Organizational Principles of Cerebellar Neuronal Circuitry

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We review our recent studies of cerebellar neuronal organization, emphasizing that consideration of organizational features of cerebellar circuitry represents a necessary step toward the understanding of how the cerebellum does what it does, in terms of both its internal information processing and its interaction with other motor structures.

Whereas a variety of nonmotor cerebellar functions has been highlighted only recently, the role of the cerebellum in motor control has been acknowledged ever since the classical investigations carried out by Gordon Holmes, who demonstrated a number of characteristic abnormalities of movement in individuals suffering from cerebellar lesions due to gunshot injuries in the First World War. However, despite a long-standing general consensus regarding what the cerebellum does in motor control, at least in terms like “coordination of motor patterns,” the understanding of how it does what it does is still rather rudimentary (see Ref. 2 for a comprehensive exposé of the many controversies surrounding this topic).

Although recent use of brain imaging techniques in humans has shed some light on cerebellar involvement in the regulation of movement, the most direct way of addressing the issue of neuronal circuitry operation is by recording the unitary activity of cerebellar neurons in a behaving animal. In such paradigms, discharges of action potentials are analyzed in relation to the motor task under study, and correlations are sought between neuronal activity and different...
features of the movement performed, such as active force, limb displacement, preparation to move, or temporal and spatial characteristics of muscle activation. Typically, the neurons recorded during behavioral studies are described exclusively in terms of their discharge patterns, but little or no information is provided regarding other characteristics, such as their connectivity or peripheral receptive fields.

However, because synaptic connections are important for determining causes and consequences of neuronal activity, both the connectivity and the activity of the same neurons must be known to understand in detail how a central nervous structure fulfills its functions. A lack of assessment of overall attributes of cerebellar neurons recorded during behavioral studies precludes a full systematization of data and is therefore likely to hamper the progress of unraveling the mode of operation of cerebellar control systems. Given the specific connectivity of the cerebellar neuronal network and the complexity of its afferent and efferent connections, any interpretation of how information is being processed from the input to the output, even in a given motor task, is bound to meet with difficulties when based on data collected from functionally heterogeneous populations of cells. Furthermore, because most cerebellar neuronal discharge patterns described do not seem to closely encode either the activity of single muscles or simple movement parameters, comparison between data collected in different studies using different motor tasks is difficult in the absence of a task-independent frame of reference for characterization of neurons.

With the above considerations in mind, in this report we draw attention to some aspects of the detailed functional connectivity of cerebellar neuronal circuitry. We suggest that emerging organizational principles of the cerebellum may provide a useful framework for characterization of neurons also in behavioral investigations and may aid in elucidating what type of afferent information reaches the cerebellar cortex, how this information is processed, and what the cerebellar output actually does.

**Zonal organization of olivocorticonuclear connections**

The regular cytoarchitecture across the cerebellar cortical sheet has been taken to indicate that regional differences in cerebellar cortical function are determined mainly by the characteristics of local afferent and efferent connections. In keeping with this notion, analyses of olivocerebellar and corticonuclear connections in the cat have demonstrated that the cerebellar cortex is divisible into a number of 1- to 2-mm-wide sagittal zones, each receiving climbing fibers from a circumscribed part of the inferior olive and projecting to a specific deep cerebellar or vestibular nucleus (Fig. 1) (15).

The organization of cerebellar olivocorticonuclear connections must reflect functional differences between zones. This is supported not least by the fact that different parts of the inferior olive receive input from specific sets of spinoolivary pathways carrying different types of information (10, 14) and that different subdivisions of the deep cerebellar nuclei project onto different descending tracts with specific roles in motor control. Therefore, each zone, or in some cases an ensemble of anatomically coupled zones, is assumed to serve a particular control function...
and receive information related to the performance of the mechanism controlled.

