr→Pkj synapses, which encode weaker responses, have the opposite effect on mf→nuc synapses.

The Relative Distribution of Plasticity Can Depend on the Type of Training

Since each gr→Pkj synapse would compete with its cohorts to set the strength of the mf→nuc synapses, the strength of the nucleus synapses should encode the average response amplitude mediated by each of the gr→Pkj synapses. This implies that the relative distribution of plasticity between cortex and nucleus can also depend on the type of training the animal has received. Figure 4 illustrates how this may work. In VOR adaptation, the mossy fibers encode head movement in one direction. In the cortex, the mossy fiber inputs may be represented more richly by activity of different granule cell subsets. Some granule cells may become active more for fast head movements, others for slower head movements (stimulus coding). Some may be active at the beginning of head turns, others later (temporal coding). When the gain of the VOR is adapted for all conditions, as occurs when the animal wears magnifying goggles, the induction of LTD at all gr→Pkj synapses would encode the need for large amplitude VOR. Since all synapses agree that the response amplitude should be high,

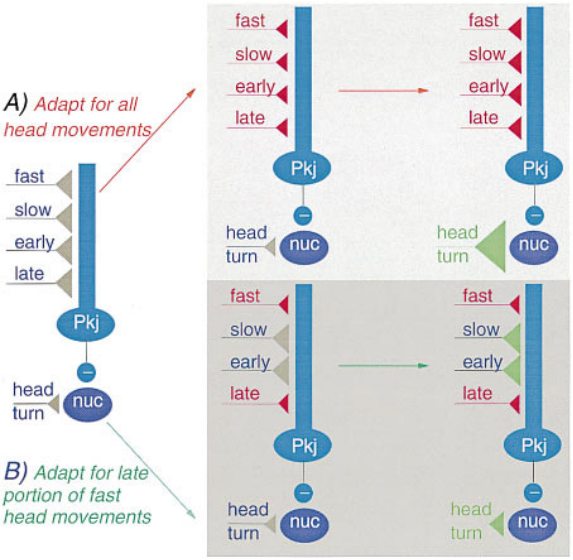

Figure 4. The Distribution of Plasticity May Depend on the Type of Training

Granule cells are assumed to encode specific aspects of head turns such as velocity (fast or slow) and time (early or late).

(A) When VOR amplitude adapts for all circumstances, the amount of plasticity induced at the mf→nuc synapse is relatively large since all gr→Pkj synapses act to increase its strength.

(B) When the VOR is adapted for specific circumstances, such as the early portion of slow head turns, less plasticity is induced at the mf→nuc synapses since some gr→Pkj synapses act to increase and others act to decrease its strength; the gr→Pkj synapses encoding other circumstances, such as the late part of fast head turns, must increase in strength to compensate for LTP at the mf→nuc synapses.

robust LTP would be induced at mf→nuc synapses. In the end, the larger amplitude VOR would be mediated by much stronger mf→nuc synapses and slightly weaker gr→Pkj synapses (Figure 4A). In this case, lesions of the cerebellar cortex could have a relatively small effect on the retention of previous adaptation.

The final distribution of plasticity might be different if the gain of the VOR must change under a more restricted set of circumstances (Figure 4B). For example, VOR gain can be changed preferentially for a particular head velocity or for a particular time during a head movement (Raymond et al., 1996). Under such circumstances, fewer gr→Pkj synapses would undergo LTD. Although these gr→Pkj synapses would act to make the mf→nuc synapses stronger, other gr→Pkj synapses would encode a smaller amplitude VOR and would act in the opposite direction, making the mf→nuc synapses weaker. In this case, the plasticity might be more evenly distributed between cortex and nucleus, and cerebellar cortex lesions would have more pronounced effects on the retention of previously learned responses.

The typical EC training protocol appears to be more like the latter of these two situations. Normally, a single tone is used, and the response must increase only at a certain time during the tone. Thus, we would expect that in well-trained animals, conditioned responses are mediated by contributions from both cortex and nucleus, and cerebellar cortex lesions should abolish response timing, as is observed.

The hypothesis also suggests that the variable results obtained from reversible lesions may be only apparently contradictory. Learning in the cerebellar cortex should be possible during inactivation of the nuclei with a local anesthetic, as was observed (Welsh and Harvey, 1991). In contrast, since infusion into the nuclei of the GABA agonist muscimol should mimic strong Purkinje cell input, training would produce acquisition in the cortex and extinction in the nucleus. This idea is consistent with the need for further postinfusion training to produce conditioned responses, as was observed (Krupa and Thompson, 1993). Thus, instead of indicating opposite conclusions for the role of the cerebellar nuclei in motor learning, these observations may be explained by the differential action of these compounds on the proposed plasticity at mf→nuc synapses.

As with all hypotheses, additional studies will eventually reveal the strengths and weaknesses of my proposal. My goal in presenting this hypothesis is to illustrate that the complexity of the cerebellum may deny the utility of globally phrased questions such as "do cerebellar cortex lesions abolish learned response expression?" Since answers to such questions may depend on many factors, our goal should be to identify exactly what those factors are. In doing so, we may find that apparent contradictions are really clues. Hopefully, careful attention to these clues will lead to a clearer understanding of the cerebellar mechanisms of motor learning.

Selected Reading

Albus, J.S. (1971). Math. Biosci. *10*, 25–61.

Buonomano, D.V., and Mauk, M.D. (1994). Neural Comp. *6*, 38–55.

du Lac, S., Raymond, J.L., Sejnowski, T.J., and Lisberger, S.G. (1995). Annu. Rev. Neurosci. *18*, 409–441.

Eccles, J.C., Ito, M., and Szentágothai, J. (1967). The Cerebellum as a Neuronal Machine. (New York: Springer-Verlag).

Gilbert, P.F.C., and Thach, W.T. (1977). Brain Res. *128*, 309–328.

Ito, M. (1984). The Cerebellum and Neural Control. (New York: Raven Press).

Ito, M. (1993). Nature *363*, 24–25.

Krupa, D.J., and Thompson, R.F. (1993). Science *260*, 989–991.

Linden, D.J., and Connor, J.A. (1995). Annu. Rev. Neurosci. *18*, 319–357.

Lisberger, S.G. (1988). Science *242*, 728–735.

Lisberger, S.G., and Sjenowski, T.J. (1993). Nature *363*, 25–26.

Marr, D. (1969). J. Physiol. *202*, 437–470.

Miles, F.A., and Lisberger, S.G. (1981). Annu. Rev. Neurosci. *4*, 273–299.

Perrett, S.P., and Mauk, M.D. (1995). J. Neurosci. *15*, 2074–2080.

Perrett, S.P., Ruiz, B.P., and Mauk, M.D. (1993). J. Neurosci. *13*, 1708–1718.

Raymond, J.A., Lisberger, S.G., and Mauk, M.D. (1996). Science *272*, 1126–1131.

Sakurai, M. (1987). J. Physiol. *394*, 463–480.

Salin, P.A., Malenka, R.C., and Nicoll, R.A. (1996). Neuron *16*, 797–803.

Tank, D.W., Sugimori, M., Connor, J.A., and Llinás, R.R. (1988). Science *242*, 773–777.

Thompson, R.F., and Krupa, D.J. (1994). Annu. Rev. Neuroscience *17*, 519–549.

Welsh, J.P., and Harvey, J.A. (1991). J. Physiol. *444*, 459–480.