The Cerebellum and Motor Learning

Mitchell Glickstein and Christopher Yeo
Department of Anatomy and Developmental Biology
University College London
London, England

Abstract

■ People with profound memory deficits can acquire new motor skills, even though on each day of training they may be unaware of having seen the training apparatus before. Similarly, rabbits can acquire or retain a conditioned nictitating membrane response despite massive lesions of the hippocampus or the cerebral cortex. Both lines of evidence suggest that subcortical structures may be sufficient for many forms of motor learning. One possible locus for motor learning is the cerebellum. This article traces the history of our knowledge of structure and function of the cerebellum. The anatomical and physiological evidence demonstrates that the cerebellum has the neural connections necessary to mediate simple forms of motor learning or reflex plasticity. Behavioral studies demonstrate that the cerebellum is involved in modification of the vestibuloocular reflex, recalibration of saccadic eye movements, and acquisition of the conditioned nictitating membrane response. Although the evidence in all three instances suggests that the cerebellum is important, there is no agreement as to whether the cerebellum is always necessary for motor learning or how it might participate. Two views are presented: one supporting the idea of the cerebellum as the locus for motor learning and the other opposing this idea. Some evidence that might resolve these disagreements is discussed. ■

INTRODUCTION

This article addresses two interrelated problems. One is the question of the neural mechanism in motor learning. What are the brain structures and pathways involved when we learn to ice skate or play the violin? How do these circuits differ from those that are involved in cognitive learning? The second question relates to the functions of the cerebellum with special reference to its spatial organization and its role in motor learning. We hope to conclude that motor learning and cognitive learning probably involve different and largely nonoverlapping areas of the brain. The cerebellum and its associated circuits are important or necessary for many forms of motor learning and reflex plasticity. The precise locus and the nature of the synaptic change are still not established. Recent studies have suggested an even more general role for cerebellar circuitry in cognitive (Leiner et al. 1986) or affective (Courchesne et al. 1988) function, but the evidence for these possible functions is still rather new and somewhat indirect.

BRAIN STRUCTURES AND PATHWAYS THAT ARE INVOLVED IN MOTOR LEARNING DIFFER FROM THOSE INVOLVED IN COGNITIVE LEARNING

Despite a profound inability of amnesic patients to store new information they are often capable of successful motor learning. For example, Milner et al. (1968) tested a severely amnesic patient, H. M., on a simple maze task. H. M.'s performance on the task improved systematically from day to day despite the fact that each day he claimed he had never seen the apparatus before. There have been several interpretations put forward to account for such differences in the loss and sparing of different classes of memory (Brooks and Baddeley 1976; Cermak et al. 1973; Martone et al. 1984; Parkin 1982). One of the simplest is the interpretation originally suggested by Corkin (1968) that motor learning uses brain structures and pathways that are different from those involved in cognitive learning.

If a tone is sounded repeatedly and followed by a puff of air to the cornea, people and animals become conditioned to blink to the tone alone. Eyeblink conditioning has been studied for over 50 years in humans and other mammals. Just as amnesic patients may improve over

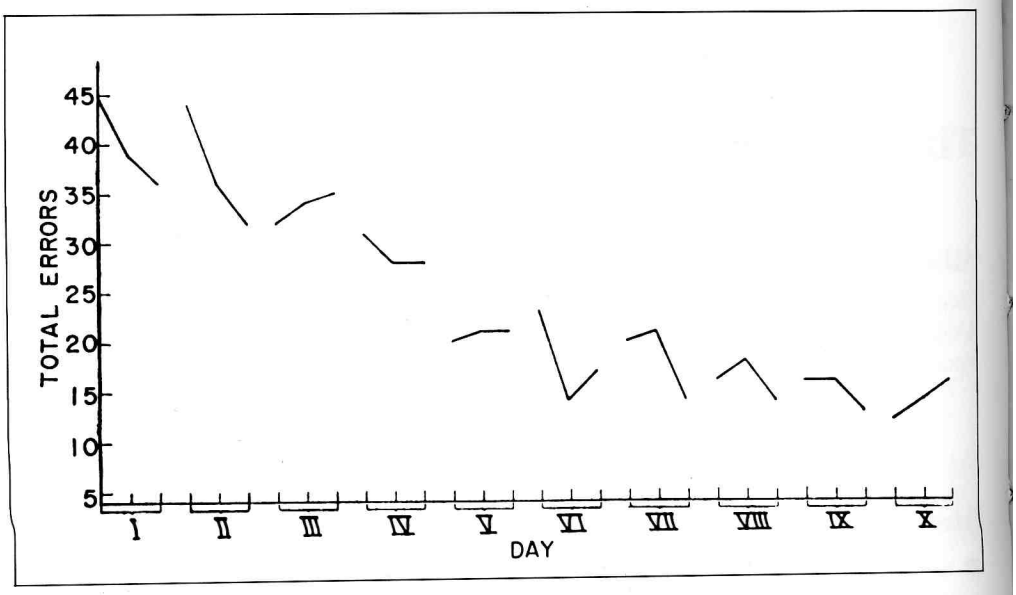

Figure 1. Performance of patient H.M. on a tactile maze task on successive days of training. H.M. improved from day to day over the period of testing despite the fact that, on each successive day of training, he denied having seen the apparatus before. [From Milner et al. (1968).]

successive days of training in a maze-learning task, they may also show normal eyeblink conditioning. Weiskrantz and Warrington (1979), for example, found successful acquisition of eyeblink conditioning in two patients suffering from Korsakoff's syndrome. Neither patient remembered having seen the apparatus before on successive days of training yet both acquired the conditioned eyeblink response and retained it on repeated testing.

A similar form of conditioning can be studied in experimental animals. An airpuff to the cornea or mild shock to the outer canthus of a rabbit's eye unconditionally elicits a reflex closure of the external eyelids and a sweep of the nictitating membrane, a third eyelid, across the cornea. The nictitating membrane is not under direct muscular control. The muscle that is principally responsible for producing the nictitating membrane response (NMR) is the retractor bulbi (Lorente de No 1932; Berthier and Moore 1980). When the retractor bulbi is activated the eyeball withdraws into the orbit, allowing the nictitating membrane to sweep passively across the cornea. The eyeblink and NMR may be conditioned by repeated presentations of a light or tone conditioned stimulus (CS) followed by the corneal or canthal unconditioned stimulus (US).

Some years ago Schmaltz and Theios (1972) showed that simple NMR conditioning is unaffected by hippocampal lesions, and Oakley and Russell (1972) demonstrated that decorticate rabbits can learn and retain the conditioned NMR taking essentially normal time to do so. These experiments made it clear that subcortical circuits can be sufficient for normal acquisition and retention of this conditioned motor response. In contrast to the lack of effect of lesions of the cerebral cortex, Richard Thompson and his associates (McCormick et al. 1981) found that cerebellar lesions abolish a previously established conditioned NMR response, and prevent its reacquisition.

This effect of cerebellar lesions on the acquisition and retention of a simple learned motor response suggests that paradoxically spared motor learning in amnesic humans or decorticate rabbits may be mediated by the cerebellum. To put these studies of the role of the cerebellum in motor learning and reflex plasticity in context, we might first look at the origins of our present understanding of cerebellar structure and function, and then review some recent anatomical studies on afferents to the cerebellum.