**Neuronal organization of intermediate cerebellum**

In pars intermedia of the cerebellar anterior lobe, three cortical zones, C1, C3, and Y, receive climbing fibers from common neurons in the rostral dorsal accessory olive and have partly overlapping projections to the deep cerebellar nucleus interpositus anterior (Fig. 1). This nucleus in turn projects to the red nucleus and via the thalamus to the motor cortex, thus connecting to the rubrospinal and corticospinal tracts, which play a crucial role in the fine control of limb movements. Accordingly, neurons in the nucleus interpositus anterior and the downstream red nucleus have been shown to strongly modulate their discharge rates during reaching movements (11). The functional spinoolivocerebellar, corticonuclear, and interpositorubrospinal connections of this cerebellar control system, as investigated in the cat, are reviewed below. Throughout the different steps of our investigation, the cutaneous receptive fields of climbing fibers have served as physiological “markers” of the connections described (Fig. 2).

**Spinoolivocerebellar input.** The specific roles of the two major types of cerebellar afferents, in particular the olivocerebellar climbing fiber system, remain enigmatic. To date, positive findings concerning the behavioral conditions for activation of climbing fibers in the awake animal are surprisingly scarce in the context of limb movement control, and it has therefore been difficult to define in this way what type of information is conveyed to the inferior olive (2). Addressing the issue from a different angle, we have analyzed in some detail the characteristics of peripheral input to cerebellar climbing fibers.

Climbing fibers in the forelimb area of the C3 zone receive a convergent multimodal input from cutaneous Aβ, Aδ, and C fibers and from muscle afferents, mainly in the group II range (13). The C fiber input originates from nociceptors, and noxious pinch of the skin results in an exceptionally vigorous activity in climbing fibers, characterized by repetitive discharge at relatively high frequencies (3). Most or all input from cutaneous receptors to climbing fibers in the C3 zone is mediated via the postsynaptic dorsal column pathway (4).

For single climbing fibers, the tactile and nociceptive input is activated from overlapping areas on the skin. Conspicuously, the receptive fields usually have an eccentrically located area of maximal sensitivity and proximal borders located close to joints and as a population, therefore, display stepwise changes in their extent (Fig. 3). These stepwise changes allow a systematization of the receptive fields into at least 8 classes and then, tentatively, into a total of more than 30 subclasses (3). The olivocerebellar projection has a detailed topographical organization (8), reflected also in the intrazonal distribution of cutaneous receptive fields. Climbing fibers with similar receptive fields terminate within 0.1- to 0.3-mm...
wide, sagittally oriented cortical strips, and these “microzones” appear to constitute a salient feature of cerebellar circuitry, underscoring the importance of the olivocerebellar projection as a major determinant of cerebellar functional organization (3).

Single climbing fibers receive input from a limited number of muscles, and there is a specific spatial relationship between cutaneous and muscle afferent input. Generally, the input originates either from muscles on a segment proximal to the cutaneous receptive field but with a similar location on the circumference of the limb or, in some cases, from muscles located just underneath the area of skin corresponding to the cutaneous receptive field. Although this should be seen merely as a description of spatial relationships, it seems that, overall, these muscles would be stretched concomitant to a firm tap to the associated cutaneous receptive field (13).

The particular spatial characteristics of the cutaneous receptive fields and their specific relationship to the convergent muscle afferent input suggest that the climbing fiber system may be tailored to carry afferent information sampled in the context of movement. One possibility would be that each microzone, or an ensemble of microzones with similar climbing fiber receptive fields, controls a set of muscles constituting an elemental output synergy and that the climbing fibers signal about some aspect of movements involving the action of this set of muscles. Indeed, the organization of corticonuclear and nucleofugal projections of the intermediate cerebellum appears to be compatible with such a scheme.

Corticonuclear connections. Although the cerebellar corticonuclear projection has been outlined at the level of single zones, little is known about the organization of connections at an intrazonal level of organization, partly because of the limited resolution of neuroanatomic tracing techniques (8). Some of these limitations can be circumvented by using instead an electrophysiological approach, which involves recording extracellular positive field potentials in nucleus interpositus anterior and determining their cutaneous receptive fields using natural stimulation of the skin (Fig. 2). These potentials reflect inhibitory synaptic currents generated by climbing fiber-activated Purkinje cells, and thus the technique can be used to map the nuclear termination areas for cortical microzones in the C1, C3, and Y zones characterized by particular climbing fiber receptive fields (9).

