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Cerebrocerebellar Communication Systems

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I. INTRODUCTION

In view of the extensive development of the cerebellar hemispheres and the cerebral cortex in mammals, it is natural to inquire whether some highly significant and unique functional interrelationship might exist between them. Furthermore, the concomitant improvement in motor skill that accompanies the development

of these two brain structures in ascending the phylogenetic scale suggests that these structures may play an important role in the execution of skilled movement, an inference that agrees with the vast array of clinical and experimental evidence. Because of the advances in and application of the cellular approach to the nervous system during the past two decades, there has been great progress in understanding the physiology of the two cortical areas and their related structures. It is now known there are outstanding differences in the organization of these cortical areas. In addition, the pyramidal neurons in the cerebrum are excitatory whereas the Purkinje cells in the cerebellum are inhibitory. These differences suggest distinct roles for these two structures. In the last few years there has been a wealth of new information about the neuronal and synaptic properties within the pathways connecting these two cortical structures. It seems worthwhile to survey the information that is known at present. In addition, an attempt is made to indicate the conceptual advances brought out by the cellular approach. Because many reviews have appeared covering portions of this general problem (18, 39, 66, 119, 120, 122, 140, 141, 192, 209, 210, 317), the scope of this present review is restricted to the properties of the neuronal connections within the cerebrocerebellar loop and subloops and the dynamic properties of these loops. In many cases, only the more recent references are listed and those articles should be consulted in order to gain the proper historical perspective for the earlier work.

The following abbreviations are used in this review:

CCT	Cuneocerebellar tract
CM	Centromedian nucleus of thalamus
DE	Dentate nucleus
DSCT	Dorsal spinocerebellar tract
IO	Inferior olivary nucleus
IP	Interpositus nucleus
LRN	Lateral reticular nucleus
NRTP	Nucleus reticularis tegmenti pontis
Pf	Parafascicular nucleus of thalamus
PHN	Perihypoglossal nuclei
PMRN	Paramedian reticular nuclei
PN	Pontine nuclei
PT	Pyramidal tract
RN	Red nucleus
RST	Rubrospinal tract
SOT	Spino-olivary tract
VA	Ventral anterior nucleus of thalamus
VL	Ventrolateral nucleus of thalamus
VM	Ventral medial nucleus of thalamus
VPL	Ventroposterolateral nucleus of thalamus

II. OVERVIEW OF CEREBROCEREBELLAR RELATIONSHIPS

Evoked-potential studies have made it clear that there are functional connections between the cerebral cortex and the cerebellar cortex. In the cat, stimula-

tion of the cerebral cortex evokes two types of potentials in the cerebellum, a short-latency (3–6 ms) wave mediated by the mossy fibers and a long-latency (12–25 ms) wave via the climbing fibers (74, 103, 109, 168, 169, 243). Similarly, stimulation of the cerebellar nuclei, which form the cerebellar outflow, evokes a potential on the cerebral surface at 1.5–2.0 ms (211, 259). By applying localized stimuli to the cerebral cortex or cerebellar cortex while recording from the other, it has been possible to map the spatial extent of the influences of one cortex onto the other. From this it is known that the cerebral pathways primarily influence the intermediate and lateral zones of the contralateral cerebellum and the intermediate and lateral zones of the cerebellum primarily influence the motor area of the contralateral cerebral cortex (18, 141, 259, 263). The lateral zone of the cerebellum receives inputs from large areas of the cerebral cortex, including many association areas as well as the sensorimotor area (10, 112, 168). The intermediate zone, on the other hand, receives its inputs primarily from the sensorimotor cortex (7, 112, 144, 168). Since the cerebrocerebellar and the cerebellocerebral influences are both primarily crossed, there is apparently a closed sensorimotor-cerebellar-sensorimotor loop through the intermediate zone and a more open association/sensorimotor-cerebellar-sensorimotor loop through the lateral cerebellum. These two loops are considered in more detail later (sect. IX*C*).

III. CEREBROCEREBELLAR PATHWAYS

There is general agreement that the main outflow from the cerebral cortex is contained in the pyramidal tract (PT) and that the messages traveling along this tract are important for the skilled usage of the musculature (29, 242, 317). The main portion of the PT arises from the motor cortex and nearby cortical areas. Before the PT fibers reach the spinal cord, they give off collaterals that innervate many brainstem nuclei (248), some of which project to the cerebellum. In addition to the small number of corticospinal fibers (500,000 in man and 40,000 in cat; see Table 1) that arise in a restricted portion of the cerebral cortex, nearly all areas of the cerebral cortex give rise to corticobulbar fibers, which pass through the internal capsule and travel along with the PT before terminating in the brainstem. Consequently, there are many more corticobulbar fibers than corticospinal fibers (20 million vs. 0.5 million in man; Table 1).

Electrophysiological evidence has confirmed that the cerebrocerebellar influences are mediated by the pyramidal tract and the accompanying corticobulbar fibers. Both the mossy-fiber and climbing-fiber responses in either the pars intermedia or vermis of the anterior lobe were still evoked by stimulating the sensorimotor cortex in "pyramidal" cats in which the brainstem was transected at the mesencephalic level, sparing only the cerebral peduncles (74, 179). Since both mossy- and climbing-fiber responses are induced by stimulating the medullary pyramid caudal to the precerebellar nuclei, it is concluded that the cerebrocerebellar relay nuclei are innervated by corticospinal collaterals as well as corticobulbar terminals (Allen, Korn, Oshima, and Toyama, manuscript in preparation; 323).

It has been established that the PT fibers are distributed into fast and slow

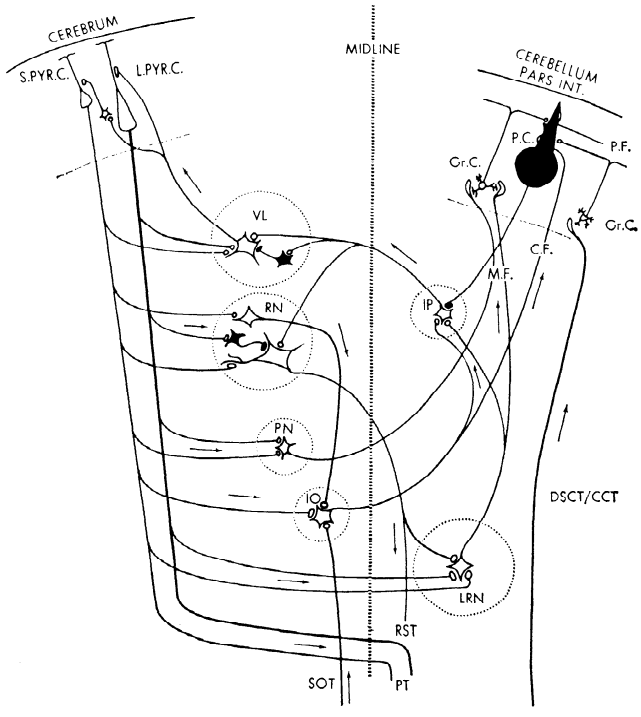

FIG. 1. Pathways from cerebral cortex to cerebellum. Most important linkages are shown for pars intermedia, which are also representative for cerebellar hemisphere. Inhibitory interneurons are shown in black. Arrows show direction of information flow. In many instances, drawing has been simplified. For example, it is likely that there is a separate rubrobulbar projection to the lateral reticular nucleus (LRN), although the rubro-LRN projection may be in large part collaterals of the rubrospinal tract (RST). Also, many of the cerebral inputs to the red nucleus (RN), pontine nuclei (PN), inferior olivary nucleus (IO), and LRN are via corticobulbar fibers in addition to collaterals of PT fibers. S.PYR.C = small pyramidal cell; L.PYR.C. = large pyramidal cell; P.F. = parallel fiber; P.C. = Purkinje cell; Gr.C. = granule cell; C.F. = climbing fiber; M.F. = mossy fiber. [Modified from Eccles (119).]

conducting groups with mean conduction velocities of 50 m/s and 14 m/s (190, 280; reviewed in 234). By measuring in the "pyramidal" cat the conduction velocities of fibers mediating the mossy-fiber and climbing-fiber field potentials in the cerebellum, Kitai et al. (179) have shown that the climbing-fiber input is mediated by the slow PT fibers, while the mossy-fiber input is activated by both the fast and slow PT fibers.

Several brainstem nuclei have been shown to receive cortical inputs and also to project to the cerebellum: notably, the pontine nuclei (PN), the inferior olive (IO), and the lateral reticular nucleus (LRN) (Fig. 1). It is generally concluded that the inferior olive is the principal source of climbing fibers (122, 123, 279). Several investigators have argued that it is not the exclusive source of climbing fibers (36, 168, 223, 231) and the nucleus reticularis tegmenti pontis (NRTP) (223, 261, 279) and the paramedian reticular nucleus (PMRN) (223) have been sug-

gested as the source for an undetermined fraction of the climbing fibers. Cervetto et al. (74) and Allen et al. (4; Allen and Ohno, manuscript in preparation) have shown that transection of the inferior cerebellar peduncle, through which the olivocerebellar fibers enter the cerebellum, eliminates the climbing-fiber field potentials in the vermis and pars intermedia of the anterior lobe and in the cerebellar hemisphere. Lesions of the brachium pontis, which carries the fibers to the cerebellum from the nucleus reticularis tegmenti pontis, never reduced the climbing-fiber fields in any of these cerebellar areas (4; Allen and Ohno, manuscript in preparation). Similarly, transection of the inferior olivary output at its decussation eliminates the nerve-evoked climbing-fiber responses in Deiters' neurons (13, 70).

All other precerebellar relay nuclei send fibers that terminate as mossy fibers. Of these, the pontine and lateral reticular nuclei are considered to be the most important cerebrocerebellar relays on the basis of number of fibers that they project to the cerebellum and the number of cortical fibers terminating within the nuclei. Since the cerebropontocerebellar pathway enters the cerebellum through the brachium pontis and the cerebroreticulocerebellar pathway enters via the restiform body, it has been possible to compare the contributions of these two pathways by creating electrolytic lesions through electrodes stereotaxically inserted into these peduncles. This approach shows that with cerebral stimulation approximately half of the early mossy-fiber input to the pars intermedia and vermis of the anterior lobe is carried by each of these two pathways, while nearly all that to the hemisphere is carried by the cerebropontocerebellar pathway (4; Allen and Ohno, manuscript in preparation).

A. Pontine Nuclei

The pontine nuclei may be divided into two components—the more ventrally located basilar pons or pontine gray and the nucleus reticularis tegmenti pontis (NRTP) that lies dorsal thereto. Both of these pontine groups receive PT fibers and project to the cerebellum through the brachium pontis. The pontine gray receives fibers from nearly the whole cerebral cortex in the cat, whereas only restricted regions of the cerebral cortex project to the NRTP (48, 56–61). Each region of the cerebral cortex terminates in a specific zone of the ipsilateral pontine gray, with limited overlap of different cortical areas onto a given pontine zone (also 322). By contrast, the cortical overlap onto a given zone in the NRTP is more extensive, suggesting that more integration of cortical information takes place along this route to the cerebellum (48). Since these two regions are of different embryological origin and are cytoarchitectonically different, it is likely that they have different functional significance (48). Many neurons in the NRTP have the long, sparsely branching dendrites characteristic of the precerebellar reticular nuclei [LRN, PMRN, and perihypoglossal nuclei (PHN)], whereas the neurons in the pontine gray have only the short, amply branching dendrites characteristic of the specific relay nuclei [e.g., inferior olive (IO)] (48). In the cat the number of pontocerebellar fibers originating from the pontine gray is probably an order of magnitude greater than the number arising in the NRTP. Consequently, the pon-

tine gray has been considered to be the more important relay and it has been studied more extensively electrophysiologically.

1) Pontine gray. Single-unit recordings from the pontine gray reveal that stimulation of the pyramidal pathway produces excitation in pontine cells with relatively short latencies: 1.7–5.2 ms from sensorimotor cortex and 1.0–2.4 ms from cerebral peduncle (8). About one-fourth of the cells sampled were innervated by both fast and slow PT fibers, the remainder solely by slow PT fibers (Allen, Korn, Oshima, and Toyama, manuscript in preparation). Intracellular recording from pontine cells indicates that pyramidally induced EPSPs have properties resembling the pyramidally induced EPSPs in motoneurons and other neurons. They have a characteristically slow time course, which is partly accounted for by the electrotonic attenuation of EPSPs generated in dendrites remote from the cell soma, and they may be facilitated by delivering two pyramidal volleys in rapid succession (9). A subsequent investigation on the synaptic noise of pontine cells by Allen et al. (11) showed that pontine cells receive synaptic impingement from the sensorimotor cortex through two types of transmission lines. One type produces small unitary EPSPs ascribed to a distal dendritic location; the other generates larger unitary EPSPs up to 8 mV in amplitude, with a time to peak as short as 0.7 ms, apparently in the proximal dendrites (246, 247). These two types of EPSPs may correspond to the endings seen electron microscopically. The majority of corticopontine terminals are small, less than 2 μm in diameter, located upon fine, distal dendrites (160; G. A. Mihailoff and J. S. King, personal communication). In addition, there are larger endings (2–6 μm) in the pontine nuclei arising from large myelinated axons. These large endings tend to form synapses more proximally upon the dendrites of pontine neurons and often do so in synaptic complexes. Mihailoff and King (personal communication) have shown in the opossum that the large endings terminating in synaptic complexes arise primarily from the cerebellar nuclei. Holländer et al. (160), on the other hand, have shown in the cat that a few corticopontine fibers form large endings, presumably not as a part of synaptic complexes. When the anatomical and electrophysiological data are combined, it seems likely that the slow PT fibers synapse upon the distal dendrites and that the fast PT fibers synapse more proximally. Thus it can be deduced that the slow PT fibers produce small unitary EPSPs and probably contribute to the slow adjustment of the excitation level of pontine cells, as has been suggested for the dendritic EPSPs in motoneurons (246, 247), whereas the fast PT fibers generate large unitary EPSPs best suited for relaying impulses with a high safety factor (11). The role of the cerebellopontine projection is discussed in section VIII.