WHAT DOES THE CEREBELLUM DO? A BRIEF HISTORICAL INTRODUCTION

In the nineteenth century experimental evidence and clinical observations began to reveal that different parts of the brain have different functions. In relatively crude, early experiments Rolando (1809) found that lesions of the cerebellum caused movement deficits in experimental animals without obvious effects on other functions. Some 15 years later Flourens (1824) extended these observations by studying the effects of cerebellar lesions in birds and mammals. Flourens argued convincingly that the cerebellum could not be the sole organ for the control of movement since movements were still possible even after the cerebellum was removed entirely. What is lacking after cerebellar lesions is the coordination and integration of movement.

From the time of Flourens onward most investigators recognized the specifically *motor* role of the cerebellum. However, interpretation of the motor symptoms caused by cerebellar lesions remained controversial. An alternative suggestion to that of Flourens was put forward some 65 years later by Luciani (1891) who argued that

cerebellar lesions did not impair coordinated movements as such. Rather, he suggested that symptoms caused by damage to the cerebellum were the result of more elemental deficits in muscle control. Luciani identified three related fundamental deficits caused by cerebellar lesions, which he called atonia, asthenia, and astasia. Atonia is the loss of muscle tone, asthenia is weakness of muscles, and astasia is a deficit in the regularity and stability of muscle contractions. Luciani interpreted the complex deficits in movement that often follow cerebellar lesions in terms of these three elementary dysfunctions.

These subtly divergent interpretations of the functions of the cerebellum powerfully influenced the views of clinical neurologists. Babinski (1913), like Flourens, interpreted the effect of cerebellar damage in his patients as a deficit in the coordination of movement. Holmes (1917, 1939), like Luciani, suggested that most of the symptoms of cerebellar lesions were the result of the three elementary muscle dysfunctions: atonia, asthenia, and astasia. Nevertheless, Holmes also recognized the existence of a more complex cerebellar ataxia, which he felt could not be simply explained in terms of these more elementary deficits.

DO DIFFERENT PARTS OF THE CEREBELLUM CONTROL DIFFERENT SETS OF MUSCLES?

Comparative Anatomy and the Localization of Function on the Cerebellar Cortex

By 1900 the locus of primary motor and sensory areas of the cerebral cortex and their topography were reasonably well identified. But most of the nineteenth-century authors were surprisingly silent on the question of the localization of function within the cerebellum. Only the laterality of cerebellar control was recognized; unlike the cerebral cortex, cerebellar lesions cause deficits that are seen principally on the same side of the body.

Physiologists, anatomists, and neurologists of the last century largely ignored the more detailed question of whether there might be localization of the control of different movements on the cerebellar cortex. The first systematic scheme for functional organization of the cerebellar cortex was suggested by the Dutch anatomist, Louis Bolk (1906). Bolk's work is discussed here not because his conclusions are correct, which in detail they are not, but because he posed the problem of cerebellar localization clearly and well. Bolk's comparative observations and functional questions remain valid, even if his conclusions do not.

Bolk reasoned that the cerebellum is probably made up of a number of centers, each of which controls the actions of a different group of muscles. Movements, Bolk suggested, can be subdivided into two basic types. For one class of movements it is necessary for muscles to cooperate across the midline of the body. Smooth rotation of the neck, for example, must involve a synchronized activation of agonist muscles on one side and an orderly relaxation of antagonist muscles on the opposite side. Movements that require such collaboration across the midline, Bolk reasoned, are probably controlled by an unpaired structure in the brain such as the vermis of the cerebellum. Unilateral movements that can be made independently are controlled by laterally placed brain structures such as the lateral lobes of the cerebellum. Bolk thus proposed that the midline cerebellar vermis controls bilaterally synchronized movement, while the cerebellar hemispheres direct unilateral movements.

Bolk described the cerebellum in a large number of mammalian species. He noted especially those animals that are skilled and precise in their ability to control a particular body part, and attempted to relate that ability to the relative size of different regions of the cerebellum. Giraffes move their necks with great precision, hence Bolk looked for an unpaired midline structure whose size might reflect the complexity of neck movements. The giraffe has an especially large lobulus simplex, the cerebellar region just behind the primary fissure. Simplex, Bolk therefore suggested, is the locus for coordinating neck movements. Starting with simplex as the coordinator of neck movements, Bolk went on to suggest a single, complete representation of the body musculature in the cerebellar cortex. The head, Bolk proposed, is controlled from the anterior lobe, and the remainder of the body is controlled from the posterior cerebellum.

Although Bolk's comparative descriptions were thorough and his thinking was provocative, it was soon recognized that his scheme for cerebellar organization was probably wrong in detail. Accordingly, Bolk's clear thinking about the problem of cerebellar localization and his excellent anatomical descriptions seem to have faded from view, along with his premature somatotopic scheme. The problem of how to interpret differences in cerebellar morphology in different animals remains unsolved.

ON INTERNAL STRUCTURE AND EXTERNAL CONNECTIONS OF THE CEREBELLAR CORTEX

Histological Organization of the Cerebellar Cortex

The structure of the cells in the cerebellar cortex and their connections were brilliantly analyzed and illustrated by Cajal (1909–11). The only output from the cerebellar cortex is from the Purkinje cells. Cajal identified four additional cell types and two sorts of afferent input to the cerebellar cortex: mossy fibers and climbing fibers. It is now recognized that the inferior olivary nucleus is the only source of climbing fibers to the cerebellar cortex. All other afferent fiber systems, including

Figure 2. The somatotopic organization of the cerebellar cortex after Louis Bolk (1906). Bolk suggested that there is a single orderly representation of the body's musculature on the cerebellar cortex. The anterior lobe and the vermis of the posterior lobe, he argued, control movements that must be coordinated across the midline of the body. The cerebellar hemispheres control independent use of the limbs. The figure shows a recreation of Bolk's theory with the mapping as applied to Professor Bolk himself. In Bolk's somatotopic scheme the tail is represented in the paraflocculi of the cerebellum, here shown as the tail of Bolk's formal attire. [Figure courtesy Professor Jan Voogd of Erasmus University, Rotterdam.]

