

# The cerebellum: an overview

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Life has been compared to a beautiful tapestry, woven in intricate design of many threads and colors. By means of physics, chemistry, physiology, anatomy, embryology and genetics we unravel this texture, separate its constituent threads and colors, but lose the pattern as a whole. These analytical sciences have enormously increased our knowledge of life's constituent elements and processes, but the pattern of the tapestry is usually neglected or ignored.

E.G. Conklin (1944) (p. 125 in Ref. 1).

IN THESE SPECIAL companion volumes of *Trends in Neurosciences* and *Trends in Cognitive Sciences*, we take a look at the 'threads', the 'colors' and the 'tapestry' of the cerebellum through the eyes of a diverse group of molecular, cellular and systems neuroscientists. These investigators have used technical advances in a variety of disciplines (e.g. molecular biology, network modeling, functional neuroanatomy and brain imaging) to develop concepts about the cerebellum that are quite different from those that existed just a few years ago. The compilation of articles addresses multiple key areas of interest to neuroscientists and cognitive theorists alike, including: (1) cerebellar development – the genes, molecules, and cellular interactions that shape and refine this process, and the long-term consequences of genetic abnormalities; (2) the organization of the major cerebellar afferent systems (the inferior-olive/climbing-fiber system, and the mossy-fiber-afferent/parallel-fiber system) and their involvement in motor learning, adaptive plasticity and central timing; (3) the potential physiological mechanisms and anatomical substrates for adaptive modification of cerebellar circuitry; (4) cerebro-cerebellar 'loops' and their participation in motor and non-motor aspects of behavior; (5) conceptual and computational models of cerebellar function; and (6) functional imaging of cerebellar activation during various language, cognitive and motor learning tasks.

Our current understanding of cerebellar function is rooted in the foundations of more than a century and a half of research. As early as 1809 it was noted that ablation of the cerebellum resulted in disturbances of posture and voluntary movement<sup>2</sup>. Subsequent theories have stressed a role for the cerebellum in the coordination of goal-directed and spontaneous movements, the regulation of posture and vestibular function (see Ref. 3 for a review). The evolution of ideas continued with theories that stressed the role of the cerebellum in regulating reflex gain, which were derived from knowledge of the involvement of the cerebellum in reflex control, and advances in anatomical and control-system approaches<sup>4</sup>. Later theoretical and experimental developments prompted an expansion of this concept to include adaptive modification of on-line motor processes<sup>5,6</sup>. More recently, the traditional concepts of cerebellar function have been challenged by work with classical conditioning, which indicates the importance of this structure for the establishment, retrieval and use of as-

sociations between stimuli to generate new context-dependent and adaptive responses<sup>7</sup>. Current ideas build on this advance to suggest a role for the cerebellum in cognitive as well as motor processes<sup>8</sup>.

Anyone examining the structure of the cerebellum is immediately struck by the seemingly para-crystalline nature of its anatomical organization. Two key components of this organization are established during cerebellar development: a highly specific and uniform laminar arrangement of cells in the cerebellar cortex; and an equally specific and uniform microcircuitry. In many respects, these features make the cerebellum an ideal system in which to study mechanisms that are critical for the development of complex neuronal systems in general. For example, at the cellular level, radial migration proceeds in both an outward (via Purkinje and nuclear neurons) and an inward (via granule cells) direction. Goldowitz and Hamre<sup>9</sup>, and Oberdick and colleagues<sup>10</sup> review the many dramatic insights that have been gained in our understanding of this process. It is now clear that the highly ordered cerebellar mosaic is a consequence of molecular cues, as well as genetic instructions. Molecular cues appear to help to guide sets of afferents to terminate within particular sagittal and rostrocaudal zones of the cerebellar cortex and might even help to specify where these afferent fibres terminate on specific cell types in cerebellar cortex.

Klockgether and Evert<sup>11</sup> describe the role of specific genetic abnormalities in the production of a group of inherited neurodegenerative disorders termed the hereditary ataxias. These disorders are characterized by progressive motor difficulties that result from degeneration of the cerebellum and its afferent and efferent connections. Importantly, there has been considerable recent progress in determining the cellular and molecular mechanisms through which these genetic abnormalities lead to neuronal degeneration and produce their devastating effects. For example, the autosomal dominant ataxias (spinocerebellar ataxias 1, 2, 3 and 7) are now known to be caused by the inheritance of unstable CAG tri-nucleotide repeats in specific genes. These repeats are thought to cause abnormal polyglutamine sequences in the proteins they encode. The abnormal proteins accumulate in the nuclei of neurons where they form intranuclear inclusions, disrupt normal cell function and ultimately produce motor difficulties.