Although there are cells of different sizes in the pontine gray, Brodal and Jansen concluded that all these cells project to the cerebellum and that there are no internuncial neurons in the pontine nuclei (52, 167). On the other hand, using light- and electron-microscopic techniques, Mihailoff and King (personal communication) have recently observed in the opposum interneurons that form synaptic terminals containing flattened vesicles upon pontine projection neurons. Sasaki et al. (260) observed a hyperpolarization after the EPSP evoked by stimulating the surface of the cerebral cortex and concluded that this is an IPSP via a recurrent

connection within the pons. However, Allen et al. (11) were not able to reverse this hyperpolarization with hyperpolarizing current or with Cl^- injection. Furthermore, no such hyperpolarization was observed when the gray matter of the cerebral cortex was eliminated (9), making it likely that this hyperpolarization is a disfacilitation of the pontine neurons resulting from an intracortical inhibition of the PT neurons. Holländer et al. (160) in their electron-microscopic study pointed out that a small fraction of the terminals on pontine neurons contain elongated vesicles, less than half the fraction seen in the inferior olive (316; see also 42). The apparent unimportance of inhibition in the pontine nuclei suggests that the pontine neurons should be able to transmit high-frequency information from the cerebral cortex.

The pontocerebellar fibers are 0.9–7.5 μm in diameter (312) and conduct at 5–45 m/s (Allen, Korn, Oshima, and Toyama, manuscript in preparation). The fast and slow PT fibers are linked with the pontine neurons in such a way that the faster PT fibers tend to innervate the faster conducting pontine fibers (Allen, Korn, Oshima, and Toyama, manuscript in preparation). Nearly all the pontocerebellar fibers terminating in the pars intermedia and hemisphere decussate in the pons before entering and terminating in the contralateral cerebellum. Many of the fibers to the vermis enter through the ipsilateral brachium pontis and distribute terminals on both sides of the midline (52, 167). Although the pontocerebellar projections have been studied, the detail is not clear enough to allow a correlation with the well-defined corticopontine projection in order to describe a corticopontocerebellar somatotopy (52, 56).

2) *Nucleus reticularis tegmenti pontis.* Although some differences are to be expected between the NRTP and pontine neurons, a preliminary investigation has shown that the pyramidal tract activates NRTP neurons in essentially the same manner as the pontine neurons (181).

B. Inferior Olive

The inferior olive is divided into the principal nucleus and the dorsal and medial accessory nuclei. Portions of each of these nuclei serve as relays for cortically induced climbing-fiber responses (45, 167, 310).

The inferior olivary neurons receive excitation from the ipsilateral cerebral cortex with relatively long latencies of 8–9 ms (23) or 12.8 ms on the average (101, 102, 267). From the latencies of the climbing-fiber responses recorded in the cerebellum, conduction velocities of cortico-olivary fibers were calculated at 5–17 m/s, indicating that the climbing-fiber responses are mediated by the slow PT fibers (179). However, two discrepancies pose problems. Anatomical studies suggest that the cortex projects primarily to the contralateral inferior olive with only a modest number of terminals in the ipsilateral inferior olive (271), although the ipsilateral inferior olive receives the strongest excitation from the cerebral cortex (74, 101, 102, 109, 168, 218, 267). Also, a consideration of the conduction distance from the cerebral cortex to the inferior olive suggests that the PT fibers innervating the inferior olive conduct at less than 7 m/s if a monosynaptic connection exists (6, 23).

If the cerebral input to the inferior olive is mediated by slow PT fibers conducting up to 17 or 20 m/s, the observed latency of about 10 ms indicates that there is an additional synapse between the PT and the inferior olive (6). Furthermore, there is the observation by Cervetto et al. (74) that much of the cerebro-olivary pathway leaves the pyramidal tract at a rostral level of the brainstem. Thus, part of the cerebro-olivary pathway may be via the red nucleus (RN), which is excited by slow pyramidal fibers conducting up to 20 m/s (305) and is considered to project to the ipsilateral inferior olive (21, 131, 159, 207, 217, 219, 241, 314). This problem needs further investigation, using primarily electrophysiological techniques.

The neurons of the inferior olive are unique in that the duration of cortically evoked action potentials averages 12 ms (101). This potential consists of a short depolarization, during which the inside becomes positive, followed by a plateau at a transmembrane potential of -8 to -30 mV. Crill (101) has concluded that this delayed depolarization is due to action currents originating from spikes propagating into the dendrites. Llinás et al. (200, 201) have recently demonstrated an electrotonic coupling between the dendrites of the inferior olive neurons, which may contribute to the delayed depolarization as well as to the synchrony of neurons within the inferior olive. Superimposed on the delayed depolarization are secondary spikes that conduct along the climbing fibers to the cerebellum (24, 101). The initial EPSP evoked by cortical stimulation is followed by an IPSP lasting 80–100 ms (22, 101) that prevents the inferior olivary neurons from firing at rates greater than 10 Hz. No interneurons have been described within the inferior olive that could underlie this inhibition (45, 167). However, large reticular neurons around the perimeter of the inferior olive both send dendrites into the nucleus (42) and display discharge characteristics compatible with a role as inhibitory interneurons (201). By comparison with the pontine neurons, the inferior olivary neurons seem capable of transmitting only low-frequency information (6), but each of these signals is carried as a high-frequency burst that exerts an intense effect on its target neuron, the Purkinje cell (122).

Nearly all the olivocerebellar fibers cross the midline before entering the contralateral cerebellum through the restiform body (45). The olivocerebellar fibers are 1–5 μm in diameter and conduct at 4.7–23 m/s (122, 123). Thus, both the cortico-olivary and olivocerebellar links are relatively slow conducting, with the consequence that the cortico-olivocerebellar pathway is slow.

The principal nucleus projects to the cerebellar hemisphere, including the paramedian lobule, whereas the cortico-olivary inputs to the pars intermedia of the anterior lobe and vermis are relayed in the dorsal and medial accessory nuclei (45, 101, 102, 167, 192, 310). Although it seems doubtful that the cortico-olivary pathway is primarily direct, the few connections that are direct appear to be organized with a somatotopy consistent with the observed electrophysiological recordings (269, 271). Spinal inputs to the vermis and pars intermedia are relayed in the caudal portions of the dorsal and medial accessory olives (45, 167, 192), with the dorsal accessory olive serving as the more important spinal relay (22, 24, 101).

C. Lateral Reticular Nucleus

The lateral reticular nucleus (LRN) is located in the ventrolateral medulla immediately caudal to the inferior olive. The LRN is divided into a parvicellular portion, a magnocellular portion, and a subtrigeminal portion. Brodal et al. (62) have shown that only the magnocellular division receives a projection from the cerebral cortex, and this is restricted to the contralateral pericruciate region in the cat. The projection from the anterior sigmoid gyrus is much stronger than that from the posterior sigmoid gyrus. In contrast to the corticopontine projection, those authors were unable to find a somatotopical projection from the cerebral cortex. An even stronger descending input, primarily to the parvicellular division, comes from the contralateral red nucleus (RN) (90, 131, 206, 207, 220, 315), either as collaterals of rubrospinal fibers or as terminals of rubrobulbar fibers. Thus, cortico-LRN influences may be transmitted indirectly via a corticorubro-LRN pathway as well as directly.

Single-unit recordings from the LRN have demonstrated the lack of somatotopical organization in the cortico-LRN connections. Although the spinal inputs had been considered to terminate primarily in the parvicellular division, neurons responding to both cortical and nerve inputs are distributed uniformly throughout the magnocellular and parvicellular divisions (2, 254), with no apparent somatotopical distinction (254).

One surprise in the study of the LRN has been the finding that these neurons are relatively difficult to activate from the cerebral cortex (254; Kitai, DeFrance, Hatada, and Kennedy, personal communication). This may be why a large number of the LRN studies have been performed using chloralose-anesthetized animals (67–69, 98, 323) even though this has been shown to obscure the somatotopy (100).

LRN neurons are activated by cortical stimulation with latencies in the range of 1.8–20 ms (68, 98, 180, 254, 323). It has been shown that LRN neurons responding with latencies of 1.8–3.0 ms are activated monosynaptically by fast-conducting PT fibers and many of those responding at 3.0–5.4 ms are activated monosynaptically by slow-conducting PT fibers (180, 323). However, these appear to constitute a minority of the LRN neurons (68, 98). Presumably most neurons are activated indirectly, either via a corticorubro-LRN pathway or other polysynaptic pathways. Many of the LRN neurons activated from the cerebral cortex at the shorter latencies appear to be innervated in part by collaterals of corticospinal or rubrospinal fibers (323; K. Toyama, personal communication), thus receiving descending information as well as corticobulbar and rubrobulbar impulses.

One characteristic feature of the LRN responses to cortical (and nerve) stimulation is a strong inhibition that may follow the excitation or appear without preceding excitation. Rosén and Scheid (254) observed inhibition beginning as early as 6 ms after cortical stimulation, 4 ms later than the earliest excitation. Bruckmoser et al. (67), observing the differential effects of pyramidal tract lesions on cortically induced excitation and inhibition of LRN neurons, concluded that pyramidal pathways play a large role in the excitation but that the inhibitory in-

fluence is mediated by a nonpyramidal pathway passing through the midbrain in the trapezoid body region.

The strong inhibition exerted within the LRN might be expected to limit the ability of LRN neurons to transmit high-frequency information to the cerebellum. However, a study of cellular properties of the magnocellular division led Kitai, Kennedy, DeFrance, and Hatada (personal communication) to suggest that these neurons may be capable of following high frequencies (69).

The LRN projects through the ipsilateral restiform body to the cerebellum (46, 167, 178; Kitai, Kennedy, DeFrance, and Hatada, personal communication). Brodal and Jansen (46, 167) concluded that both the parvicellular and magnocellular divisions project to the whole ipsilateral hemicerebellum except the flocculus and nodulus, which receive input from the subtrigeminal division. They concluded that the parvicellular division projects primarily to the vermis and the magnocellular to the pars intermedia and lateral zone, although none of their lesions was restricted to the lateral zone. Field-potential analyses demonstrate that one-half of the early cortical input to vermis and pars intermedia is mediated by the restiform body and presumably is an LRN projection (4; Allen and Ohno, manuscript in preparation). However, this early cortical input via the LRN is much less to the cerebellar hemisphere—25% and 0% to the medial crus I and the lateral crus II, respectively. Recently, Clendenin et al. (82) have shown that very few LRN neurons project to the cerebellar hemisphere. Therefore, it is likely that the magnocellular division projects primarily to the intermediate zone of the cerebellum, including the paramedian lobule.

D. Other Relay Nuclei

Other brainstem nuclei that receive cortical inputs and project to the cerebellum, making small contributions to the cerebrocerebellar pathways, are the PMRN, the PHN, and the external cuneate nucleus (89, 270). The PMRN and PHN project to vermis and pars intermedia of the anterior lobe, as well as to lobules VIII and IX (55, 291). These fibers enter the cerebellum through the restiform body, with slightly more than half the fibers projecting ipsilaterally (55, 291). The ventral subdivision of the paramedian reticular nucleus receives from the sensorimotor cortex bilaterally but without apparent somatotopy (270). The PHN and dorsal subdivision of the PMRN are innervated by the face sensorimotor area (coronal gyrus) bilaterally (270), suggesting they are related to control of the tongue (47, 270, 291). The cerebral projections to the PMRN and PHN appear to be scanty, and the most important descending inputs come from undetermined pontomesencephalic and subcortical structures, respectively (47, 51, 270). These nuclei still await physiological investigation (273). Cooke et al. (89) have suggested that some neurons of the exteroceptive component of the cuneocerebellar tract (CCT) are excited from the forelimb sensorimotor cortex. However, a more thorough study is necessary in order to determine the significance of this pathway. There are many other potential long-latency cerebrocerebellar loops—for example,

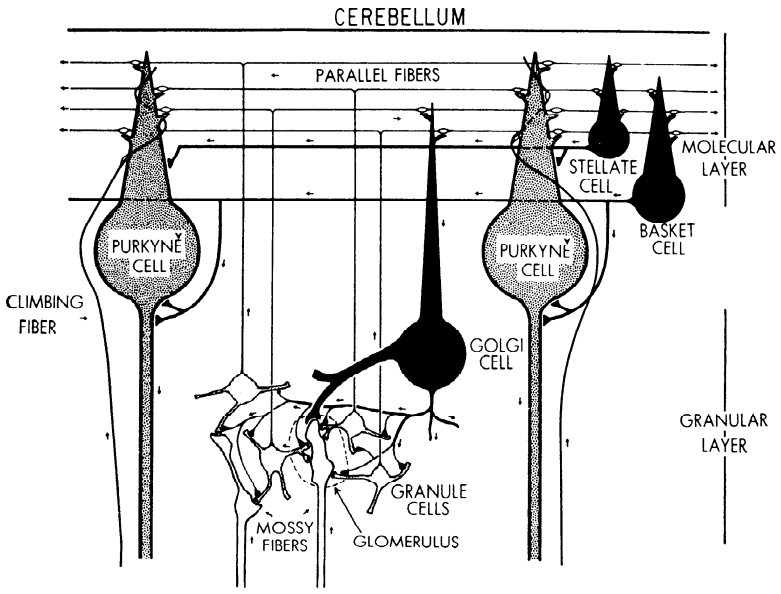

FIG. 2. Diagrammatic representation of neuronal connections within cerebellar cortex. Basket, stellate, and Golgi cells are inhibitory. Diagram illustrates a section along folium. Basket and stellate cells send their axons perpendicular to direction of parallel fibers, synapsing on a band of Purkinje cells. [Modified from Eccles (118).]

corticospinal activation of spinocerebellar and spinoreticular tract neurons (reviewed in 89).