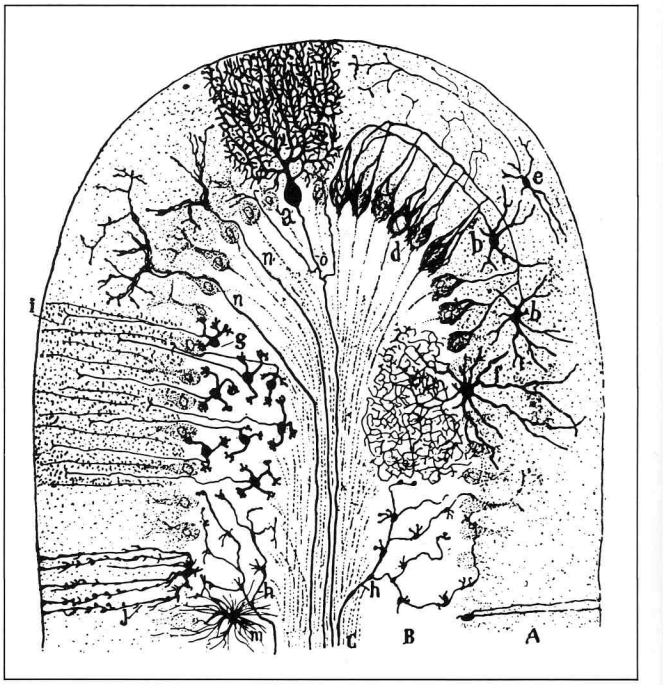

Figure 3. The figure shows the major cell types and afferent fiber systems to the cerebellar cortex. The output cells are the large Purkinje cells (a), which, when viewed as in the plane of the diagram, have a rich and profusely branched dendritic tree. The Purkinje cells are acted on by two sorts of afferent fibers. One type of fiber, the climbing fiber (n), arises in the contralateral inferior olivary nucleus, and synapses directly on the dendrites of Purkinje cells. The other type of incoming fiber, the mossy fiber (h), synapses on the dendrites of the granule cells (g). Granule cells in turn send an axon toward the surface of the cerebellar cortex where they branch to contact an array of Purkinje cells. The diagram illustrates a section of cerebellum cut perpendicular to the cerebellar folia. Because the axons of the granule cells form parallel fibers (i) that spread along the folium, they appear to be cut off and short. In fact they can reach a length of several millimeters. Conversely, the rich dendritic branching of the Purkinje cell is seen only in this plane of cutting which is transverse to the cerebellar folium. When viewed in a section cut 90° to this diagram, the dendritic tree of the Purkinje cell would be seen as a very narrow arbor. The other cell types illustrated are basket cells (b), stellate cells (e), and a glial cell (m). (A) is the molecular layer, (B) is the granular layer, and (C) is the layer of white matter. [From Cajal (1909–11).]

those from the spinal cord, the vestibular nuclei, and the pons terminate as mossy fibers. Mossy fibers synapse on the dendrites of granule cells. The axons of granule cell axons ascend to the molecular layer where they branch to form parallel fibers, each of which makes synapses on the dendrites of many Purkinje cells. Climbing fibers terminate differently: they ascend through the layers of granule cells to make many hundreds of synapses directly on the dendrites of the Purkinje cell. Each olivocerebellar fiber branches to form a few climbing fibers. Each climbing fiber contacts only a single Purkinje cell. In contrast, mossy fibers connect to a large number of Purkinje cells via parallel fiber relays.

There are, then, two entirely different sorts of afferent fiber to the cerebellar cortex. A central unanswered question is to establish the differential role of these two afferent systems in the function of the cerebellum. As we shall see, there have been intriguing suggestions about a possible role for these two different fiber systems in motor learning.

The Sensory Input of the Cerebellum

One important clue to cerebellar function must come from understanding its sensory inputs. The nineteenth-century anatomists recognized major spinal afferent pathways to the cerebellum that ascend in the lateral funiculi of the cord, together with another powerful input from the vestibular system. These anatomical facts helped to interpret the deficits caused by cerebellar lesions. If the cerebellum is involved in the control of individual muscles and the integration of movement, the afferent input from spinocerebellar and vestibulocerebellar pathways must play a role in such motor integration. On the basis

of the anatomical and physiological evidence then available Sherrington (1906) proposed that the cerebellum is "the head ganglion of the proprioceptive system."

Knowledge about the nature of afferents to the cerebellum was increased with the advent of techniques for recording electrical activity on the surface of the cerebellar cortex. Adrian (1943), studying evoked potentials to somatosensory stimulation, found a relatively orderly somatotopic organization of the entire body surface on the anterior lobe of the cerebellum. The tail was represented anteriorly and upper parts of the body were represented more caudally. The primary fissure separates the anterior lobe from the representation of the head, which is located just behind it in the posterior lobe in the lobulus simplex. A short time later, Snider and Stowell (1944) described a second representation of the body surface in the posterior lobe, with the head represented rostrally and the tail caudally. The somatotopic representations so described are consistent with the known anatomical organization of the major spinocerebellar afferent pathways.

One problem must be taken into account in evaluating studies of afferent pathways to the cerebellum. It is clear that mossy and climbing fibers are differentially sensitive to anesthetic agents (see, for example, Eccles et al. 1968). Barbiturate anesthesia depresses the response of the cerebellar cortex to its mossy fiber input: chloralose anesthesia tends to preserve the mossy fiber response while reducing that to the climbing fibers. All electrophysiological studies of sensory input to the cerebellum must be evaluated in relation to possible biasing effects of the anesthetic used.

In addition to demonstrating a rough somatotopic organization, electrophysiological studies began to add new and important information about other afferents to the cerebellum. For example, Snider and Stowell (1944) found that light flashes and clicks also evoked potentials on the cerebellar cortex of cats. Sherrington's concept of the cerebellum as the head ganglion of the proprioceptive system had to be expanded.

The Corticopontocerebellar Pathway

The spinocerebellar tracts relay cutaneous and proprioceptive information directly to the cerebellar cortex. In many animals, especially humans and other primates, the terminals of spinal and vestibular afferent fibers occupy only a relatively small percentage of the cerebellar cortex. There is, however, another and much larger afferent pathway to the cerebellar cortex. This pathway arises in the pontine nuclei and ascends to the cerebellum by way of the middle cerebellar peduncle. Nearly all of the fibers in the middle cerebellar peduncle are axons of cells whose cell bodies lie in the pontine nuclei. There are far more fibers in the middle cerebellar peduncle than in all of the other afferent and efferent fiber systems of the cerebellum combined (Tomasch 1969). Most of the input to the pontine nuclei is from the cerebral cortex. In human and the higher primates the corticopontocerebellar pathway is truly massive.

Cortical Input to the Pontine Nuclei

Clearly, knowledge of the anatomical organization of the corticopontocerebellar pathway is an important basis for understanding the functions of the cerebellum. Cajal (1909–11) recognized that one source of corticopontine fibers is from collateral branches of the pyramidal tract axons as they pass through the pons. Cajal thought of these collaterals as a sort of power amplifier for the motor system. If a direct command to the motor neurons by way of the corticospinal tracts should prove inadequate to move a limb the cerebellum would increase the power of the output from the descending motor tracts, thus matching the necessary force to contract the relevant muscles.

Cajal's speculations were limited by the fact that he thought that all synaptic connections are excitatory. The widespread nature of the pontine terminals on the cerebellar cortex, he suggested, would produce an "avalanche of conduction" that could be used to overcome resistance to movement. But Cajal recognized that, in addition to the collaterals of the corticospinal tract, in many animals there must be other corticopontine fibers. The basis pedunculi contains the great majority of the fibers that descend from the cerebral cortex to the brainstem. On the basis of light microscopy Tomasch (1969) estimated that in humans there are some 20,000,000 fibers in the basis pedunculi and only about 1,000,000 in each pyramidal tract. These counts are based on light microsopic evidence, hence they may not reflect the number of axons that are too small to be seen without higher magnification. Nevertheless, the relative size of these tracts suggests that the proportions Tomasch reported are in fact correct. Allowing for an additional 1,000,000 corticobulbar fibers this would leave about 18,000,000 or 90% of the fibers in the basis pedunculi to terminate in the pontine nuclei.