The cerebellum is perhaps one of the few sites in the central nervous system where the pattern of intrinsic connections is known in considerable detail. This knowledge has been the catalyst for many of the models and theories of cerebellar function. De Zeeuw and colleagues<sup>12</sup> describe several unique features about the microcircuitry in the inferior olive, the source of climbing fibers to the cerebellar cortex. They propose that these features are consistent with recent proposals that the olive plays an important role in both motor learning and central timing. On the other hand, they argue that the microcircuitry of

the olive does not support the proposal that it functions as a comparator of intended and achieved movements.

Indeed, a major focus of cerebellar research is its contribution to motor learning and adaptive plasticity. Strata and Rossi<sup>13</sup> provide a novel suggestion about how climbing fibers could be involved in these processes. In experiments where the Purkinje cells were deleted, or the activity of cerebellar cortex was depressed, the terminal climbing-fiber branches retracted. In contrast, when extra postsynaptic sites were available, there was a robust outgrowth of terminal arbors. Strata and Rossi propose that climbing fibers might undergo dynamic adjustments in their anatomical features that enable them to participate in physiological plasticity.

Daniel and colleagues<sup>14</sup> examine the precise physiological mechanisms through which the cerebellum is thought to contribute to motor learning, namely Long Term Depression (LTD) of synaptic transmission at parallel-fiber/Purkinje-cell synapses. They first summarize what is known about the mechanisms involved in LTD induction, from activation of voltage-gated calcium channels, activation of ionotropic and metabotropic glutamate receptors, to stimulation of protein kinase C and nitric oxide formation. They then examine the role of intracellular calcium release in LTD induction, localize the sources and targets of nitric oxide, and indicate a postsynaptic site for LTD expression. Finally, they argue in favor of a role for LTD in motor learning based on recent experiments using transgenic mice.

Ito<sup>15</sup> reviews the role for LTD in one particular form of motor learning – adaptive modification of the vestibulo-ocular reflex (VOR). Indeed, he has pioneered the use of the VOR as a model system for examining cerebellar function. Ito's presentation focuses on three different experimental approaches: the effects of cerebellar lesions on VOR adaptation, the activity of cerebellar neurons during adaptation, and the consequences of pharmacological or genetic manipulations of the cerebellum on VOR adaptation. He uses results from these studies to bolster his arguments for the involvement of the cerebellum and LTD in VOR plasticity. Yeo and Hesslow<sup>16</sup> present evidence for cerebellar involvement in another form of learning, the associative learning that occurs during classical conditioning of nictitating membrane and eye-blink responses. Yeo and Hesslow, as well as Ito, address the major questions that face this field of research, such as: where are the sites of motor learning – cerebellar cortex and/or the deep nuclei? How much of the learning in various paradigms is cerebellar and how much is extra-cerebellar? Is the cerebellum a site of long-term storage of adapted and conditioned responses?

Two articles in the *TICS* issue examine computational frameworks that can be used to describe how the cerebellum executes its role in coordinating movement and other aspects of behavior. Thach<sup>17</sup> proposes that the cerebellum participates in a large range of motor and cognitive processes by providing a site for stimulus-response linkage through trial and error learning. The parallel fiber is the proposed agent of stimulus-response linkage. Thus, according to Thach, the parallel fiber serves as a combiner of downstream motor and cognitive elements. Wolpert and his col-

leagues<sup>18</sup> examine the structure of the cerebellum and conclude that it supports certain types of models of the motor apparatus. These include 'inverse' models that provide the neural command necessary to achieve a particular desired trajectory, and 'forward' models that predict the consequences of actions, and overcome time delays associated with feedback control. Wolpert *et al.*'s computational model of the cerebellum includes multiple paired forward and inverse models. They argue that this arrangement can be advantageous for motor learning and control.

The last three articles in the compilation deal with the recent evidence that the cerebellum contributes to non-motor, as well as motor function. It has long been known that the cerebellum receives input from a wide variety of sources, including areas of frontal, prefrontal, cingulate and posterior parietal cortex. This information was thought to be funneled into the motor system to generate and control movement. Middleton and Strick<sup>19</sup> review the new findings that cerebellar output is more widespread than previously thought and might target those same cortical areas that provide input to the cerebellum. Furthermore, they summarize the recent evidence that cerebellar signals to non-motor areas of cortex are involved in cognitive operations. Desmond and Fiez<sup>20</sup> review the results of functional imaging studies of the cerebellum that have provided many new insights into its function. These studies indicate that the cerebellum is involved in such diverse activities as working memory, implicit and explicit learning and memory, and language. In addition, motor and non-motor functions appear to be distributed within different regions of the human cerebellar cortex. Finally, Schmahmann's analysis<sup>21</sup> of the behavioral consequences of cerebellar lesions in humans suggests that cognitive and emotional changes might be prominent or even the principal manifestations of cerebellar damage in selected patients. Indeed, he proposes the identification of a specific neurological condition termed the 'cerebellar cognitive affective syndrome' in which cerebellar damage leads to a 'dysmetria of thought' by depriving cognitive circuits of the benefit of cerebellar modulation. Thus, Schmahmann and others have viewed the cerebellar influence on cognitive processes as analogous to its influence on motor processes.