IV. CEREBELLAR CORTEX

A. Neuronal Organization

The organization of the elements within the cerebellar cortex has been extensively reviewed by Eccles et al. (122); although the numerical relationships have been recomputed by Palkovits et al. (235–238), the basic idea of cerebellar cortical operation remains the same (120). Briefly, the mossy fibers and climbing fibers exert their influences on the Purkinje cell in different manners (Fig. 2). The climbing fiber, after branching deep in the white matter of the cerebellum (26, 27, 142), innervates approximately 10 Purkinje cells (134, 221, 222) by forming hundreds of synapses on the dendritic tree of each (122). This synaptic arrangement makes the climbing fiber-Purkinje cell synapse one of the most potent in the central nervous system. A discharge in the entering climbing-fiber axon can lead to an intense depolarization of the Purkinje cell (122, 123) and 1–5 spikes are propagated down the Purkinje cell axon (164). The distribution of the climbing-fiber branches from a given olivary neuron appears to be distributed in the sagittal plane so the Purkinje cells in the anterior lobe and posterior lobe receive the same climbing-fiber information (25–27, 142). On the other hand, there is a tremendous

divergence and convergence within the mossy-fiber input so that on the average each mossy fiber innervates 460 granule cells, and many thousands of mossy fibers ultimately influence each Purkinje cell via the 80,000 parallel fibers synapsing on its dendritic tree (235–238). In addition to the excitatory effects through the mossy fiber-granule cell-Purkinje cell channel, the mossy-fiber input exerts a lateral feed-forward inhibition via the basket cell and a feedback disfacilitation of the Purkinje cell input via the Golgi cell inhibition of granule cells (122). These connections within the cerebellar cortex for the mossy-fiber system allow the discrimination of a multitude of different input patterns (205). The Purkinje cell can respond to an input from the cerebral cortex with all gradations of excitation, inhibition, or both. The information-processing capabilities that these connections give to the mossy-fiber system have been described in detail by Marr (205), Eccles (120), and Sabah (257). Thus in contrast to the single climbing fiber with a strong influence on the Purkinje cell, there is a large number of mossy fibers each with a very weak, almost insignificant, influence on the Purkinje cell. And yet, while the climbing fiber activates the Purkinje cell only 1–4 times/s, the remainder of the Purkinje cell's 20–40/s spontaneous discharge rate is due to the constant bombardment via the mossy fibers.

B. Input Fibers

Both the pontine and LRN axons form mossy-fiber terminals synapsing upon the granule cells (35, 264). Each granule cell on the average has four dendritic "claws," each one receiving a different mossy fiber (122). In order for a granule cell to be excited to discharge an impulse, it must be bombarded by two or more of the mossy-fiber impulses in near synchrony (4, 129). This requirement is the basis of the demonstration that mossy fibers from the pons and LRN tend to converge onto common granule cells in the pars intermedia (4). It is likely that these respective mossy fibers convey different aspects of the cerebral information. Nevertheless, they cooperate in the activation of the granule cells. Szentágothai had previously described that, for the spinal inputs, the spinocerebellar or "specific" fibers terminate on the lower granule cells whose parallel fibers synapse on the lower portion of the Purkinje cell dendritic tree close to the soma and that the "nonspecific" or LRN fibers terminate on the granule cells synapsing on the Purkinje cell's distal dendrites (122). This suggested that the LRN fibers provide a background upon which the "specific" fibers can influence the Purkinje cell (122; S. T. Kitai, personal communication). For the portion of LRN neurons carrying the fast mossy-fiber input to the cerebellum, this cannot be true (see also 264). However, these neurons represent a small fraction of the LRN (see sect. III*C*). It may be necessary, therefore, to consider the LRN as being in part a "specific" relay and in part "nonspecific". It is interesting that the specific cerebrocerebellar pathways (pontine, inferior olivary) are organized strictly somatotopically and are crossed, whereas the nonspecific pathways (NRTP, LRN, PMRN, PHN) carry less somatotopical information and integrate information from the ipsilateral cerebral cortex as well as the contralateral cortex (55, 62, 67, 97, 98, 270, 291).

In this way, there is apparently cooperation between the specific mossy- and climbing-fiber systems of the cerebrocerebellar pathway and a tendency for the nonspecific mossy-fiber systems to cooperate with the specific systems.

C. Purkinje Cell Responses

Purkinje cells respond to cortical inputs via the mossy-fiber system by a short-latency single spike discharge with a latency of 4–8 ms (6), which is due to the mossy fiber-granule cell-Purkinje cell linkage. A second type of response is an inhibition at 8–12 ms. Presumably this is due to a mossy fiber-granule cell-basket cell-Purkinje cell linkage, although this may be due in part to a Golgi cell inhibition of the background granule cell excitation of the Purkinje cell, leading to a disfacilitation. A given Purkinje cell response to cortical stimulation may include the excitation and/or inhibition, depending on the cortical area stimulated (6, 7). This suggests that there is a fine pattern within the cerebrocerebellar pathway and that some Purkinje cells may be "on beam" to a specific mossy-fiber input while others are "off beam."

The Purkinje cell is activated through the climbing-fiber system at a latency of 12–20 ms (6, 144, 218) with the characteristic climbing-fiber response consisting of 3–5 spikes. In contrast to the mossy-fiber input, the climbing-fiber response fluctuates widely in latency from one stimulus to the next.

The mossy-fiber responses (excitation and inhibition) have a lower threshold to cortical stimulation than does the climbing-fiber excitation (6, 179). The mossy-fiber responses are elicited by a single shock, are increased by a second shock (at an interval of 2 ms), but are not influenced by adding a third shock to the train. On the other hand, the climbing-fiber response is difficult to elicit without two shocks and increases with the addition of a third shock to the train. The mossy-fiber excitation follows repetitive stimulation up to 70 Hz; the climbing-fiber response fails between 5 and 20 Hz (6). These properties are all consistent with those observed for the precerebellar relay nuclei and suggest that the mossy-fiber system is capable of transmitting high-frequency information.

D. Purkinje Cell Integration

Systematic recordings from Purkinje cells in the pars intermedia of the anterior lobe in cats have demonstrated that neurons in lobules III and IV receive mossy- and climbing-fiber inputs primarily from the hindlimb area of the sensorimotor cortex (7). Likewise, Purkinje cells in lobule V (and apparently VI) respond to mossy- and climbing-fiber inputs from the forelimb area of the sensorimotor cortex. Furthermore, the nerve inputs follow the same somatotopy (7, 127, 147). Within this overall scheme, one response pattern may be elicited by a given cortical point, another pattern by a different cortical point, and still other patterns by individual peripheral inputs (7). From this study, as well as other studies of natural cutaneous stimulation (125–127), it is clear that the individual Purkinje cell

performs an independent computation on a specific subset of the inputs available to it (116, 117, 120, 121).

Although the somatotopy of the input to the paramedian lobule has not been studied at the single-unit level, evoked-potential studies suggest a similar projection pattern, but with the forelimb sensorimotor cortex represented anteriorly (lobule VIIB) and the hindlimb cortex posteriorly (lobule VIIIA). In addition, the paramedian lobule receives inputs from anterior ectosylvian gyrus, anterior portions of lateral and suprasylvian gyri, orbital gyrus, and presylvian gyrus (168). Although these inputs have not been specifically checked to the pars intermedia of the anterior lobe in as great detail, it is likely that some of these areas also project there (144).

Single-unit recordings from crura I and II of the cerebellar hemisphere have shown that individual Purkinje cells integrate inputs from several areas of cerebral cortex, especially nonprimary or association areas, including medial wall of anterior sigmoid gyrus (area 6), proreate gyrus, orbital gyrus, ectosylvian gyrus, and presylvian gyrus in the cat (Allen and Ohno, manuscript in preparation), which is in agreement with the earlier evoked-potential studies (168). There is a clear tendency for the medial wall anterior to the cruciate sulcus to project to lateral crus II and for the lateral anterior sigmoid gyrus to project to medial crus I in a manner similar to the adjacent lobulus simplex. Orbital, presylvian, and anterior ectosylvian gyri send inputs to all portions of crura I and II.

A systematic single-unit study of the dorsal and ventral divisions of paraflocculus has not been performed. However, in evoked-potential studies, Jansen (168) described inputs to the posterior dorsal paraflocculus from lateral anterior sigmoid close to the presylvian gyrus, anterior ectosylvian gyrus, medial wall of prorcate gyrus, and anterior portion of lateral gyrus. Weak potentials were evoked in the anterior part of dorsal paraflocculus from middle suprasylvian and orbital gyri. Weak inputs to the ventral paraflocculus were only obtained from the lateral anterior sigmoid gyrus close to the presylvian gyrus.

The somatotopical organization to the vermis is not as neat as it is to the pars intermedia. Near the midline, the forelimb area of the pericruciate sensorimotor cortex projects to lobule V and the hindlimb area to lobules II–IV. However, near the paravermal vein, which separates the vermis from the pars intermedia, the hindlimb input projects to lobules II–V (243; Allen, Azzena, and Ohno, manuscript in preparation).

This summary of the somatotopy within the cerebrocerebellar projections is abbreviated and the reader is urged to consult the review of Evarts and Thach (141) for additional detail.

Because evoked potentials tend to overestimate the significance of a given input, it will be necessary to refine the somatotopical projection with single-unit studies of Purkinje cell responses. However, from the information now at hand, it seems possible to conclude that there is a strict forelimb-hindlimb somatotopy from cerebral cortex to intermediate zone, whereas there is a large convergence of inputs onto the lateral zone, apparently with less somatotopy. This appears to hold true for both cat and monkey (109, 112, 168).

V. CEREBELLAR NUCLEI

A. Synaptic Organization

The Purkinje cell, the only output element of the cerebellar cortex, inhibits the neurons of the cerebellar nuclei (122, 165). Each nuclear neuron probably receives terminals from up to 200 Purkinje cells or more (see sect. IX*B*). In addition, some of the cerebellar afferents provide excitatory collaterals to the nuclear neurons.

The responses of interpositus and dentate neurons in cat to stimulation of the contralateral cortex can be generalized into several components: a relatively weak early excitation (E_1) at 4–6 ms, inhibition (I_1) at 7–10 ms, a strong long-lasting excitation (E_2) at 11–15 ms, inhibition (I_2) at 18–28 ms, and a rebound at 30–50 ms (5; Allen, Azzena, and Ohno, manuscript in preparation). The presence and size of each component depend on the cortical area stimulated and vary from one neuron to another. The late excitation is the most common component and the early excitation is the rarest.

The initial excitation-inhibition sequence can be attributed to the early pontine and LRN inputs to the pars intermedia and the pontine inputs to the hemisphere. The early excitation would be due to collaterals of these mossy fibers to the interpositus and lateral nuclei and the subsequent inhibition to the Purkinje cell discharge with a latency of 4–8 ms. Lesions of individual cerebellar peduncles suggest that the early excitation of the interpositus neurons, when it occurs, is primarily transmitted by the LRN fibers traveling in the restiform body. One curious feature is that there is a dearth of excitatory collateral action from the short-latency "specific" mossy fibers via the pons for the cerebral input and from the dorsal spinocerebellar tract/cuneocerebellar tract (DSCT/CCT) for the spinal input (121, 124).

For the late excitation-inhibition sequence, the inhibition should be due to the activation of Purkinje cells by climbing fibers and also by mossy fibers presumably of LRN origin. Using Deiters' nucleus as a model to study cerebellar nuclear integration, Allen et al. (12) showed that the climbing fibers from both forelimb and hindlimb provide excitatory collaterals to most Deiters' neurons, but that the Purkinje cell-induced inhibition is specific to either the forelimb or hindlimb. Eccles et al. (128) concluded from a study of nerve inputs to fastigial neurons that excitatory collaterals from the LRN are in part responsible for the late excitation and provide a nonspecific excitation of the nuclear neurons which the Purkinje cells modulate. In a similar study of interpositus, they concluded that the LRN plays a less important role and that other relay nuclei may provide collateral excitation (J. C. Eccles, I. Rosén, P. Scheid, and H. Táborík̀ová, personal communication). Intracellular studies of dentate neurons in the cat showed that a large portion of the late excitation from cortex is disinhibition (165; Allen and Ohno, manuscript in preparation). The remainder is presumably due to climbing-fiber collaterals (213; E. Mugnaini, personal communication) and perhaps to a lesser extent to LRN collaterals.

Although the collaterals of the cerebropontocerebellar pathway exert insignificant excitation on nuclear neurons, stimulation of the brachium pontis does evoke a short-latency excitation in a small fraction of interpositus and dentatus neurons (304; Allen, Azzena, and Ohno, manuscript in preparation). Using the Nauta method, Mugnaini (personal communication) has found degeneration in the interpositus nucleus after brachium pontis lesions, whereas transection of spinocerebellar pathways led to less significant degeneration (cf. 214). Pending electron-microscopic confirmation, these observations may suggest that the pontocerebellar fibers send a few collaterals to interpositus and lateral nuclei. An attractive alternative is that the NRTP, whose axons also pass through the brachium pontis, sends collaterals to the cerebellar nuclei (299) and so serves as the cerebral equivalent of the LRN. As a generalization, it can be postulated that collaterals from the "reticular" mossy-fiber relay nuclei innervate the cerebellar nuclei and that the "specific" mossy fibers largely bypass the cerebellar nuclear neurons on the way to the cerebellar cortex. It should be noted that in addition to the collaterals the inputs to the cerebellar nuclear neurons may include fibers specifically terminating within the cerebellar nuclei. Although there may be some somatotopic pattern in the activation of nuclear neurons by collaterals of reticulocerebellar fibers, it is probable that the collaterals in general provide a nonspecific drive which the Purkinje cells can modulate down by inhibition or up by disinhibition.