Which Cells in the Cerebral Cortex Project to the Pontine Nuclei?

By far the largest input to the cerebellum is from the pontine nuclei and the largest input to the pontine nuclei is from the cerebral cortex. To understand the possible role of this corticopontocerebellar circuit in motor control and its possible role in motor learning it is necessary to know its anatomical organization.

Experiments using retrograde tracing with horseradish peroxidase (HRP) have given a consistent picture of the organization of the corticopontine fiber system. Animals are injected with HRP or wheatgerm agglutinin HRP so

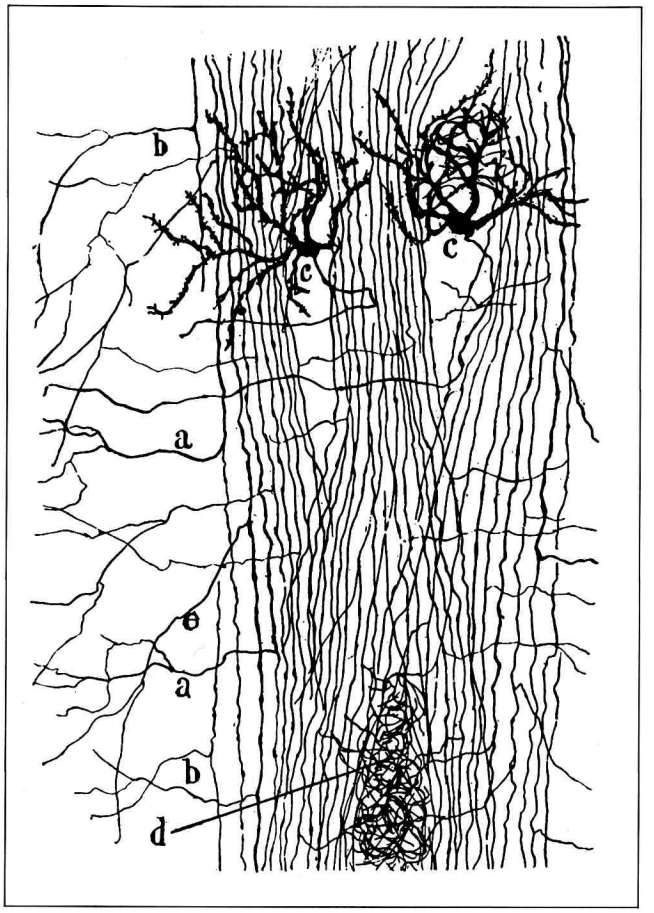

Figure 4. Longitudinal section through the pontine nuclei. The figure illustrates the fact that as corticospinal fibers traverse the pontine nuclei they give off collaterals (a, b) to pontine cells (c). (d) Fiber plexus formed by collaterals. Cajal believed that in primitive animals, such collaterals of the corticospinal tract were the only input to the pontine nuclei. In humans there are many more purely corticopontine fibers than corticospinal collaterals, since the number of descending cortical fibers in the basis pedunculi greatly exceeds the number in the pyramidal tracts (see text). [From Cajal (1909–11).]

as to fill the entire pontine nuclei on one or both sides. An appropriate time is allowed for the HRP to be transported retrogradely from axonal terminals in the pontine nuclei and the brain is then processed to reveal the distribution of retrogradely labeled cortical cells.

These retrograde tracing experiments have revealed that all cortical neurons that project to the pontine nuclei are layer V pyramidal cells. In some cases the cell bodies of corticopontine axons are further restricted to a single sublamina within layer V. In the rat barrel field, for example, all corticopontine cells are strictly confined to a single sublamina Vb (Glickstein et al. 1987). In favorable sections all pyramidal cells in lamina Vb are labeled after pontine HRP injection, and no other cells in the barrel field cortex. Corticopontine cells often branch to send collaterals to other subcortical targets. For example, cells in layer Vb of the rat barrel field also project to the thalamus, superior colliculus, and medulla (Glickstein et al. 1987). Visual corticopontine cells in the cat branch to project to the superior colliculus (Baker et al. 1983).

Which Areas of the Cerebral Cortex Project to the Pontine Nuclei?

Animals vary in the distribution of corticopontine cells. In rats, for example, nearly all areas of the cerebral cortex project to the pontine nuclei; in monkeys only about half. In monkeys corticopontine projections are sparse or absent from frontal and temporal association areas. In rats the only cortical area with sparse projections to the pontine nuclei is a small zone in the temporal cortex, areas TE2 and TE3 of Zilles (Legg et al. 1989).

In neither rats nor monkeys is the distribution of corticopontine cells uniform. Some areas of cortex have many cells that project to the pons, some areas of cortex project only sparsely. In all mammals studied to date there is a powerful projection to the pontine nuclei from motor areas of the cerebral cortex. Rats and monkeys differ sharply in the way the pattern of sensory areas projects to the pontine nuclei. In rats visual corticopontine projections arise from the primary visual cortex as well as adjacent visual areas. In monkeys nearly all visual projections arise not from the primary striate cortex but from extrastriate visual areas in the superior temporal sulcus and the parietal lobe (Glickstein et al. 1985). The pattern of connections between the cerebral cortex and cerebellum demonstrates that this massive system of fibers has connections that make it appropriate for the sensory guidance of movement. Recent evidence suggests that the afferent inputs to the cerebellum may also play a role in motor learning.

THE CEREBELLUM AND MOTOR LEARNING

Some 20 years ago David Marr (1969) suggested that the circuitry of the cerebellum was consistent, not only with the control of ongoing movement but also with a role for the cerebellum in the acquisition and execution of learned movements. Marr proposed that if activation of a set of parallel fibers is repeatedly followed by climbing fiber activation on the same Purkinje cell, the parallel fiber input alone would eventually be able to activate that Purkinje cell. An important modification to Marr's theory was made by James Albus (1971) who suggested that the climbing fiber afferents, rather than facilitating the connection between the parallel fiber and the Purkinje cell, tend to weaken that connection. Marr and Albus both emphasized the role of the cerebellar cortex as a pattern detector. For example, if 25 mossy fibers were to be either in an on or off state and if the Purkinje cell could recognize combinations of 5 of these at a time,