It should be recognized that the articles in this compilation represent a mere sample of current cerebellar research. Space considerations alone required the initial list of 75 potential contributors to be trimmed down to those finally included. The list of references at the end of each article should provide an important resource to guide those interested in obtaining additional information on a particular topic.

One of our goals in combining these special issues was to review the dramatic increases in our knowledge about the cerebellum without neglecting or ignoring either the cerebellum's 'constituent elements and processes' or the 'pattern of the tapestry.' However, what distinguishes brain cells from cells in other organs is the capacity of ensembles of neurons in the working brain to produce behavior. While this feature depends on development and the integrative properties of neurons, it is not explained by them. We are far from a complete understanding of cerebellar function. Indeed, we are still discovering the full range of behaviors that are under cerebellar control. We believe that

new insights into cerebellar function will most likely come from an integrative approach which recognizes that, when considering brain function, the whole is always greater than the sum of the parts.

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# T I C S O V E R V I E W

This special issue of *TINS* is devoted to describing the current, exciting research on the cellular, molecular and physiological mechanisms of the cerebellum. Our sister journal, *TICS*, is also a specially themed issue and contains articles on learning, language and cognitive functions of the cerebellum. Subscriptions to *TICS*, and single copies of the issue are available – see advertisement on p. IV.

## Cerebellar learning in vestibulo–ocular reflex, by M. Ito

The vestibulo–ocular reflex automatically stabilizes the visual image on the retina during head movements by evoking eye movements in the opposite direction to the head movements. This reflex has been studied extensively as a model system for understanding the functions of the cerebellum. In this review, Ito focuses on studies that have suggested a role for the flocculus in the learning mechanisms that contribute to the vestibulo–ocular reflex.

## Cerebellum and conditioned reflexes, by C.H. Yeo and G. Hesslow

Recent advances in our understanding of the role of the cerebellum in classically conditioned eyeblink responses are reviewed by Yeo and Hesslow. This article therefore focuses on role of the cerebellum in learning new movements rather than on the modification of existing reflexes, and discusses the important contributions of the mossy and climbing fibres in this type of motor learning.

## What is the role of the cerebellum in motor learning and cognition? by W.T. Thach

This article proposes that the role of the cerebellum is to provide a substrate for the combination of single-response elements into larger groupings, so that the occurrence of a sensory or experiential context automatically triggers a combined response. The key contribution of parallel fibres to this combining and coordinating function is reviewed.

## Internal models in the cerebellum, by D.M. Wolpert, R.C. Miall and M. Kawato

A computational perspective on the role of the cerebellum in motor learning and control is provided by this article. Wolpert and colleagues suggest that the cerebellum instantiates both inverse and forward models to solve a specific problem in motor control: the conversion of a desired hand or eye trajectory into appropriate motor commands.

## Cerebellar output: motor and cognitive channels, by F.A. Middleton and P.L. Strick

Anatomical evidence for distinct output channels that project to individual cortical areas including areas of premotor and prefrontal cortex are described. This article reviews recent advances in our understanding of the specific neural substrates that facilitate the participation of the cerebellum in both motor and cognitive aspects of behaviour.

## Neuroimaging studies of the cerebellum: language, learning and memory, by J.E. Desmond and J.A. Fiez

Recent neuroimaging results that provide evidence for the involvement of the cerebellum in working memory, implicit and explicit learning, memory and language are described in this review. The current problems faced by researchers who utilize neuroimaging techniques to examine cerebellar function are highlighted. This review culminates with a series of outstanding questions that need to be addressed by researchers investigating cerebellar function using neuroimaging methods.

## Dysmetria of thought: clinical consequences of cerebellar dysfunction on cognition and affect, by J.D. Schmahmann

The contribution of the cerebellum to higher cognitive function is discussed in this review. The results of clinical investigations into the cognitive and emotional effects of acquired cerebellar lesions in adults and children are described and the concept of 'dysmetria of thought' in cerebellar cognitive affective syndrome is advanced.