Within interpositus and lateral nuclei, small interneurons have been described that are innervated by collaterals of larger cerebellar nuclear neurons giving rise to the efferent fibers and also by cerebellar afferents (77–81, 215). These interneurons, in turn, synapse upon the somata and dendrites of the large cerebellar nuclear neurons. Based on the elliptical synaptic vesicles of these interneurons, Chan-Palay (80) has suggested that they are inhibitory interneurons. In the preceding description, it was not necessary to invoke interneuronal mechanisms to explain any of the observed responses (172, 255). However, these interneurons may make secondary contributions to the responses of the nuclear neurons and their role should be considered more carefully in future experiments.

B. Corticonuclear Projection

The cerebellar cortex can be laid out in more-or-less longitudinal strips that project onto their own cerebellar nuclei (192, 313). These strips do not necessarily correspond with the medial, intermediate, and lateral zones of Jansen and Brodal (166) and Chambers and Sprague (75, 76), but may intercept two of these zones. For example, different portions of the paramedian lobule may project to different regions in the interpositus and lateral nuclei (93, 313). The vermis projects to fastigial and most of the ansiform and paraflocculars lobules project to the lateral nucleus (49, 313). For a more detailed description of the corticonuclear projection, the reader is referred to the recent review by Jansen (192).

C. Nuclear Integration

The somatotopical projection from the cerebral cortex to interpositus is not as clear as it is to the Purkinje cells of the pars intermedia. Some interpositus neurons receive inputs restricted to the forelimb or hindlimb areas of the sensorimotor cortex. However, the great majority of interpositus neurons receive converging inputs from the forelimb and hindlimb cortical areas. The early excitation and inhibition are more restricted to a single limb than are the late excitation and inhibition. The late excitation shows the most convergence. This suggests that the afferents underlying the late input to the cerebellum (E_2 and I_2) carry less somatotopically restricted information than the afferents underlying the early input. Furthermore, there is apparently more forelimb/hindlimb convergence onto interpositus within the afferent collateral connections than within the corticonuclear projection. Since interpositus is the final output for the intermediate zone of the cerebellum, there is a question whether the output from that zone can mediate the integrative control of a single limb. Even though interpositus neurons display less somatotopical sharpness than Purkinje cells, the strongest cortical and peripheral inputs still represent the same limb in 74% of the neurons (5). Furthermore, localized stimulation of the pars intermedia is known to have a specific effect on one limb (reviewed in 114). It may be assumed that information specific to a certain limb can pass through the interpositus nucleus, even if a lesser degree of specificity exists than is present for the Purkinje cell. Eccles et al. (130) have shown that with peripheral inputs the somatotopy present at the level of interpositus is preserved through the next relay, the red nucleus.

A different kind of convergence occurs upon the dentate neurons. Individual neurons in the cat may respond to inputs from the supplementary motor area, the secondary somatosensory area, the presylvian gyrus, and the orbital gyrus, in addition to portions of the sensorimotor cortex (10; Allen and Ohno, manuscript in preparation). As with interpositus, there appears to be convergence within both the afferent inputs to dentate neurons and the corticonuclear projections. There are regional differences in the responses of dentate neurons to the different cerebral inputs. Similar results have been observed in the monkey. Individual dentate neurons may respond to inputs from the premotor area, supplementary motor area, prefrontal area, and in many cases to motor and somatosensory cortex (Allen, Gilbert, and Yin, manuscript in preparation). The significance of each of these cerebral areas projecting to dentate is not clear. What is clear is that dentate nucleus (DE) integrates the signals from much wider areas of cerebral cortex than does interpositus. And it is likely that each of these areas is in some way concerned with movement.

VI. CEREBELLOCEREBRAL PATHWAYS

All three cerebellar nuclei have influences on the cerebral cortex. The main ascending bundle is the brachium conjunctivum, which carries the axons of the

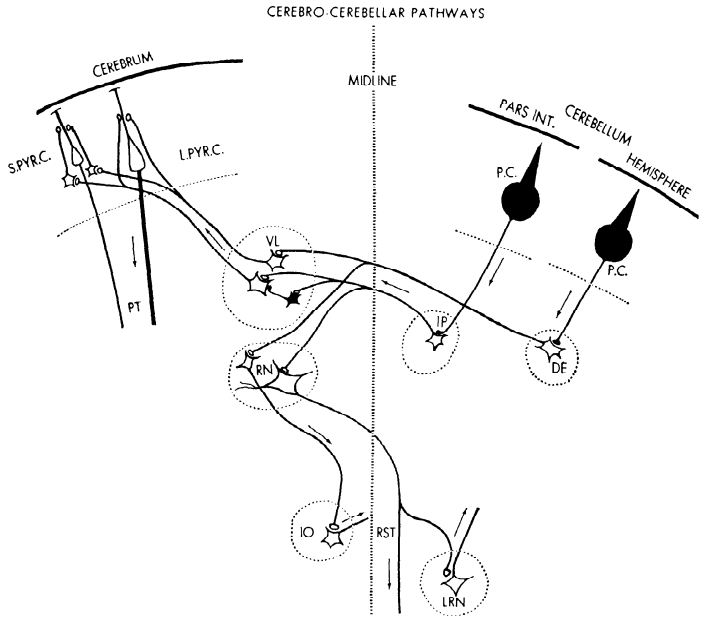

FIG. 3. Pathways from cerebellum to cerebrum. Most important linkages are shown from pars intermedia and hemisphere of cerebellum to cerebral cortex and through red nucleus. Same conventions are used as in Fig. 1. [Modified from Eccles (118).]

interpositus and lateral nuclei to the contralateral thalamus and RN (Fig. 3). The largest projection is to the ventrolateral nucleus of the thalamus (VL) (reviewed in 192), which provides the major thalamic input to the motor cortex (258, 259, 309). Anatomical and physiological studies have shown a significant projection to the ventral anterior nucleus of thalamus (VA) and have suggested weaker projections to other nuclei, such as ventral medial nucleus of thalamus (VM), ventroposterolateral nucleus of thalamus (VPL), centralis lateralis, and zona incerta (17, 20, 84, 85, 208, 259, 262, 312; reviewed in 18, 192).

The interpositus and lateral nuclei also project to the RN (18, 91, 145, 192, 209). The anterior and posterior interpositus nuclei terminate mainly in the caudal, magnocellular division, which gives rise to the crossed rubrospinal and rubrobulbar tracts; the dentate axons terminate in the anterior, parvicellular division, which gives rise to the uncrossed rubro-olivary tract (131, 207, 217). These distinctions within the RN are clearest in the primate, but are also evident to some degree in lower species. It has been argued that the anterior RN gives rise to a rubrothalamic tract, forming a dentatorubrothalamic pathway (43, 86, 209). Some of these experiments, however, were inconclusive because stimulation or lesions within the anterior RN also affect the many cerebellothalamic fibers passing near or through the RN (204). Other experimental results are not so easily dismissed (37, 43). However, Anderson (16) reported that none of the rubral neurons she recorded from could be activated antidromically from the thalamus.

By injecting radioactive leucine into the RN and by using autoradiographic techniques, Edwards (131) has shown that there is no significant projection to the thalamus. In light of these findings, the possibility of a physiologically important dentatorubrothalamic pathway seems remote (also 241).

The fastigial nucleus has also been reported to project to the ventral thalamic complex (VL/VA) via the ascending limb of the uncinate fasciculus (19, 175, 192), but these projections appear to be rather weak compared to that from interpositus and dentate. However, fastigial fibers traveling in the uncinate fasciculus terminate in the pontomedullary reticular formation (192), from which fibers can be traced to the intralaminar thalamic nuclei (229), in particular the centromedian nucleus/parafascicular nucleus (CM/Pf) complex (265). The CM/Pf complex is capable of inhibiting the transmission through VL (83, 244). Thus, the fastigial nucleus may be capable of modulating the cerebellocerebral transmission.

A. Red Nucleus

Toyama et al. (295, 296) and King et al. (176) have shown that the vast majority of the interpositorubral endings are collaterals of the interpositothalamic fibers (Fig. 3). Because considerable work has been done on the interpositorubral connection, this system may partly serve as a model for the cerebellothalamic connection.

Intracellular recordings from the red nucleus reveal a monosynaptic EPSP elicited from the contralateral interpositus nucleus. The EPSP elicited through this interpositorubral connection has a fast rising phase, with a time to peak of 0.4 ms and large unitary EPSPs of 0.8 mV, suggesting a somatic origin for the EPSP (295). Recent electron-microscopic studies of the interpositorubral connections in the opossum, rabbit, and cat have revealed that the interpositus axons form synapses on the soma and proximal dendrites of large rubral neurons (176, 227).

Examination of unitary EPSPs reveals that there is no failure of transmission when they are evoked by stimulating a single interpositus axon at low stimulus rates. With a compound EPSP, there is no facilitation or depression when tested at repetition rates of 1–200/s or when tested with double shocks at intervals down to 3 ms (295). These observations suggest that the interpositorubral synapse provides a very stable, constant transmission and is capable of transmitting high-frequency information (16, 104, 295).

B. Thalamus

After stimulation of the cerebellar nuclei or the brachium conjunctivum, EPSPs are evoked monosynaptically in VL thalamic neurons (244, 309). The EPSP elicited through the cerebellothalamic connection reaches its peak in 1.3 ms and has unitary EPSPs of 0.8–3.2 mV (309). However, by comparison with

the EPSPs elicited in neurons of the RN, those evoked in thalamic neurons are slightly slower. Electron-microscopic studies have indicated that the cerebellothalamic fibers form very few synapses on the somata but that the majority are formed on the proximal dendrites (154, 155, 290; J. A. Rafols, personal communication). The EPSP is not facilitated or depressed when two volleys are delivered at intervals as short as 1 ms (309). These synaptic properties provide a high efficacy of synaptic transmission for the cerebellothalamocortical pathway. It has been shown that VL spikes can follow stimulus rates as high as 100 Hz (274).

Uno et al. (309) reported that the monosynaptic EPSP could be evoked from either interpositus or dentate, but that a disynaptic IPSP could be evoked in some neurons only from interpositus (Fig. 3). In the glomerulus that cerebellar endings form in VL, there are processes of intrinsic neurons that receive synapses from the large cerebellar endings and form synapses with flattened vesicles upon the dendrites of VL neurons (154, 155; J. A. Rafols, personal communication). Presumably these neuronal connections underlie the disynaptic inhibition from the cerebellar afferents. Later IPSPs followed in most neurons (309), which were thought to result from the recurrent inhibitory mechanisms described by Eccles (115) and Purpura (244) for the ventrobasal complex.

VII. CEREBRAL CORTEX

A. Neuronal Organization

The cerebral cortex to which the cerebellothalamocortical pathway projects, i.e., primarily the precruciate in the cat and the precentral in the primate, has the same basic neuronal organization as other cerebral areas. The output neurons of the cerebral cortex, the pyramidal cells, have their cell bodies in the third and fifth layers of this six-layered structure, but their apical dendrites extend through the remaining cortical layers to the surface, as shown in Figure 4. The semidiagrammatic drawing of Figure 4 is based primarily on anatomical studies (reviewed in 278). However, the recent intracellular study of the neuronal circuitry in the visual cortex by Toyama et al. (294) provides a physiological confirmation for some of these connections. Small to large pyramidal neurons lie in layer III and small to giant pyramidal neurons lie in layer V. Although the giant pyramidal or Betz cells are impressive by their size, they make up only a few percent of the corticofugal fibers [about 3% (194)]. Towe et al. (293) have concluded, from electrophysiological studies, that the larger, fast-conducting pyramidal fibers arise from neurons in layer V and the smaller, slow-conducting pyramidal fibers arise from layer III. Naito et al. (225) have concluded that the fast- and slow-conducting PT fibers both arise from layer V. This conclusion would be consistent with the results of Toyama et al. (294) in the visual cortex, where they have shown that the pyramidal cells in layer V give rise to the corticofugal efferents, whereas those in layer III are the association and commissural efferent cells. The

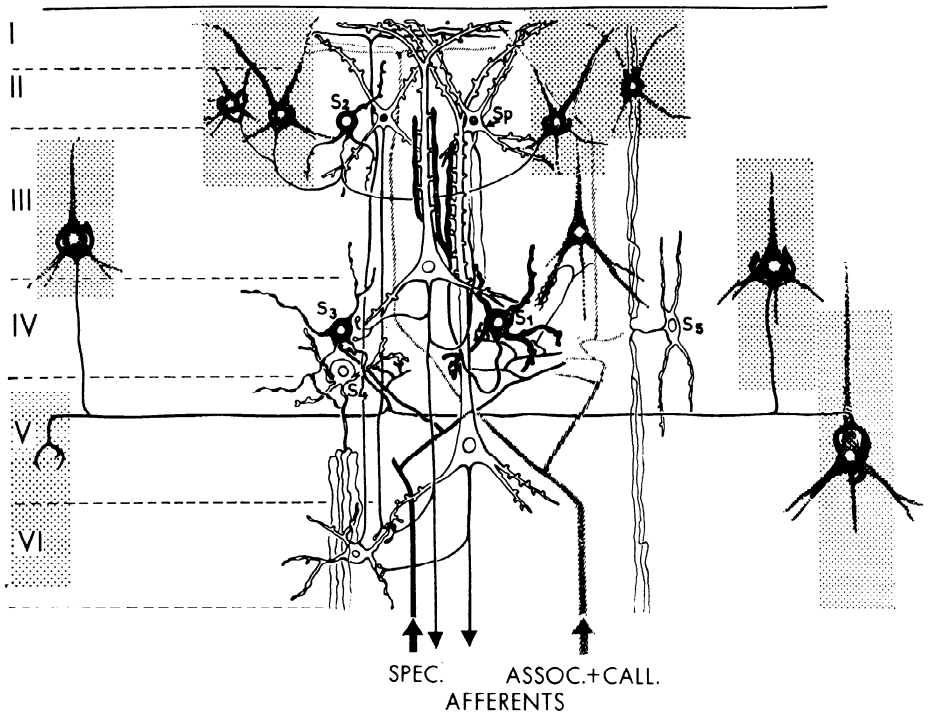

FIG. 4. Semidiagrammatic drawing of most important cell types of cerebral cortex. Two pyramidal cells are placed centrally in layers III and V. Connections of specific afferents are contrasted with those of association and callosal afferents. Three types of stellate cells (S_1, S_4, S_5) in layer IV exert an excitatory influence in vertical direction. Stellate interneurons of type S_1 exert relatively powerful synaptic connections with pyramidal neurons via cartridge synapses established around apical dendrites. Stellate cells S_2 and S_3, in layers II and IV, respectively, form pericellular endings laterally and are presumed to be inhibitory. Star-pyramidal cells (Sp) are shown in layer II. [From Szentágothai (278).]

specific afferent fibers synapse profusely upon the stellate-shaped interneurons of layer IV and also directly upon the basal or apical dendrites of the pyramidal neurons (not shown). The excitatory stellate neurons (S_1, S_4, S_5) primarily exert their influence in the vertical direction, acting on the pyramidal cell dendrites and the stellate cells of layers II, IV, and VI. The inhibitory stellate cells (S_2, S_3) of layers II and IV exert their influence in a horizontal direction. Those of layer IV may send processes up to 500 μm laterally, forming their synapses on the somata of pyramidal cells and also synapsing upon the excitatory interneurons of layer IV. These inhibitory interneurons of layer IV may also be innervated by recurrent collaterals of the pyramidal cells. Although layer IV is much thinner in the motor cortex (277), it is likely that the stellate cells of this layer operate in a similar way as those of sensory cortex.