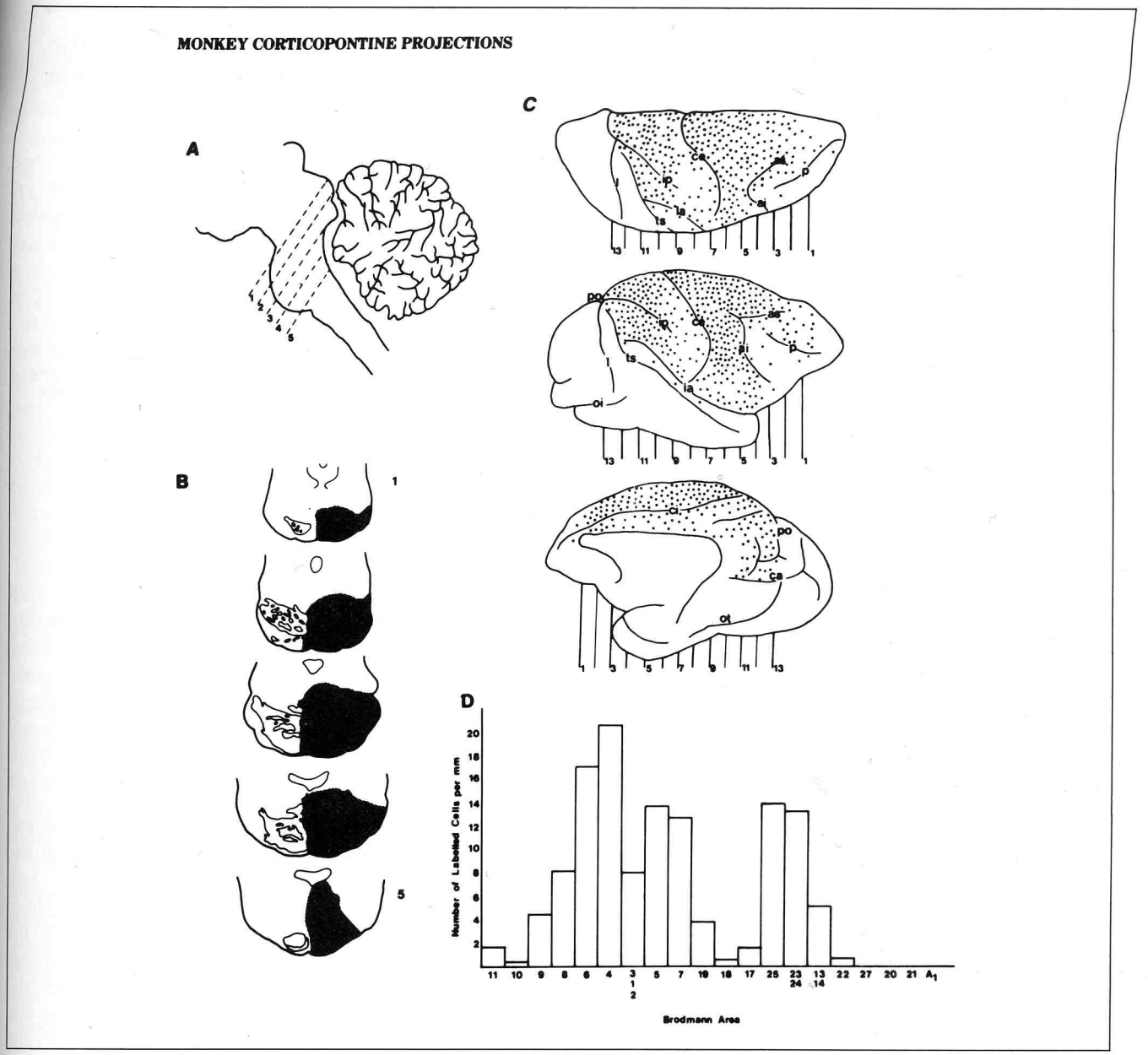

Figure 5. The distribution of the cells of origin of corticopontine fibers in the monkey. The largest source of corticopontine fibers is from cells in the motor areas 4 and 6. There is also a powerful input to the pontine nuclei from predominantly visual areas within the superior temporal sulcus of the monkey (area 19) and adjacent areas of the parietal lobe (area 7a). [From Glickstein et al. (1985).]

the total number of possible combinations would be combinations of 5 out of 25 or over 50,000 possible sets of 5 parallel fibers. The climbing fiber would act as a sort of "teacher" to change the efficacy of a particular combination of parallel fiber inputs to the Purkinje cell.

The idea that the cerebellum might be involved in motor learning was received with interest in many quarters, enthusiastically by some and sceptically by others. The Marr/Albus model is still with us. It is a major theoretical guide for some and a source of controversy among neural scientists today. The theoretical suggestions influenced a number of studies that were directed at looking into the possible role of the cerebellum in motor learning and reflex plasticity.

The Vestibuloocular Reflex and its Modifiability

If you turn your head to the left there is a reflex connection to the extraocular muscles that tends to move the eyes in an equal and opposite direction to the right. The vestibuloocular reflex (VOR) allows us to fixate ob-

jects while moving our heads and hence it is essential for maintaining clear vision during rapid head movement. The minimal circuitry for the VOR begins in the receptors in the semicircular canals and connects by way of the vestibular nuclei to the extraocular motor neurons. Thus, there is a simple three neuron reflex arc whereby a turn of the head to the right facilitates a compensatory movement of the eyes to the left. The VOR is a so-called "open-loop" reflex since, unlike other reflexes, such as the stretch reflex, the output of the VOR does not affect the input. Like all open-loop reflexes, the VOR is at risk of inaccuracy since it lacks feedback. Hence it must be capable of recalibration. There is now good evidence that the VOR is highly modifiable and that this modifiability requires the cerebellum. Gonshor and Melville-Jones (1973) studied the effects of modifying visual input on the VOR. When subjects wore reversing prisms in front of their eyes the normal VOR becomes maladaptive. Movement of the head to the right, if followed by movement of the eyes to the left, further destabilizes the image rather than helping to fixate it. When reversing prisms were worn continuously for several days the gain of the VOR was gradually attenuated and eventually even reversed in phase. Now when the head was moved to the right there was a reflex tendency to move the eyes in the *same* direction.

A number of studies have explored further the plasticity of the VOR. Miles and his collaborators (1974, 1980), for example, have shown that lenses that increase the image size produce an increase in the gain of the vestibulo-ocular reflex. Similarly, decreasing the image size will decrease the gain of the VOR.

Plasticity of the VOR requires the cerebellum. Lesions of the cerebellum abolish the ability to modify the VOR and abolish modifications that were acquired previously (Robinson 1976). Although the role of the cerebellum in adaptation of the VOR is well established, the exact locus of plasticity and its mechanism remain controversial. Masao Ito and his colleagues (1972, 1973), for example, have presented evidence that the anatomical locus of the modification of the VOR in rabbits is in the flocculus, a division of the cerebellar cortex. Ito's evidence is consistent with the idea that a modification of parallel fiber to Purkinje cell synapses under the influence of a climbing fiber input may be the neural basis for changes in the VOR. Others argue that although the cerebellum may be essential for adaptation of the VOR, the actual locus of plasticity is not within the cerebellar cortex but in stuctures or circuits afferent or efferent to it (Lisberger 1988).