Most sites in the nucleus interpositus anterior display receptive fields similar to those of single climbing fibers in the C3 zone, indicating a low degree of convergence between microzones with different climbing fiber receptive fields. On the other hand, because the termination areas for microzones belonging to different classes and subclasses of receptive fields appear to have a single, topographically organized representation in the nucleus, the findings suggest that there is a convergence in the corticonuclear projection between microzones with similar climbing fiber receptive fields. These ensembles of functionally coupled microzones have been proposed to constitute the operational units, or “modules,” of the control system (6).

Interpositorubrospinal output. The orderly topographical organization of the cerebellar cortical projection to nucleus interpositus anterior provides the necessary frame of reference for characterizing the relationship between the input and output of specific modules in this control system. Each module can be identified by the mapping of receptive fields of positive field potentials in the nucleus. The set of forelimb muscles controlled by the module via the rubrospinal tract is then assessed by inspection of the forelimb movement evoked on microstimulation of the same nuclear site.

The movements usually involve two or more segments of the forelimb and are not reduced to single joint movements even at threshold stimulation, suggesting that the motor control exerted from the nucleus interpositus anterior is organized in simple muscle synergies. On stimulation in the nucleus, movements evoked at proximal joints are usually flexion movements, i.e., retraction of the limb at the shoulder and flexion at the elbow. Movements at the wrist, on the other hand, are quite diverse, with similar proportions of flexion and extension. Digit movements consist mainly of dorsiflexion of central or ulnar digits.

The data indicate that there is a specific relationship between the efferent “muscle field” and the climbing fiber receptive field of the module. For example, stimulation of sites with distal receptive fields evokes the highest percentage of digit movements, whereas sites with proximal receptive fields have the lowest proportion of such movements. Perhaps more importantly, movements often display a directional specificity relative to the receptive field, such that stimulation of sites with climbing fiber receptive fields on the dorsum of the paw frequently evokes palmar flexion at the wrist, whereas stimulation of sites with receptive fields on the ventral side of the forearm and paw evokes dorsiflexion at the wrist (5).

**General discussion**

**Modular organization of cerebellar circuitry.** The above findings suggest that the cerebellar
neuronal network controlling forelimb movements via the corticospinal and rubrospinal tracts has a modular organization (Fig. 4). Each module is proposed to consist of one or several microzones in the C1, C3, or Y zones projecting onto a common efferent cell group in nucleus interpositus anterior. By definition, a module receives homogeneous climbing fiber input from cutaneous receptors and, in turn, controls a specific set of muscles in the limb. In many cases, the relationship between the receptive field and the projective field of the module is such that the set of muscles controlled via the rubrospinal tract would act to withdraw from, or prevent movement toward, a stationary stimulus presented to the cutaneous area corresponding to the climbing fiber receptive field. However, in its simplest form this rule has exceptions and the precise functional relationship between the input and the output from a module still awaits a conclusive description.

Nevertheless, there seems to be little doubt that the intermediate cerebellar control system consists of a number of specialized components (10). The significance of the multimodal input to climbing fibers is not clear, and it is an open question how input from different peripheral receptors may contribute to cause climbing fiber activation in specific behavioral contexts. In principle, afferent signals from different modalities may either summate, indicating that multimodal input is a necessary requirement for climbing fiber activation, or they may interact in more complex ways. It is noteworthy, for example, that the transmission of peripheral input to the inferior olive appears to be modulated by task-dependent mechanisms in awake animals. The mechanism underlying the gating is not known but could entail interactions between input from different afferent modalities (1, 13).

Alternatively, the task-dependent modulation is an expression of descending control of afferent impulse traffic. A possible role for such a mechanism could be to allow the climbing fiber system to make selective use of information from different types of peripheral receptors, depending on the requirements of the particular motor task. Whatever its function, the gating is clearly a key feature of the climbing fiber system and probably partially explains the abundance of negative findings in the literature concerning the conditions for activation of climbing fibers during active movements (2).
Nociceptive input, plasticity and motor adaptation. The powerful nociceptive activation of climbing fibers to the C1, C3, and Y zones is remarkable but can be tied in with other features of cerebellar physiology related to its presumed role in motor control. First, climbing fiber activity has been implicated in a mechanism subserving heterosynaptic plasticity in the cerebellar cortex, and this plasticity has been suggested to constitute a neuronal substrate for motor adaptation and learning. Second, trauma to the motor apparatus commonly results in activation of nociceptive input and often gives rise to adaptation of posture and movement patterns so as to minimize further injury and facilitate healing. Therefore, if one proposes that the cerebellum may be involved in trauma-related adaptation of posture and movement, the uniquely strong nociceptive activation of climbing fibers makes functional sense. Whether climbing fibers signal specifically about “motor errors,” as suggested by another popular theory of inferior olivary function (2), is a different matter, but there is little doubt that movements resulting in nociceptive activation are at least in some sense erroneous and that, in this context, pain is an efficient teaching signal for adjusting motor behavior.