These neuronal connections provide a basis for the columnar organization of the cerebral cortex. This same columnar organization, which has been well de-

scribed for primary sensory cortex (reviewed in 66), has recently been demonstrated for the motor cortex by Asanuma and coworkers (29, 31–33). All neurons in a column 0.5–2.0 mm in diameter are related to one muscle group. For example, one column may be related to thumb flexion, another to thumb extension, etc. (31). Adjacent columns, often with antagonistic actions, can inhibit each other via the lateral inhibitory mechanism shown in Figure 4.

B. Cortical Afferents

The specific thalamic afferents to the motor cortex arise from the VL nucleus and terminate in layers III and IV, synapsing upon neurons in layers III–V as shown in Figure 4 (also 277). Nonspecific thalamic afferents arise from the association nuclei of the thalamus (lateralis posterior and pulvinar) and the nonspecific or intralaminar nuclei (278). In addition, callosal afferents arrive from the corresponding region of the contralateral motor cortex (30, 240, 281). Corticocortical afferents impinge upon the motor cortex from the primary somatosensory area (171, 239), the secondary somatosensory area (171, 239), and the supplementary motor cortex, area 6 (110, 240, 319). The nonspecific thalamic, callosal, and association cortical afferents terminate primarily in layers III–VI, but also in layers I and II (157, 228). Nauta (228) noted that these afferents terminate near the pyramidal cell soma much less frequently than do the specific thalamic afferents.

Stimulation of VL elicits a monosynaptic EPSP in the fast-conducting pyramidal neurons at 1.4–1.7 ms (14, 152, 321). Later EPSPs were found in both fast and slow groups of pyramidal neurons, presumably due to disynaptic and polysynaptic linkages through the stellate cells of layer IV (Fig. 3). In addition, collaterals of slow pyramidal neurons exert a monosynaptic excitatory action upon fast pyramidal neurons (281). The EPSPs evoked in fast and slow pyramidal cells by VL stimulation are followed by long-lasting inhibition, presumably due to disynaptic (294) or trisynaptic feed-forward inhibitory mechanisms and recurrent inhibition (132, 321). Recurrent inhibitory influences are exerted by slow-conducting PT neurons onto both fast and slow neurons, but from fast-conducting PT neurons only onto fast neurons (132).

In contrast to the specific afferents, Toyama et al. (294) have shown that the callosal afferents monosynaptically excite neurons in layers II–VI. However, other electrophysiological studies and laminar-field analyses indicate that the nonspecific thalamic, callosal, and association afferents primarily exert their influences on the pyramidal neurons in the superficial layers of the cortex either monosynaptically or disynaptically. Stimulation of the nonspecific nuclei produces an EPSP of slow time course in cortical neurons (95, 96, 182, 183, 197, 203, 224, 245). Nacimiento et al. (224) demonstrated that EPSPs induced by stimulation of the CM have latencies of 5–20 ms, a time to peak of 15–50 ms, and a duration of 50–100 ms.

Creutzfeldt and Lux (94) have shown by injection of current through the microelectrode that the amplitude of the VL-evoked EPSP changes linearly as a

function of the membrane potential (also 245). On the other hand, the EPSP evoked from the nonspecific thalamic nucleus, CM, does not change systematically with the change of the membrane potential. Thus it may be concluded that the nonspecific afferents synaptically excite the distal portion of the apical dendrites of pyramidal cells, while the specific afferents form synapses on the proximal dendrites of pyramidal cells. This hypothesis is in agreement with the results of laminar-field analysis by Spencer and Brookhart (272). Within this tendency for nonspecific, association, and callosal afferents to terminate distally on PT cell dendrites, there may be differences among the different populations of PT neurons, which can only be worked out electrophysiologically. Thus, the EPSP induced by the callosal afferents has a time to peak of 1.3 ms in fast PT cells and 14 ms in slow PT cells (226). Although the callosal afferents apparently terminate more distally than the specific afferents for both groups of PT neurons, the callosal input to the slow PT neurons appears to be distributed even more distally than to the fast PT neurons.

With repetitive stimulation of the specific and nonspecific thalamic nuclei, the EPSPs in the PT neurons increase in the manner of the augmenting and recruiting responses, respectively (96, 152, 245).

Intracellular studies have shown that the fast and slow PT neurons have different membrane properties as well as synaptic properties (234, 280). Slow PT cells have a lower threshold to intracellularly applied current and show less adaptation to rectangular currents (185). The fast-conducting PT cells accommodate more rapidly to linearly rising currents. However, the rate of impulse discharge to applied current is much more sensitive to current strength for the fast PT cells (184). These membrane properties may be responsible for the fact that fast-conducting PT cells discharge phasically, whereas slow-conducting PT cells discharge tonically (135).

C. Pyramidal Cell Integration

Stimulation of the cerebellar nuclei or brachium conjunctivum has confirmed that the cerebellothalamocerebral pathway is capable of activating the pyramidal neurons (73, 83, 158, 198, 321). Yoshida et al. (321) have shown that the fast-conducting PT neurons are excited disynaptically at 2.7–3.5 ms after stimulation of the brachium conjunctivum, which just allows for the relay in the VL thalamus. In contrast, the slow-conducting PT neurons are excited trisynaptically because the thalamocortical signals first synapse upon the excitatory stellate cells of layer IV and are then relayed to the small pyramidal cells (Fig. 3).

Sasaki and coworkers (259, 263) and Massion and coworkers (211, 212, 250, 251) have performed the most careful mappings of the cerebellum upon the cerebral cortex. Sasaki's group has stimulated the fastigial, interpositus, and lateral cerebellar nuclei of the cat and mapped the evoked potentials onto the frontal, parietal, and nearby mesial regions of the cerebral cortex (259, 263). They found responses only for stimulation of interpositus and lateral nuclei. Since interpositus has more neurons than lateralis in the cat (Table 1), interpositus stimulation evoked a larger

response, but the projection pattern was the same for both nuclei. In the cat, these two nuclei project primarily upon the anterior sigmoid gyrus or motor cortex and upon the middle suprasylvian gyrus, which is considered to be an association cortex of the parietal region. In contrast to the specific thalamocortical afferents to the anterior sigmoid gyrus that relay in VL and terminate in layers III–IV, the input to the parietal cortex relays in VA, is later by about 2 ms, and synapses in the superficial layers of the cortex. Although these two thalamocortical systems apparently underlie the augmenting response of the anterior sigmoid and the recruiting response of the suprasylvian, respectively, stimulation of interpositus or lateralis at 5–12 Hz does not lead to the augmenting or recruiting response (259; but see 143).

Massion and Rispal-Padel (211) have recorded evoked potentials from an array of electrodes in the anterior and posterior sigmoid gyri while stimulating the cerebellar nuclei. Based on Woolsey's map for motor function in the cat (320), they concluded that fastigial and lateral nuclei project to the motor area controlling axial and proximal muscles and that the interpositus nucleus projects to the motor area related to the proximal and distal musculature. In related studies they have shown that the topography of the thalamocortical projection supports this conclusion (250). Rispal-Padel et al. (250) and Strick et al. (275, 276) have shown that this concept needs some modification because a restricted region of the VL can reach a relatively wide zone of the motor cortex.

This question of the somatotopy in the cerebellocerebral projection, which relates to the roles of the cerebellar nuclei in regulating the proximal and distal musculature, is important in understanding the role of the cerebellum in controlling movement. For such a crucial question, these experiments should be performed in the monkey, with its well-developed motor cortex, and single-unit recordings should be performed on PT neurons whose muscle group can be easily determined. By comparing the experiments of Sasaki's group under light barbiturate anesthesia and those of Massion's group under chloralose anesthesia, it seems safe to conclude that the fastigial projections to the motor cortex through VL are weak compared to those from interpositus and lateralis. As suggested earlier, the most likely influence of fastigial nucleus upon the motor cortex is a modulation of the cerebellothalamocerebral signals via the connection from uncinate fasciculus to medial reticular nucleus to intralaminar thalamic nuclei (sect. VI).

VIII. SUBLOOPS

A. Organization

The description of the cerebrocerebellar loop has emphasized the most important connections in the normal flow of information between the cerebrum and the cerebellum. However, nearly all the nuclei considered to serve as relays in this flow of information receive inputs from both the cerebrum and cerebellum (Fig. 5): for example, pontine gray (50, 56, 208, 322), IO (111, 148, 271), LRN (62, 69,

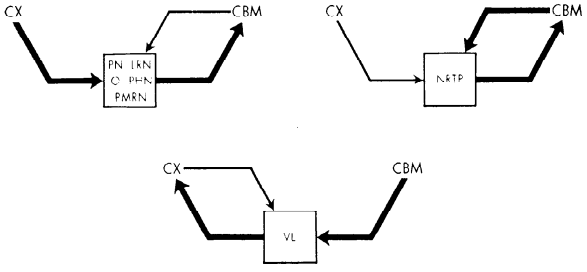

FIG. 5. Schematic representation of cerebral and cerebellar influences on cerebrocerebellar and cerebellocerebral relay nuclei. Width of arrows indicates relative strength of influences. Cerebral influences (CX) are exerted by corticobulbar, corticospinal, and corticothalamic fibers. Cerebellar influences (CBM) are exerted by projection neurons arising in cerebellar nuclei.

84, 99, 208, 287, 312), NRTP (48, 53, 54, 297), PMRN (270, 287), PHN (84, 270, 287), and VL (192, 249). In this regard the rubrospinal neurons may serve as a model, even though they are not properly considered a part of the cerebrocerebellar loop. In contrast to the somatic excitatory synapse that the RN neurons receive from the cerebellum (176, 227), the cerebral-induced EPSP is smaller and has a slower time course (305, 306) via synapses that have been histologically located on the distal dendrites (177). That this difference in EPSP shape for the cerebral- and cerebellar-induced EPSPs can be explained by electrical considerations related to somatodendritic location has been further confirmed by sectioning the cerebellorubral pathway. Subsequent to such a lesion, the cortical fibers sprout and form synapses onto the somatic sites vacated by the cerebellorubral endings, giving rise to a larger, faster rising EPSP (303).

Another subloop exists between the VL thalamus and motor cortex (Fig. 5). The corticothalamic fibers have been shown to be slower conducting than the thalamocortical fibers [4–10 m/s compared to 7–35 m/s (309; see also 258)]. The corticothalamic influences have been shown to be mediated by slow-conducting collaterals of fast and slow PT cells (133) as well as by non-PT fibers. By comparison with the rapidly rising EPSP induced by the cerebellar afferents, the cortically induced EPSP has a summit time of 3.5–10.0 ms (309). Consistent with this is the observation that the corticothalamic fibers form small endings about 1.5 μm in diameter, which terminate in more distal dendritic locations than do the cerebellothalamic fibers (155; J. A. Rafols, personal communication).

Electrophysiological experiments suggest that the corticothalamic excitatory influences arise primarily from the cortical region to which the VL neuron projects (251, 258), although additional corticothalamic influences have been suggested to arise outside of this cortical zone (258). Cortical stimulation also leads to inhibitory effects on VL neurons. The spatial extent of the cortex exerting this inhibition on a VL neuron is considered to be larger than for the excitatory effect (251, 258). Unfortunately, the latency of the inhibitory effect as a function of cortical region stimulated is not clear. This leaves three possible mechanisms: *1*) corticothalamic activation of inhibitory interneurons within VL; *2*) cortical activation of neurons in nucleus reticularis that in turn inhibit VL neurons (212, 266); *3*) antidromic activation of VL thalamocortical relay neurons that exert recurrent collateral inhibition on other VL neurons (15). This problem requires further study.