On Saccadic Calibration

Saccadic eye movements are rapid conjugate shifts in eye position that serve to point the fovea toward a target of interest. Although saccadic eye movements can still be made after complete cerebellectamy, the ability to modify

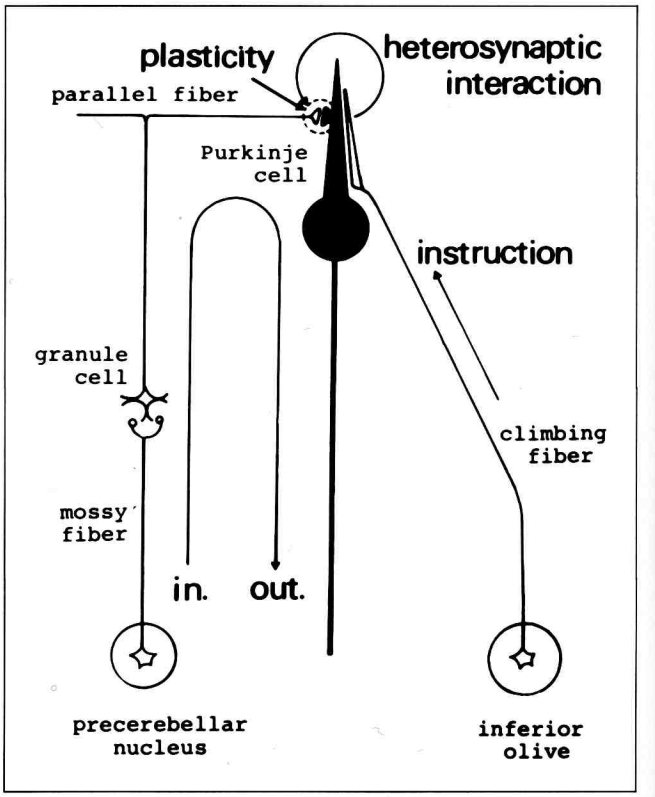

Figure 6. The diagram illustrates a proposed role of the major cell types and afferent fibers to the cerebellum in plasticity (see text). [From Ito (1984).]

them is lost. Optican and Robinson (1980) studied saccadic eye movements in monkeys in which a lesion had been placed in one of the extraocular muscles. As a consequence of muscle damage, saccades were inaccurate. A monkey, when confronted with a light 20° to the right, for example, might make only a 10° saccade toward the target. Over successive days of testing, however, the accuracy of the saccade increased until its normal amplitude was restored. Such recalibration of the saccade amplitude also requires the cerebellum; lesions abolish it.

On Eyeblink Conditioning in Rabbits

Large, unilateral lesions that include the cerebellar cortex and nuclei abolish conditioned NMR in rabbits and prevent relearning (McCormick et al. 1981). Nearly all of the output from the cerebellar cortex is to the cerebellar nuclei. The number of cells in the cerebellar cortex is much greater than that in the nuclei, hence there is a massive funnelling of information from the cerebellar cortex onto the cerebellar nuclei. A small lesion in the nuclei effectively interrupts the flow of information from a large territory within the cortex. Yeo et al. (1985a) and Thompson and his colleagues (Clark et al. 1984) studied the effects of lesions within the cerebellar nuclei on the conditioned NMR of rabbits. Small lesions of the anterior

interpositus nucleus completely abolished a previously acquired conditioned NMR response.

Since the major input to the cerebellar nuclei is from the cerebellar cortex, the obvious next step was to see if there is a specific area of cerebellar cortex that is critical for the conditioned NMR. Yeo et al. (1985b) found that small lesions of the hemispheric portion of lobule VI (HVI) abolished the conditioned NMR response and did not impair the unconditioned response. Much larger lesions of the cerebellar cortex outside of this critical focal zone did not seem to affect either the conditioned or the unconditioned response.

If conditioning is continued for a long time, animals with lesions of the cerebellar cortex HVI may reacquire the conditioned NMR, but they do so at a far slower rate than normal (Hardiman et al. 1988). If the lesion is extended to include the cerebellar cortex just adjacent to HVI, in lobule HVII, the conditioned response is permanently abolished. In control experiments in which only HVII was destroyed there was no effect on the conditioned or the unconditioned response.

Cerebellar cortical lesions that include both HVI and HVII abolish the conditioned nictitating membrane response. The climbing fiber input to these areas comes mainly from a region of the inferior olivary nucleus on the medial edge of the principal olive and adjacent dorsal accessory olive (Yeo et al. 1985c). These olivary areas are activated by trigeminal afferents from around the eye and they produce climbing fiber activation in lobule HVI. The climbing fiber may therefore be the representation of the UCS. HVI also receives mossy fiber afferents from auditory and visual areas of the pontine nuclei (Yeo et al. 1985c; Wells et al. 1989). These inputs to HVI are consistent with a very simple implementation of the Marr/Albus model: the CS might be represented by a mossy fiber input and the US as a climbing fiber input to lobule HVI. Modification of the CS-activated parallel fiber to Purkinje cell synapses would be produced by US-activated climbing fiber inputs to these same Purkinje cells. How might this suggestion be tested?

Destruction of the Inferior Olivary Nucleus

One prediction of the Marr/Albus model would be that lesions of the climbing fiber afferents to the cerebellar cortex or of the inferior olive itself should act like removing the US input to the cerebellar cortex. Normally, if the US is withdrawn but CS presentation is continued, there is a gradual waning of the amplitude and frequency of conditioned responses, a phenomenon known as extinction. So, if the rabbit is first successfully conditioned, the conditioned response might still be present in such a trained animal immediately after a lesion is made in the inferior olive. If the olive lesion interrupted the US pathway, the conditioned response might be present immediately after the operation but then decline, despite continued pairing of CS with UCS. Extinction-like effects were reported in two cases by Thompson and his colleagues (McCormick et al. 1985). In our own studies, however, we found that inferior olivary lesions immediately and completely abolished the conditioned NMR (Yeo et al. 1986).

The Marr/Albus theory need not be rejected on the basis of our observation, however, since destruction of the climbing fibers has other important effects on the cerebellar cortex. Lesions of the inferior olive cause an immediate increase in the resting firing rate of the Purkinje cells on which they synapse (Colin et al. 1980; Montarolo et al. 1982). The Purkinje cells whose climbing fiber input is removed now fire at roughly three times their normal rate. Because of the inhibitory effect of the Purkinje cell on cells in the cerebellar nuclei (Eccles et al. 1967), such lesions would then turn off the associated cerebellar nuclei and hence block the output from the cerebellum.

IS THE CEREBELLUM THE LOCUS OF MOTOR LEARNING: TWO VIEWS

Yes: One view would hold that the cerebellum is the site of motor learning. According to this view, the actual locus of motor learning is in the cerebellar cortex: learning comes about by an association between mossy fiber and climbing fiber inputs. Classical conditioning provides a relatively direct test of this idea. Pontine mossy fiber input relays the conditioned stimulus (CS) to the cerebellar cortex. Mossy fibers, in turn, relay their information to granule cells whose parallel fiber axons contact the Purkinje cells in the molecular layer. The unconditioned stimulus (UCS) is relayed to the cerebellar cortex by climbing fibers whose cell bodies are in the inferior olivary nucleus. The repeated pairing of a mossy fiber input carrying the CS and a climbing fiber input carrying the UCS leads to a change in the synaptic efficiency of the connection between the parallel fiber and the Purkinje cell. In Albus' theory, the result would be a decrease in the efficacy of the parallel fiber to Purkinje cell connection. With repeated pairing of CS and UCS the CS alone would come to lower the Purkinje cells' firing rate. Because of the known inhibitory nature of Purkinje cells on cells in the cerebellar nuclei, this would cause an increase in the firing rate of nuclear cells on which the Purkinje cells terminated. The result would be a movement elicited by the previously neutral CS.