Cerebellar output, coordination, and braking. At the behavioral level of analysis, “coordination” seems a rather clearly identifiable aspect of motor control, and in neurological practice a lack of motor coordination is well established as a symptom specifically indicative of cerebellar malfunction. Clinical findings suggest that, whereas the cerebral cortex and basal ganglia cooperate in producing the components that make up a skilled movement, the cerebellum appears to adjust parameters so as to adapt and coordinate these components to yield a seamless whole. However, when one is trying to reduce motor behavior to the level of neural circuit operation, the term coordination is less helpful and does not in any straightforward way suggest what one should be looking for. For example, if cerebellar output forms the basis for linking different movement components to each other in a smooth and well-timed fashion, what should be expected from the connectivity of cerebellar control systems and their activity during the performance of a motor task?

In single-joint movements, cerebellar inactivation causes a degradation of the normal pattern of agonist-antagonist activation, and the resulting hypermetria and tremor are typical cerebellar symptoms that are further exaggerated beyond simple summation when movements involve multiple joints. Accordingly, the dysmetria seen with reversible lesions of nucleus interpositus anterior during reaching movements in cats suggests that the output from this nucleus may be significant for a properly timed “braking” of such movements. Further important clues as to what the cerebellar output might do are provided by recent studies using monkeys trained to perform a reach-to-grasp movement. In this paradigm, neurons in the nucleus interpositus anterior were shown to greatly increase their discharge rates specifically in relation to the coupling between reach and grasp, whereas only lesser activation was seen when any of the two components was performed in isolation (11).

The movement repertoire found on stimulation in nucleus interpositus anterior in the present investigation is in some respects compatible with both a braking action and a role in coupling between different limb segments. Note, for example, that the dominance of flexion movements at proximal joints, although making it unlikely that this system is the driving motor system for reaching or explorative movements, suggests that output from nucleus interpositus anterior could contribute to a braking action during the extension phase of such movements. On the other hand, at least in simplistic terms, the multitjoint nature of the output would make it suitable for the coupling of movements at different limb segments. More complex output synergies could be established by concurrently activating, in a mediolateral sequence, sets of selected modules via mossy fiber-parallel fiber input from the spinal cord or cerebral cortex (7). Such a selection would depend on long-term synaptic plasticity induced by the climbing fiber system.

Finally, it is worth noting that if the output from single modules in the intermediate cerebellum relates to the coupling of different components of compound movements and this function is implemented by the activation of a set of muscles together acting on more than one joint of the limb, then it is highly unlikely that the discharge patterns of single nuclear neurons will correlate strongly with the activity of single muscles or faithfully represent simple movement parameters. Such an organization may thus, in part, explain the very mixed findings in the literature concerning what cerebellar neuronal activity actually encodes.

In conclusion

The present work adds to the accumulating body of evidence for a highly specific organization of cerebellar olivocorticoinuclear modules controlling forelimb movements via the rubrospinal and corticospinal tracts. Together with
previous investigations of the detailed functional organization of cerebellar systems controlling the lateral vestibulospinal tract (14) or the vestibulo-ocular reflex (12), our data support the notion that all cerebellar motor control systems are divisible into microcomplexes or modules. By exposing the complexity and specificity of the cerebellar neuronal circuitry, we believe that these findings underscore the fundamental importance of characterizing and systematizing individual neurons recorded in awake behaving animals. Discharge patterns alone will not provide complete answers to how cerebellar neuronal activity operates in regulating motor behavior.

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