It has been shown electrophysiologically that branches of the same interpositus axons innervate RN, VL, and NRTP (295, 299). With the use of the electron microscope, it has been observed that large endings with similar ultrastructural features are present in the VL/VA complex, RN, pontine gray, and IO (154, 155; J. S. King, G. A. Mihailoff, and J. A. Rafols, personal communications). For the VL/VA complex, RN, and NRTP neurons, the cerebellar input is numerically much more important than the cerebral input (18, 54, 176, 177). Likewise, electrophysiological and anatomical considerations suggest that the cerebellar inputs are located on proximal dendrites and in some cases soma, whereas the cerebral inputs are located on the distal dendrites (155, 176, 177, 227, 305, 309; J. A. Rafols, personal communication). On the other hand, the cerebral inputs are more important than cerebellar nuclear inputs to the pontine gray, IO, LRN, PMRN, etc. With the electron microscope and electrophysiology, it has been shown that the corticopontine fibers terminate primarily on distal dendrites (160; G. A. Mihailoff and J. S. King, personal communication), with the fast PT fibers tending to terminate somewhat more proximally (11; Allen, Korn, Oshima, and Toyama, manuscript in preparation). A fraction of the pontine neurons receive monosynaptic EPSPs from the cerebellar nuclei (260, 304; Allen, Korn, Oshima, and Toyama, manuscript in preparation). In general, the EPSP has a faster time to peak than the corticopontine inputs. By correlating this with the observation of Mihailoff and King (personal communication) that large noncortical endings (2–6 μm) terminate on proximal and intermediate dendrites of pontine neurons in similar synaptic complexes (160) as the cerebellar nuclear endings in the RN and VL/VA complex (154, 176; J. A. Rafols, personal communication), it becomes likely that the cerebellopontine influences are exerted more proximally than the corticopontine influences. The cortico-olivary and cortico-LRN pathways are complicated by the possibility that a large fraction of these inputs may be relayed through portions of the RN that receive cerebellar inputs. The relative sites of cerebral and cerebellar synapses must be worked out in more detail for these nuclei primarily concerned with cerebral information. From what is known it seems likely that, regardless of whether the nucleus is primarily relaying cerebrocerebellar or cerebellocerebral information, the cortical inputs synapse distally and the cerebellar inputs proximally and that the primary function of the nucleus is determined by the relative numbers of the two inputs. It seems likely that for the VL/VA complex, the RN, and the NRTP the cerebellar input provides the major driving force and that the cerebral input provides a background or modulatory influence (Fig. 5). For the other group of nuclei (i.e., pontine gray, IO, LRN) these two roles would be reversed. However, for these nuclei the role of the cerebellar inputs must be carefully considered.

Based on these considerations, it may be necessary to reconsider the role of the NRTP Although most neurons receive both cortical and cerebellar inputs, the cerebellar input clearly provides the major driving force for the NRTP neurons (54, 181, 299). Thus, rather than considering the NRTP as a relay in the cerebrocerebellar pathway, we must consider that it is the relay in a cerebellocerebellar loop that can be modified by cerebral inputs (Fig. 5).

These considerations suggest that in addition to the main cerebrocerebellar loop, there is a strong cerebello-NRTP-cerebellar subloop, and weaker cerebellocerebellar subloops through pontine gray, IO, LRN, etc. Similarly, there should be a weak corticothalamocortical subloop. Three other potential subloops of unknown strength are cerebellorubro-LRN-cerebellar (Kitai, DeFrance, Hatada, and Kennedy, personal communication), cerebellorubro-olivocerebellar (192, 209, 241, 314), and cerebellorubrocerebellar (92).

B. Functional Significance

Any consideration of the functional significance of a given subloop requires a knowledge of the somatotopy within the loop and the integrational properties of the neurons in each of the nuclei along the loop. In every subloop investigated so far there seems to be some preservation of somatotopy within the subloop. For example, the fastigial and interpositus cerebellar nuclei have been shown to project to the divisions of the inferior olive that send their axons to the corresponding zones of the cerebellar cortex (111). Similarly, the fastigial nucleus sends axons to that portion of the LRN (parvicellular) projecting to the vermis (208, 287). However, the somatotopy has not been worked out in any greater detail than this. The question that remains is whether there is a strict preservation of information within the loop so that the cerebral and cerebellar signals integrated by the relay nucleus are somatotopically related. For example, do the regions of cerebellar pars intermedia and interpositus related to the hand or a given hand movement project to the pontine neurons whose axons terminate in the same cerebellar region? Furthermore, are the cerebral inputs to these pontine neurons related to the same hand movements? Or, alternatively, are the cerebellar inputs to the pontine nuclei providing a general diffuse background action on the pontine neurons, with little or no specific somatotopical information? There is insufficient information to settle these questions at the present time. Brodal et al. (50) and Yuen et al. (322), using anatomical techniques, have shown that the corticopontine and cerebellopontine projections overlap within the pontine gray. The results of these studies allow the possibility that the pontine nuclei may be integrating signals from cerebral cortex and cerebellum with the same somatotopic information. However, the degree of somatotopic specificity within these two input systems and the way in which they interact at the level of the pontine neurons can only be worked out electrophysiologically.

There are several possibilities for the functions of these subloops, as outlined below.

I. The cerebrum and cerebellum provide independent inputs to the relay nucleus; the input synapsing close to the soma provides the dominant driving force, while that synapsing on the distal dendrites provides a biasing or modulating influence on the neuron. This possibility probably holds true for the rubrospinal neurons, where the output does not effectively influence either its cerebral or cerebellar inputs and hence is not part of a closed feedback loop.

II. They could form a negative-feedback system to turn down the input. This seems an unlikely possibility for the subloops between precerebellar nuclei and cerebellar nuclei, although it may be a possibility for the thalamocortico-thalamic subloop (3, 170).

III. They could form a positive-feedback system with one of several functions.

A. A reverberating circuit that is not necessarily somatotopically organized, but provides a diffuse input to the cerebellar nuclei, giving a background discharge upon which the Purkinje inhibition is superimposed.

B. A reverberating circuit that is somatotopically organized to provide a memory as Tsukahara et al. (298–300) proposed for the cerebello-NRTP-cerebellar loop. This requires *1*) that the precerebellar nuclei receive a stronger input from cerebellar nuclei than any other input and *2*) that they send many synaptic endings to the cerebellar nuclei *3*) but few to the granular layer of the cerebellar cortex. (Note that these three requirements also hold for option A above). This possibility is unlikely for the pontine gray, which receives fewer fibers from cerebellar nuclei than from cortex. In addition, recent experiments (Allen, Azzena, and Ohno, manuscript in preparation) suggest that the pontine gray sends few collaterals to the cerebellar nuclei, whereas the pons is the well-known source for mossy fibers going to the granular layer. On the other hand, the NRTP fulfills requirement *1* (48, 54) and seems to fulfill requirement *2* from the work of Tsukahara et al. (299, 304). A check on requirement *3* has not been made anatomically or physiologically and requires small lesions or localized stimuli delivered within the NRTP to determine its site of action.

C. The feedback signal from the cerebellar nuclei to the precerebellar nuclei could serve as a cerebellar-triggered signal to sample the other inputs to the precerebellar nuclei. This mechanism could only work if *1*) the discharge of the precerebellar nuclei required the simultaneous arrival of two or more afferent impulses. Other requirements are *2*) that the precerebellar nuclei receive important afferent inputs from sources other than the cerebellar nuclei and *3*) that the precerebellar nuclei send many terminals to the granular layer of the cerebellar cortex. Requirements *2* and *3* are the requirements of a specific relay nucleus and may be considered to apply for the pontine gray, IO, LRN, etc. With this mechanism, the cerebellar nuclei could at crucial times request additional or more specific cortical information above and beyond what they would normally receive. One must be critical of this possibility because the cerebellar nuclei have a continuous discharge at 30–50 Hz (124) and that might seem like too high a sampling rate. The question that must be asked at this stage is: Is there any precedent for this kind of sampling mechanism in the central nervous system? Allen et al. (4) found that the cerebrocerebellar signals from the sensorimotor cortex to the pars intermedia are carried almost equally by mossy fibers of the corticopontocerebellar and cerebro-LRN-cerebellar pathways. However, the signals stop at the granular layer unless both pathways are acting simultaneously. Since the two pathways are so different (the pons relays only cortical information, whereas the LRN integrates cortical, spinal, and other descending inputs), it seems likely that the required conjunction provides the basis for a sampling mechanism.

Option I may hold for all the subloops considered. However, the neuronal machinery differs for the nuclei under consideration and these other possibilities must be considered. Kornhuber (186) recently proposed that, in addition to serving as an output relay from the cerebellar cortex, the cerebellar nuclei have a specific function of their own, namely, a hold function to hold a limb position between the rapid movements preprogramed by the cerebellar cortex. He bases his proposal on the fact that a lesion of the cerebellar nuclear efferents results in an intention tremor or a "holding" tremor. He concludes his discussion of the cerebellar nuclei with the statement, "On the basis of this theory of an independent (hold) function of the cerebellar nuclei, we might predict that the cerebellar nuclei have separate afferents at least from the pontine nuclei (not only collaterals from fibers to the cortex)" (186). The requirements for the precerebellar relay that Kornhuber mentions as underlying his proposed "hold function" for the cerebellar nuclei appear to correspond with those for the memory that Tsukahara et al. (299) have proposed for the cerebello-NRTP-cerebellar loop. (An alternative explanation for the intention or ataxic tremor is provided in the next section).

This consideration of the function of the subloops, although preliminary, points out the need for detailed investigation in this area.

IX. CEREBROCEREBELLAR LOOP

A. Entering and Leaving the Loop

Figures 6 and 7 summarize the most important connections for the cerebrocerebellar loops through the pars intermedia and cerebellar hemisphere. There are several points where the cerebrocerebellar loop can interact with other systems in controlling movement. Somatosensory information enters at several of these points within the loop. The somatosensory inputs converge directly onto the Purkinje cells of the pars intermedia (and vermis) and on the precerebellar relays to this portion of the cerebellum (233), i.e., the LRN (2, 254) and the dorsal and medial accessory nuclei of the inferior olive (22, 101, 102, 196, 218). The cerebral (pontine) and peripheral (spinocerebellar) inputs have their own separate mossy fiber-granule cell pathways, finally converging upon the Purkinje cell (7). In the normal operating range, it is likely that these two signals add linearly upon the Purkinje cell. In contrast, the cerebral and peripheral inputs summate upon the inerior olive neurons and are more effectively transmitted when they reach the olivary neurons simultaneously (7, 146).

Somatosensory information also enters at the motor cortex via the corticocortical pathway from the primary somatosensory cortex and via other spinothalamocortical routes (66, 139, 253, 318). Rosén and Asanuma (252) have shown that the somatotosensory information impinging on the PT neurons to the distal musculature arrives from the portion of the digit that would make contact during the activity of those PT neurons. In addition, other inputs impinge on the PT neurons from the contralateral motor cortex, as well as from ipsilateral association

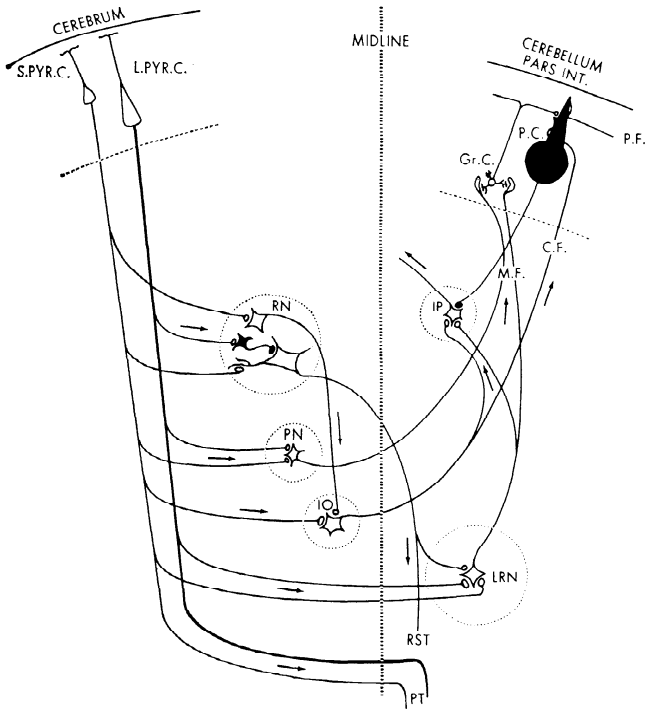

FIG. 6. Cerebrocerebellar loop through pars intermedia. Most important neuronal pathways entering and leaving pars intermedia are shown, employing conventions of Fig. 1. Main cerebral area sending to and receiving from intermediate zone of cerebellum is the sensorimotor cortex. Note spinal inputs to inferior olive and to cerebellar cortex. Other spinal inputs not shown enter loop at lateral reticular nucleus and cerebral cortex. It appears that a large fraction of cerebro-olivary projection to pars intermedia relays in anterior, parvicellular division of red nucleus. It is unlikely that these red nucleus neurons receive a cerebellar input from interpositus, but it is not clear whether they receive an input from dentate (131, 176, 207). [Modified from Eccles (119).]

areas, for example, from area 6, the supplementary motor area. The callosal afferents monosynaptically excite both the fast and slow PT cells (226). The callosal fibers innervating the fast PT cells conduct at 7–14 m/s, whereas the callosal fibers to the slow PT cells conduct at 3–4 m/s. In contrast with the cerebellothalamocortical input through VL, which exerts its influence on the proximal dendrites, the corticocortical and callosal inputs are thought to exert their influence more distally (see sect. VII*B*). It may be concluded that the cerebellar input provides the dominant input to the PT neurons, whereas the somatosensory, somatosensory cortical, association, and callosal afferents exert subsidary, albeit important, influences on the PT neurons.

Individual neurons of the VL integrate signals from the basal ganglia as well as the important cerebellar input and the weaker cerebral input. Stimulation of the ansa lenticularis, the main outflow from the basal ganglia, leads to a monosynaptic excitation of the VL at 0.7–0.9 ms in nearly 20% of the neurons (108).