No: The alternate view is that the cerebellum operates only in real time, continuously adjusting motor output. There is no evidence that the circuitry of the cerebellar cortex participates in long-term storage. If the cerebellum appears to play a role in motor learning, such a role is entirely illusory. It may play an important, perhaps even a necessary role in providing information to structures outside the cerebellum where motor learning in reality takes place. The abolition of a motor habit that appears to follow cerebellar lesion may simply result

from a generalized impoverishment of all classes of movement. The conditioned response, for example, is typically weaker than the unconditioned response. Cerebellar lesions might appear to abolish the conditioned response and leave the unconditioned response intact, whereas in reality the lesion merely delays the conditioned response and thus its appearance is masked by the response to the unconditioned stimulus.

There is as yet no convincing evidence to support either point of view unequivocally. As we have seen, lesions of the cerebellum impair or abolish several types of motor conditioning and reflex modification. Therefore the cerebellum probably plays a powerful, perhaps even a necessary role in motor learning and the execution of learned movement. But there is no conclusive proof that it is the actual locus of motor learning. Moreover if the cerebellum is the locus for certain forms of motor learning it is not the only possible locus, since some learned motor response may be reacquired even after the cerebellum is destroyed.

Two recent reports must be taken into account in assessing the possible role of the cerebellum in motor learning. Welsh and Harvey (1989) argue that the effects of cerebellar lesions are not specific to the conditioned response. Rather, they suggest that cerebellar lesions produce a weakening and a slowing of all movements. Since the conditioned response is typically weaker than the unconditioned response, the apparent loss of conditioning is misleading. They find, using unpaired presentations of the CS as probe trials, that long-latency conditioned NM responses may survive even after the cerebellar nuclei have been ablated. In our own studies, however, we find very few responses to the probe trials alone and those few that do appear are grossly inappropriate in time and extremely weak. Moreover, in some of their cases, cerebellar lesions did appear to abolish the CR. The possibility remains that in the cases in which the conditioned NMR was not abolished a critical portion of the cerebellum may have been spared. In our own studies lesions of the cerebellar cortex lobules HVI and HVII completely abolished the conditioned NMR and response to the unconditioned stimulus was not diminished (Yeo and Hardiman 1988).

Although the cerebellum may normally be involved in NMR conditioning, the NMR response may be reacquired, even after the cerebellum has been removed completely. James Bloedel and his colleagues (Kelly et al. 1988) demonstrated that the conditioned NMR may survive in a decerebrate rabbit in which the cerebellum is also removed. However, although these results demonstrate that other circuits may sustain conditioning in such a reduced preparation, the powerful effect of cerebellar lesions on the conditioned response suggests that it plays a critical role in motor learning in the intact brain.

We favor the idea that the cerebellum and its associated circuits are the major locus for conditioning. All of the associated cerebellar circuitry appears to be linked in a logical circuit. Lesions of the appropriate region of the inferior olivary nucleus projecting to HVI and neighboring cerebellar cortex abolish the conditioned response, as do lesions of the appropriate target zones in the anterior interpositus nucleus. Lesions either of the appropriate region of the red nucleus (Rosenfield et al. 1985), which receives its major input from the anterior interpositus nuclei or of descending rubrobulbar fibers, also abolish the conditioned NMR, while leaving the unconditioned response intact. Thus, there is an organized cerebellar circuit involved in NMR conditioning. Lesions of any one element in this circuit impair or abolish the conditioned NMR. Lesions outside it do not. The Marr/Albus view of the cerebellum as a site for motor learning is still attractive, pulling together much of the experimental evidence. Even though other brainstem structures may also be involved in such conditioning, with the cerebellum intact, motor learning occurs faster, more powerfully, and more reliably.

REFERENCES

Adrian, E. D. (1943). Afferent areas in the cerebellum connected with the limbs. *Brain, 66*, 289–315.

Albus, J. S. (1971). A theory of cerebellar function. *Mathematical Bioscience, 10*, 25–61.

Babinski, J. F. F. (1913). Exposé des travaux scientifique. Paris

Mason. Trans. Clarke, E. and O'Malley, C. D. (1968). *The Human Brain and Spinal Cord*. Berkeley and Los Angeles: University of California Press, 674–677.

Baker, J., Gibson, A., Mower, G., Robinson, F., & Glickstein, M. (1983). Cat visual corticopontine cells project to the superior colliculus. *Brain Research, 265*, 222–232.

Berthier, N. E. & Moore, J. W. (1980). Role of extraocular muscles in the rabbit (oryctolagus cuniculus) nictitating membrane response. *Physiological Behavior, 24*, 931–937.

Bolk, L. (1906). *Das cerbellum der Säugetiere*. Jena G. Fisher, 337.

Brooks, D. N. & Baddeley, A. (1976). What can amnesic patients learn? *Neuropsychologia, 14*, 111–122.

Cermak, L. S., Lewis, R., Butters, N., & Goodglass, H. (1973). Role of verbal mediation in performance of motor tasks by Korsakoff patients. *Perceptual and Motor Skills, 37*, 259–262.

Clark, G. A., McCormick, D. A., Lavond, D. G., & Thomson, R. F. (1984). Effects of lesions of cerebellar nuclei on conditioned behavioural and hippocampal neuronal responses. *Brain Research, 291*, 125–136.

Colin, F., Manil, J., & Desclin, J. C. (1980). The olivocerebellar system I. Delayed and slow inhibiting effects: An overlooked salient feature of cerebellar climbing fibers. *Brain Research, 187*, 3–27.

Corkin, S. (1968). Acquisition of motor skills after bilateral medial temporal lobe excision. *Neuropsychologia, 6*, 255–265.

Courchesne, E., Yeung-Courchesne, R., Press, G. A., Hesselink, J. R., & Jernigan, T. I. (1988). Hypoplasia of cerebellar vermal lobules VI and VII in autism. *New England Journal of Medicine, 318*, 1349–1354.

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

Eccles, J., Provini, L., Strata, P., & Taborikova, H. (1968). Analysis of electrical potentials evoked in the cerebellar anterior