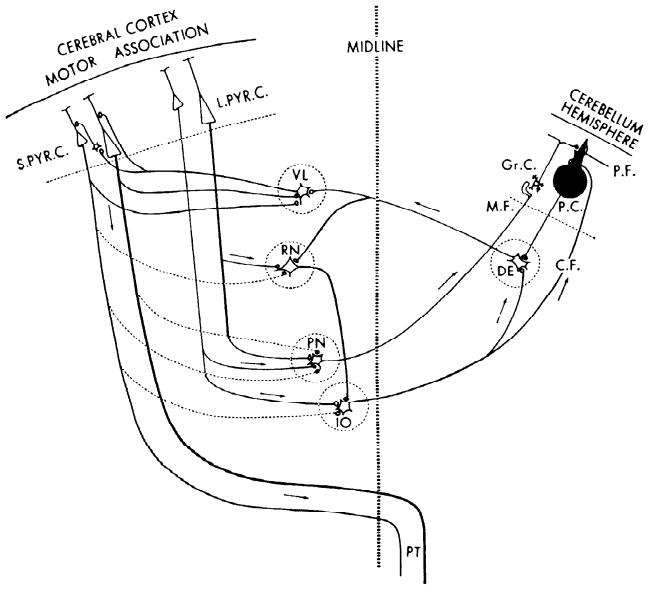

FIG. 7. Cerebrocerebellar loop through cerebellar hemisphere. Pyramidal tract is shown with dashed lines to precerebellar relay nuclei to emphasize the fact that primarily corticobulbar fibers from association cortex carry information to cerebellar hemisphere. Outflow of cerebellar hemisphere feeds back to motor cortex, which does send its signals down the pyramidal tract. Only anterior, parvicellular portion of red nucleus is shown here.

The pallidothalamic fibers form the same type of small endings on the distal dendrites of the VL neurons as do the corticothalamic fibers (154, 155). The pallidothalamic EPSP is not followed by an IPSP as is the cerebellothalamic EPSP. Desiraju and Purpura (108) reported that other VL neurons received cerebellothalamic and pallidothalamic PSPs at 2–6 ms, suggesting di- and polysynaptic connections via interneuronal pools within the thalamus. For these VL neurons, the two inputs were commonly reciprocally related. Although the cerebellothalamic is clearly the stronger of these two afferent systems, both can work together in generating the VL output. Some somatosensory, visual, and auditory inputs also impinge on the VL neurons.

The two main points of exit from the cerebrocerebellar loop are the pyramidal tract and the rubrospinal tract.

B. Informational Capacity of the Loop

Having considered the various components of the cerebrocerebellar loop, as shown in Figures 6 and 7, we may now begin to think of the capabilities of this loop. In man, 0.5×10^6 corticospinal fibers leave the cerebral cortex, giving off collaterals to the brainstem nuclei relaying the cerebrocerebellar information. In addition, 20×10^6 corticobulbar fibers innervate the same relay neurons, apparently providing a more significant input than the PT collaterals. Of the relay nuclei

TABLE 1. *Number of neurons or fibers in hemibrain*

Structure	Cat		Man	
	Number	Reference	Number	Reference
Corticobulbar (cerebral peduncle–corticospinal)			19,700,000	289
Corticospinal	40,000	317 (corrected according to 292)	500,000	195, 289 (corrected according to 292)
Pontine gray			21,000,000	289
N. reticularis tegmenti pontis				
Brachium pontis				
Inferior olive	70,260	134	454,340	134
	67,700	(corrected) 221	532,000	
Principal nucleus			451,000	(2 adults) 222
Medial accessory nucleus			62,000	
Dorsal accessory nucleus			19,000	
Lateral reticular nucleus				
Magnocellular division				
Parvicellular division				
Restiform body			520,000	(underestimate) 288
Granule cells	1,100,000,000	236	5,000,000,000 -50,000,000,000	44
Purkinje cells	755,000	221	7,100,000	189, quoted in 288
	625,000	235	7,500,000	44
			12,000,000	202, quoted in 288
Cerebellar nuclei	22,900		311,000	156
Fastigial nucleus	7200	J. Szentágothai, personal communication	5200	156
Globose nucleus (interpositus posterior)	5100		16,200	156
Emboliform nucleus (interpositus anterior)	4600		10,400	156
Dentate nucleus	6000		285,000	156
Brachium conjunctivum			782,000	156
			400,000	311
Red nucleus				
Parvicellular division				
Magnocellular division	450	151; quoted in 209	100	209, based on 232
			150–200	150
Rubro-olivary tract (uncrossed)				
Rubrobulbar tract (crossed)			50	268, quoted in 209
Rubrospinal tract			10	268, quoted in 209
Ventrolateral nucleus of thalamus				

projecting to the cerebellum, the pontine gray is numerically most significant with 21 $\times$ 10^6, in contrast to 0.5 $\times$ 10^6 for the inferior olive and as yet undetermined quantities in the LRN and NRTP. It is unlikely that the corticospinal and corticobulbar fibers are uniformly distributed to all regions of the pontine gray. It is important to realize that the number of corticobulbar fibers increases phylogenetically, as does the association cerebral cortex and the cerebellar hemisphere. Also, the cerebellar hemisphere receives inputs primarily from association areas of the cerebral cortex. Thus, it seems likely that the pontine nuclei projecting to the cerebellar hemispheres receive primarily corticobulbar inputs from association cortex, while the pontine nuclei projecting to the pars intermedia receive primarily collaterals of corticospinal fibers. The 21 $\times$ 10^6 mossy fibers arising from the pontine gray in man diverge to innervate 5–50 $\times$ 10^9 granule cells in the cerebellar

cortex, with a subsequent convergence onto 7–12 × 10^6 Purkinje cells. This strong divergence and convergence in the mossy-fiber system within the cerebellar cortex, leading to an overall convergence, provides this system with a multiplicity that may give it the ability to make fine computations (120, 121, 205, 257). The neurons of the inferior olive, which provides the major source of climbing fibers, if not the exclusive source, branch to contact 10–15 Purkinje cells. Each Purkinje cell in turn forms up to 10–50 terminal branches [10–20 in cat (215), 30–50 in rat (78)]. Since there are about 25 times as many Purkinje cells as cerebellar nuclear neurons in both cat and man (Table 1), it may be assumed that, on the average, each nuclear neuron receives terminals from 200 or more Purkinje cells. In the rat, some neurons in the central portion of the lateral nucleus receive terminals from a small number of Purkinje cells, while those in the surrounding region are impinged upon by hundreds of Purkinje cells (78, 81). This kind of cytoarchitectural detail is not known for the cerebellar projection onto VL thalamus and red nucleus. However, Toyama et al. (295) have shown electrophysiologically that about 50 interpositus axons converge on each rubrospinal neuron. Likewise, Tsukahara et al. (299) have shown that about 50 interpositus axons converge on each NRTP neuron.

A feeling for the computational ability of the cerebellum can be gained by realizing that there are 14 times as many Purkinje cells as PT fibers and 10,000–100,000 times as many granule cells operating on circuits to the corticospinal pathways. Also, there is a net convergence ratio for the cerebellum of about 40:1 (288), which is the ratio of the inputs coming from and the outputs returning to the cerebral cortex. When this ratio is compared with that of 4.8:1 for the dorsal root and ventral root fibers of the spinal cord (1, quoted in 38; 28, quoted in 288), it becomes reasonable to think that the cerebellum is capable of performing a fine computation on the information carried by its afferents and subsequently fed back through the loop to the cerebrum (120, 121, 257).

C. Loop Operation

The considerations in sections IV and V*C* suggest that the pars intermedia integrates cortical inputs primarily restricted to the sensorimotor cortex to which the signals are returned. Furthermore, there is a forelimb/hindlimb somatotopy within the cerebrocerebellar portion of this loop and it is likely that the somatotopy is preserved along the cerebellocerebral segment. Thus, there is good reason to think of this loop through the pars intermedia as a closed loop.

Within the pars intermedia, the Purkinje cells (plus inferior olive and LRN) integrate both cortical and peripheral inputs that represent the same limb (7). Because the pars intermedia receives both cortical and peripheral inputs and feeds back to the cerebral cortex and to the periphery via the rubrospinal and pyramidal tracts, it is possible to think of two separate loops passing through the pars intermedia, one cerebrally oriented and the other peripherally oriented. In fact, the Purkinje cells can be fired by either cortical or peripheral inputs alone.

However, the fact that the Purkinje cells and inferior olive neurons related to the pars intermedia integrate cortical and peripheral inputs from the same limb (7, 196, 218) suggests that these two inputs should cooperate in the normal operation of the pars intermedia. Furthermore, there is the suggestion that information may be transmitted more efficiently through the cerebellum when the cortical and peripheral inputs arrive simultaneously (7). More insight into this problem should be obtained once the trigger features of the cerebral and peripheral inputs to a given Purkinje cell have been worked out in the same way as Rosén and Asanuma (252) have done for the PT neurons.

As depicted in Figure 8, it may be assumed that the pars intermedia participates in a skilled movement in the following way (7). The pyramidal cells in the motor cortex send signals down the spinal cord, activating the motoneurons and giving rise to a movement. Simultaneously with the PT discharge to the spinal motoneurons, the pars intermedia of the cerebellum is notified of the intended movement by way of PT collaterals. As a result of the movement, cutaneous, muscle, and joint receptors are activated, sending their signals to the same zone of the cerebellum by way of the spinocerebellar tracts. However, the direct cortical inputs to the cerebellum arrive much earlier than the spinal inputs following the movement. Therefore, the Purkinje cell would summate the cortical input representing the motor command to move and a spinal input describing the movement resulting from a previous motor command. In this way, the peripheral input may

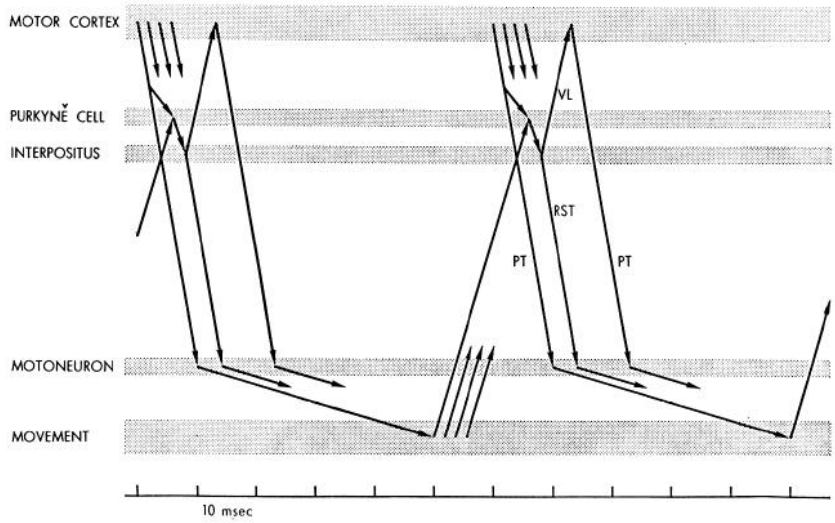

FIG. 8. Diagram of timing of signals within cerebrocerebellar and spinocerebellar loops involving the intermediate zone. Times chosen were based on data obtained for forelimb of cat and monkey (31, 88, 125, 137, 139). In each case, minimum possible time was not chosen. For man and for hindlimb movements, longer loop times must be considered. Note that after the pars intermedia operates on descending motor signals, its output can reach the motoneurons rapidly via rubrospinal and corticospinal tracts, updating the intended movement before it progresses very far. (Allen, Azzena, and Ohno, unpublished.)

provide important information about limb position and velocity of the ongoing movement that the pars intermedia can coordinate with the information from the motor cortex for the next phase, as it promotes an effective movement. Since the Purkinje cell performs a continuous integration of nerve and cortical inputs, its evaluation of the command and evolving movement is constantly being updated, and the signals to the motor cortex and rubrospinal tract are modified accordingly (116, 117, 120). Since the result of the computation can influence the motoneuron through the fast pathways of the rubrospinal and pyramidal tracts, movement can be modified at the earliest stages, before a significant fraction has been executed. Although it might be possible to consider that the pars intermedia may be part of a follow-up correcting mechanism, as the vermis apparently is (117, 121), it seems more reasonable to think that the pars intermedia uses its extensive sensory information in conjunction with the cerebral input to constantly update the intended movement just as it is about to begin and in response to each subsequent motor command throughout the movement. Follow-up correction, which is a less efficient way to control skilled movement, could be performed adequately by the cerebral cortex (88, 139, 216). Although the pars intermedia may cooperate with the cerebral cortex in follow-up correction, the pars intermedia probably would not perform follow-up correction by itself unless the cerebral cortex were not functioning properly.

The cerebellar hemisphere, on the other hand, integrates inputs primarily from association cortex plus sensorimotor cortex and returns it to the motor area. This pathway tends to funnel information from wide areas of cerebral cortex through the cerebellar hemisphere onto a small area of cerebral cortex and may be best viewed as an open loop. In the cat there is a very weak input from peripheral nerves (10, 147, 214; Allen and Ohno, manuscript in preparation). In the primate, this input becomes less significant (112; Allen, Gilbert and Yin, manuscript in preparation), leaving the cerebellar hemisphere primarily as a center for integrating association and motor cortical signals. In order to correctly assess the operation of the cerebellar hemisphere, it would be necessary to understand the functional significance of the output from the various association areas projecting to the hemisphere and the patterns of association signals impinging upon the cerebellar hemisphere during a movement. This kind of information is not yet available. However, the experiments of Kornhuber and coworkers (105, 186) may provide some insight. In human subjects performing a volitionally initiated movement of the index finger, potentials were recorded from the scalp overlying the cerebral cortex before the movement began. As early as 0.8 s before the movement, a slowly rising negative potential, the readiness potential, develops over large regions of the cerebral cortex bilaterally. About 60 ms before the onset of the movement a sharp negative wave appears over the hand area of the contralateral motor cortex.