lobe by stimulation of hindlimb and forelimb nerves. *Experimental Brain Research, 6*, 171–194.
Flourens, P. (1824). Recherches expérimentales sur les propriétés et les fonctions du systéme nerveux dans les animaux vertébrés. Paris. Trans. Clarke, E. and O'Malley, C. D. (1968). *The Human Brain and Spinal Cord*. Berkeley and Los Angeles: University of California Press, 657–661.
Glickstein, M., May, J., & Mercier, B. (1985). Corticopontine projection in the Macaque: the distribution of labelled cortical cells after large injections of horseradish peroxidase in the pontine nuclei. *Journal of Comparative Neurology, 235*, 343–359.
Glickstein, M., Legg, C., & Mercier, B. (1987). Laminar organization of the cortex in the posteriomedial barrel field of rats. *Journal of Physiology, 388*, 42.
Gonshor, A. & Melville-Jones, G. (1973). Changes of human vestibulo-ocular response induced by vision-reversal during head rotation. *Journal of Physiology (London), 234*, 102–103.
Hardiman, M. J., Glickstein, M., & Yeo, C. H. (1988). Kainic acid lesions of the cerebellar cortex abolish the classically conditioned nictitating membrane response of the rabbit. *Society of Neuroscience Abstracts, 14*, 784.
Holmes, G. (1917). The symptoms of acute cerebellar injuries due to gunshot injuries. *Brain, 40*, 461–535.
Holmes, G. (1939). The cerebellum of man. *Brain, 62*, 1–30.
Ito, M. (1972). Neural design of the cerebellar motor control system. *Brain Research, 40*, 81–84.
Ito, M. (1984). *The Cerebellum and Neural Control*. New York: Raven Press.
Ito, M., Nishimaru, N., & Yamamoto, M. (1973). Specific neural connections for the cerebellar control of vestibulo-ocular reflexes. *Brain Research, 60*, 238–243.
Kelly, T. M., McAlduff, J. D., & Bloedel, J. R. (1988). Presence of eyeblink conditioning in the decerebrate decerebellate rabbit. *Society of Neuroscience Abstracts, 14*, 169.
Legg, C., Mercier, B., & Glickstein, M. (1989). Corticopontine projection in the rat: The distribution of labelled cortical cells after large injections of horseradish perioxidase in the pontine nuclei. *Journal of Comparative Neurology, 286*, 427–436.
Leiner, H., Leiner, A., & Dow, R. (1986). Does the cerebellum contribute to mental skills? *Behavioral Neuroscience, 100*, 443–454.
Lisberger, S. G. (1988). The neural basis for learning of simple motor skills. *Science 242*: 728–735.
Lorente de No, R. (1932). The interaction of the corneal reflex and vestibular nystagmus. *American Journal of Physiology, 103*, 704–711.
Luciani, L. (1891). Ii Cervelletto. Firenze: Successori le Monnier. Trans. Clarke, E. and O'Malley, C. D. (1968). *The Human Brain and Spinal Cord*. Berkeley and Los Angeles: University of California Press, 662–668.
Marr, D. (1969). A theory of cerebellar cortex. *Journal of Physiology (London), 202*, 437–470.
Martone, M., Butters, N., Payne, M., Becker, J. S., & Sax, D. S. (1984). Dissociations between skill learning and verbal recognition in amnesia and dementia. *Archives of Neurology, 41*, 965–970.
McCormick, D. A., Lavond, D. G., Clark, G. A., Kettner, R. E., Rising, C. E., & Thompson, R. F. (1981). The engram found? Role of the cerebellum in classical conditioning of the nictitating membrane and eyelid response. *Bulletin of the Psychonomic Society, 18*, 103–105.
McCormick, D. A., Steinmetz, J. E., & Thompson, R. F. (1985). Lesions of the inferior olivary complex cause extinction of classically conditioned eyeblink response. *Brain Research, 359*, 120–130.
Miles, F. A. & Fuller, J. H. (1974). Adaptive plasticity in the vestibulo-ocular responses of the rhesus monkey. *Brain Research, 80*, 512–516.
Miles, F. A. & Eighmy, B. B. (1980). Long-term adaptive changes in primate vestibulo-ocular reflex I. Behavioural observations. *Journal of Neurophysiology, 43*, 1406–1425.
Milner, B., Corkin, S., & Teuber, H. L. (1968). Further analysis of the hippocampal amnesic syndrome: 14 year follow up study of H. M. *Neuropsychologia, 6*, 215–234.
Montarolo, P. G., Palestini, M., & Strata, P. (1982). The inhibitory effect of the olivocerebellar input on the cerebellar Purkinje cells in the rat. *Journal of Physiology, 332*, 187–202.
Oakley, D. A. & Russell, I. S. (1972). Neocortical lesions and Pavlovian conditioning. *Physiology and Behavior, 8*, 915–926.
Optican, L. & Robinson, D. A. (1980). Cerebellar-dependent adaptive control of primate saccadic system. *Journal of Neurophysiology, 44*, 1058–1076.
Parkin, A. J. (1982). Residual learning capacity in organic amnesia. *Cortex, 18*, 417–440.
Ramón y Cajal, S. (1909–11). Histologie du systeme nerveux. C.S.I.C., Madrid, Trans. into French by L. Azoulay (reprinted 1952).
Robinson, D. A. (1976). Adaptive gain control of vestibulo-ocular reflex by the cerebellum. *Journal of Neurophysiology, 39*, 954–969.
Rolando, H. (1809). Saggio sopra la vera struttura del cervello del'uomo e degl'animali e sopra le funzioni del sistema nervosa: Sassari. English trans. Clarke, E. and O'Malley, C. D. (1968). *The Human Brain and Spinal Cord*. Berkeley and Los Angeles: University of California Press, 653–658.
Rosenfield, M. E., Dovydaitis, A., & Moore, J. W. (1985). Brachium conjunctivum and rubro-bulbar tract: Brain stem projections of red nucleus essential for the conditioned nictitating membrane response. *Physiology and Behavior, 34*, 751–759.
Schmaltz, L. W. & Theios, J. (1972). Acquisition and extinction of a classically conditioned response in hippocampectomized rabbits (oryctolagus cuniculus). *Journal of Comparative Physiology and Psychology, 79*, 328–333.
Sherrington, C. (1906). *The Integrative Action of the Nervous System*. New Haven, Yale.
Snider, R. S. & Stowell, A. (1944). Receiving areas of the tactile, auditory and visual system in the cerebellum. *Journal of Neurophysiology, 7*, 331–357.
Tomasch, J. (1969). The numerical capacity of the human corticoponto-cerebellar system. *Brain Research, 13*, 476–484.
Weiskrantz, L. & Warrington, E. K. (1979). Conditioning in amnesic patients. *Neurophysiology, 17*, 187–194.
Wells, G. R., Hardiman, M. J., & Yeo, C. R. (1989). Visual projections to the pontine nuclei in the rabbit: Orthograde and retrograde tracing studies with WGA-HRP. *Journal of Comparative Neurology, 279*, 629–652.
Welsh, J. P. & Harvey, J. A. (1989). Cerebellar lesions and the nictitating membrane reflex: Performance deficits of the conditioned and unconditioned response. *Journal of Neuroscience, 9*, 299–311.
Yeo, C. H. & Hardiman, M. J. (1988). Loss of conditioned responses following cerebellar cortical lesions is not a performance deficit. *Sociey of Neuroscience Abstracts, 14*, 3.
Yeo, C. H., Hardiman, M. J., & Glickstein, M. (1985a). Classical conditioning of the nictitating membrane response of the rabbit I. Lesions of the cerebellar nuclei. *Experimental Brain Research, 60*, 87–98.
Yeo, C. H., Hardiman, M. J., & Glickstein, M. (1985b). Classical conditioning of the nictitating membrane response of the

rabbit II. Lesions of the cerebellar cortex. *Behavioral Brain Research, 60*, 99–113.

Yeo, C. H., Hardiman, M. J., & Glickstein, M. (1985c). Classical conditioning of the nictitating membrane response of the rabbit III. Connections of cerebellar lobule HVI. *Experimental Brain Research, 60*, 114–126.

Yeo, C. H., Hardiman, M. J., & Glickstein, M. (1986). Classical conditioning of the nictitating membrane response of the rabbit IV. Lesions of the inferior olive. *Experimental Brain Research, 63*, 81–92.

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