These experiments suggest that many cerebral areas participate in the planning and carrying out of a voluntary movement. It is certainly the association areas that participate in the translation of the idea to move into a patterned activation of certain motor cortical columns and their elemental movements

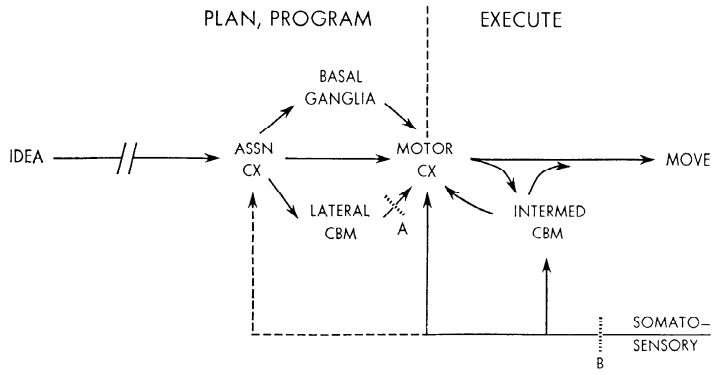

FIG. 9. Scheme showing proposed roles of several brain structures in movement. Thin dashed line represents a pathway of unknown importance. Heavy dashed lines at *A* and *B* represent lesions described in text. It is proposed that basal ganglia and cerebellar hemisphere are involved with association cortex in programing of volitional movements. At the time that the motor command descends to motoneurons, engaging the movement, the pars intermedia updates the intended movement, based on the motor command and somatosensory description of limb position and velocity on which the movement is to be superimposed. Follow-up correction can be performed by motor cortex when cerebellar hemisphere and pars intermedia do not effectively perform their functions.

(Fig. 9). Furthermore, it is to be expected that the association areas projecting to the cerebellar hemisphere are among those in the premotor chain. Since the hemisphere appears to perform its function without the aid of direct peripheral inputs, the hemisphere would appear to be more suited for participation in planning the movement than in actual execution and updating of the movement as was proposed for pars intermedia.

As suggested in Figure 9, the most reasonable possibility for the lateral cerebellum is that it participates in the programing or long-range planning of the movement. Its function is largely anticipatory, based on learning and previous experience and also on preliminary, highly digested sensory information that some of the association areas receive. However, the fact that the cerebellar hemisphere may receive somatosensory information from association areas (34, 174, 256) does not imply that the lateral cerebellum is primarily a processor for sensory information relayed by the association areas. In the cat, some of the association areas projecting to the lateral cerebellum do not receive any somatosensory information (10). It is likely that the extent of these nonsomatosensory association areas is greater in primates.

Once the movement has been planned within the association cortex, with the help of the cerebellar hemisphere and basal ganglia, the motor cortex issues the command for movement (138, 141, 186). At this point the pars intermedia makes an important contribution by updating the movement based on the sensory description of the limb position and velocity on which the intended movement is to be superimposed. This is a kind of short-range planning as opposed to the long-range planning of the association cortex and lateral cerebellum. This hypothesis is consistent with the observation by Thach (283, 284, 286) that the activity

of dentate neurons tends to slightly precede that of motor cortical neurons, whereas that of interpositus neurons tends to follow.

Certainly both of these cerebellar zones must cooperate in the performance of every skilled movement. Every movement initiated centrally has some kind of a program; therefore it is preprogramed to some degree. Likewise, every volitional movement has the potential of being updated as it begins and throughout its duration. If both cerebellar zones perform their jobs well, very little follow-up correction would be necessary by the cerebral cortex. To better visualize the roles of the cerebellar zones, let us consider and compare the following two types of movement—skilled movements, such as reaching for an object, and rapid, ballistic movements, such as a boxer striking at his opponent. In the former example, the movement is somewhat provisional and cannot be completely preprogramed. Consequently, there is the need and also the opportunity for the movement to be continuously updated during its execution. In the latter case, the movement must rely on preprograming because, with the rapidity with which it must be performed, the movement could not be adequately updated once it begins.

In learning a movement, we first execute the movement very slowly because it cannot be adequately preprogramed. Instead, it is performed largely by cerebral intervention as well as the constant updating of the pars intermedia. With practice, a greater amount of the movement can be preprogramed and the movement can be executed more rapidly. For learned movements Eccles (117) and Ito (163) view the cerebellum as providing an internal substitute for the external world. This eliminates the need for peripheral sensory input and allows one to increase the speed of the learned movement by preprograming. This cerebellar operation we consider to take place in the lateral zone. Thus, we can consider that many of the trained movements are largely preprogramed, whereas many of the exploratory movements, which constitute a large fraction of our movement repertoire, are not completely preprogramed but are provisional, subject to continuous revision. The role of the cerebellum, presumably the pars intermedia, in our untrained or exploratory movements is attested to by the clumsiness and slowness with which they must be performed when the cerebellum is ablated and we must rely on cerebral control alone.

It is intersting to compare the number of neurons in interpositus and dentate for cat and man in Table 1. In the cat, interpositus is slightly larger than dentate; in man, dentate is 10 times larger than the interposed nuclei (globose and emboliform). Thus, man's greater flexibility in skilled movement would seem to be due to his greater capacity to preprogram his movements.

Additional insight can be gained by observing movement control when specific portions of the cerebellar operation are interfered with (63 65, 87, 162, 187, 188, 308). With cooling of dentate (Fig. 9, *line A*), a monkey conditioned to perform movements between two target zones *1*) shifts to slower movements, *2*) needs external cues (e.g., auditory, visual) to locate the target zones, and *3*) develops errors in rate and range in attempting the movement (63, 65). Each of these alterations in the movement is consistent with the notion that the movement is primarily preprogramed. The movement shifts to a slower one in an attempt to

use somatosensory cues, but even these are not enough to halt the movement at the appropriate position. A tremor often results because the movement is so ineffectively preprogramed that the pars intermedia cannot perform its normal function of updating a movement that is already a good "guess." Instead, errors occur and tremor then appears as the motor system attempts to bring the movement back on course using follow-up correction.

Lesion experiments also support the conclusion that ataxia and ataxic tremor are due to interference with the function of the dentate nucleus (41, 113; but see 324). Carrea and Mettler (72) have described the tremor as resulting from lesions of the ventral brachium conjunctivum, which mediates the outflow from the ventrolateral dentate (71). The clinical evidence tends to support the above observations in primates that ataxic tremor results from selective lesions of dentate (191).

Growden et al. (153) have proposed that ataxic tremor and ataxia are the manifestation of a single neurological deficit. Observation of animals with dentate/interpositus lesions led them to conclude that ataxic tremor results from making a misdirected movement and then attempting to correct it. In agreement with this, Horvath et al. (162) have described the ataxic tremor during dentate cooling as following the initiation of movement.

Although the tremor occurs with lesions of dentate, interpositus may not be a part of the follow-up corrective mechanism responsible for the ataxic tremor. By completely transecting the brachium conjunctivum and eliminating the outflow of interpositus as well as dentate, the ataxic tremor is apparently similar to that when dentate alone is blocked (72). Therefore, a spinocerebrospinal loop may be involved in the follow-up correction (88, 139, 216; but see 199). This is in part supported by Holmes' observation that the cerebellar patient must exert conscious control over each phase of movement (161).

The great ability of the primate nervous system to preprogram movements is perhaps best seen by eliminating the somatosensory inflow from the periphery by sectioning the dorsal columns or dorsal roots (Fig. 9, *line B*). It should be emphasized that movements are impaired under this condition and more intricate tests must be designed to detect the details of the deficits. However, it is remarkable how well some movements can still be performed (282).

Lashley (193), in describing movements in a patient with the dorsal roots cut on one side, reported that the slower movements of the limb were the most seriously affected. The more rapid movements were least affected. These observations suggest that preprograming of movements in the primate is an important feature of performance and that the more rapid the intended movement, the more the motor system relies on this preprograming.

When limb deafferentation is combined with a dentate/interpositus lesion, the ataxia and ataxic tremor are much more severe than with the cerebellar lesion or deafferentation alone (199). However, the movements that the recovered monkey makes can be performed without visual clues. This has led Liu and Chambers to conclude that there is "a central programming of movements, with continuous monitoring by central feedback mechanisms" (199). Koslovskaya et al. (187, 188), using dentate cooling and peripheral nerve block in monkeys performing

elbow movements without visual cues, concluded that the "movements seemed to be guided primarily by internal and secondarily by external cues. When the external cue was withdrawn, movements could be guided accurately by internal cues. Cooling of the dentate nucleus increased the dependence on external cues, implying that the use of internal cues had been interfered with" (188).

In summary, it seems quite possible that the premotor association areas and the lateral cerebellum are responsible for preprograming of movements. Once the motor command is formulated and dispatched to the spinal cord, the pars intermedia updates the preprogramed movement based on the somatosensory inputs. The pars intermedia continues to update the movement, keeping it on course.

X. CONCLUDING COMMENTS

A. Fast and Slow Components of Cerebrocerebellar Loop

In describing the cerebrocerebellar loop, it emerges that there are fast and slow loops through the cerebropontocerebellar mossy-fiber system and a slow loop via the climbing-fiber system. Considering the cerebrocerebellar system from the point of view of a closed loop, the signals may traverse the mossy-fiber loop in 10 ms, because this loop includes the fast-conducting PT fibers and a monosynaptic connection from the VL neurons back onto the fast PT cells, as depicted in Figures 6 and 7. In contrast the slower loop through the climbing-fiber system may take 25 ms because this loop involves the slow PT fibers, the slowly conducting olivocerebellar fibers, and a disynaptic connection from VL back onto the slow PT cells. Furthermore, for the slow loop the cerebellothalamic and thalamocortical fibers may be the slower conducting fibers within each pathway, as has been found within the afferent systems to the visual cortex (230) and somatosensory cortex (307) and within the callosal afferents to the motor cortex (226) (see sect. IX*A*).

It is not clear what the roles of these two cerebrocerebellar loops are (see ref 40 for a theoretical discussion of one possibility). Clearly, they are not independent because they interact within the cerebellum where the loops share Purkinje cells and cerebellar nuclear neurons. Because of the collateral influences within the cerebral cortex, Oshima (234) has suggested that the tonically discharging slow PT cells provide a baseline excitation of the fast PT cells, poising them for their phasic action. Tsukahara et al. (302) have proposed that the fast and slow PT fibers interact at the red nucleus. The slow PT cells would tonically excite the rubrospinal neurons in the absence of fast PT cell activity (Fig. 6). When the fast PT cells discharge intensely, the rubrospinal neurons would be inhibited (301, 302), thereby allowing the fast PT fibers to override the rubrospinal influences on the motoneurons.

The spinovermis-spinal pathways are concerned in the control of automatic movements and postures (121). However, it is possible that the slow cerebrocerebellar loops operate on more tonic aspects of such volitional activities as

standing, holding, etc., whereas the fast cerebrocerebellar loop operates on more phasic aspects of volitional movements. Although the climbing-fiber and slow pontocerebellar loops are relatively slow compared to the fast pontocerebellar loop, it must not be overlooked that they still operate many times faster than the spinocerebellospinal loop and are capable of greatly increasing the efficiency of movement control.

It has not been the purpose of this review to consider the very interesting problem of how the many descending influences on the spinal motor centers are coordinated. The role of the cerebrocerebellar loops in this coordination should be very important and deserves further investigation.

B. Missing Links

The primary purpose of this review has been to describe anatomical and physiological properties of the linkages within the cerebrocerebellar loop that determine the dynamic characteristics of this loop. It has also helped us to formulate a number of problems that need to be solved in order to better understand the control of movement.

Now that the basic loops and subloops have been established, it is important to work out the somatotopy within the pathways and loops and the integrational properties of the neuronal elements within each loop. For the electrophysiological studies, it will be important to use species where the somatotopy is clear. This certainly implies much more investigation on primates. In addition to the electrophysiological techniques, anatomical techniques must be used to clarify the projections from the precerebellar nuclei onto the cerebellum. The retrograde studies provide the basic pattern within the projections to the cerebellum, but they do not provide the necessary detail to define the somatotopy within each component of the cerebrocerebellar pathway, e.g., the cerebropontocerebellar pathway (56). Some of the newer anatomical techniques should be applied to this problem.

Relating to the dynamic operation of the loops, additional information is needed on the capabilities of synaptic connections. At the single-neuron level, this can be obtained by a combination of intracellular techniques (295, 305) and electron-microscopic degeneration techniques (176). At the system level, this requires obtaining the numbers of neurons in each structure within the loop (288) (Table 1) and also obtaining the divergence/convergence numbers at each relay (235–238, 295).

Once the capabilities of the loops have been determined, it will be necessary to determine the significance of the inputs that the neurons integrate during volitional movement (106, 107, 136, 137, 139, 283, 284, 286). The goal would be to understand the way each neuronal type in the premotor chain and in the cerebrocerebellar loop fires in relation to the movement. Ideally, experiments should be designed to approach as closely as possible the type of free-will movement studied by Kornhuber and coworkers (105). Admittedly, it is easier to quantitate the more stereotyped, conditioned movement. However, this seems to restrict our study to the point where the motor system is no longer relying on its full neuronal ma-

chinery. The challenge is to design more natural movements (149) and the techniques to describe them.

With the parallel advances in our understanding of the organization of the basal ganglia (173), it is clear that attempts must be made to interrelate the cerebrum, cerebellum, and basal ganglia in studies of movement (106, 107, 138, 186, 286). Advances will be made by attempting to tie together observations from acute and chronic animal experiments with observations from clinical studies designed to study differences in movement parameters in normal, cerebellar, and Parkinson patients where the pathology is clear. Attempts should be made to compare the control of axial, proximal, and distal musculature. Most clinical tests really determine the motor function of the proximal musculature. An emphasis should be made on developing tests for distal motor function as well.

Our greatest conceptual advances will probably be made by tying together the above experimental and clinical studies with theoretical and model studies.

XI. SUMMARY

It has been the goal of this review to describe the connections between the cerebral cortex and the cerebellum from both the anatomical and physiological points of view. Emphasis is placed on the dynamic properties and integrative properties of the linkages within the cerebrocerebellar loops in order to begin considering the capabilities of the loops and subloops. The problem of somatotopy within the loops is also considered. Putting this information together, the possible roles of the lateral and intermediate zones of the cerebellum in the control of movement are discussed. It is suggested that the premotor association areas and the lateral cerebellum are responsible for the preprograming of movements. Once the motor command is formulated and transmitted from the motor cortex to the spinal cord, the pars intermedia would update the preprogramed movement, based on the peripheral sensory inputs. Finally, an effort is made to point out the deficiencies in our present knowledge and to suggest approaches to these problems.

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