Neuronal circuit function and dysfunction in the cerebellum: from neurons to integrated control

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Introduction

This special issue follows the meeting *The Cerebellum: From Neurons to Higher Control and Cognition* held in Pavia, Italy, on 8-9 July 2010.[1]

Ever since the early anatomical discoveries by Golgi and Ramon Y Cajal (1-3), cerebellar neuroscience has provided pioneering observations on the nature of ionic channels, synaptic transmission and circuit organization, expanding to such an extent that it still represents a benchmark for brain sciences (2). Cerebellar investigations are providing amongst the highest resolution recordings at cellular and subcellular level, innovative techniques for neuronal circuit analysis and functional imaging of higher control functions. This stimulating experimental activity is supported by remarkable attempts to develop realistic computational models and multi-scale brain theories, projecting cerebellum neuroscience towards the integration of molecular-cellular mechanisms into circuit and systemic level dynamics. The clinical interest in the cerebellum has also been revitalized by this structure's core involvement not just in motor pathologies like ataxia but also in cognitive pathologies like autism and dyslexia.

The papers included in this issue cover cerebellum neuronal circuit functions and synaptic plasticity, moving from neurons to integrated control and considering the potential causes of cerebellar ataxia and motor learning dysfunction. Current models of the cerebellum are reviewed (Dean and Porrill) and several genetic mutations are considered in relation to their ability to alter cerebellar neuron excitability (Libster et al., Empson et al.), synaptic transmission and long-term synaptic plasticity (Le Guen and De Zeeuw, Rinaldo and Hansel). Finally, the impact of transcranial magnetic stimulation (TMS) on cerebellar long-term synaptic plasticity (Colnaghi et al., Koch) is evaluated as TMS emerges as a new tool for eliciting long-term synaptic plasticity in the human brain with potential implications for neurological rehabilitation.

Cerebellar connections and functions: sensory-motor and cognitive aspects

Although the cerebellum is fundamental for motor coordination and learning, it also appears to be strongly implicated in cognition, attention and emotions (4-8). Different parts of the cerebellum contribute to distinct aspects of behavior. The *vestibulo-cerebellum*, constituted by the flocculo-nodular lobe, regulates equilibrium and vestibulo-ocular reflexes: it receives mostly vestibular and ocular inputs. The *spino-cerebellum*, including the vermis and the intermediate part of the hemispheres, is involved in movement execution, including feedback adjustments; it receives somatosensory, labyrinthine, visual and auditory input. The *cerebro-cerebellum*, represented by the lateral part of the cerebellar hemispheres, plays an important role in preparation, initiation and timing of motor acts via the dentate nuclei; its principal inputs arise from the premotor and posterior parietal cortex. Prominent among these connections are the loops involving the cortico-cerebellar oculomotor system (9,10). Moreover, the association and limbic areas are largely connected with the posterior lobe of the cerebellum, in particular crus I and II.

Reciprocal connections appear to transmit information through the cortico-nuclear microcomplex to the deep cerebellar nuclei and from there to the thalamus and back to the cerebral cortex (11-13). By maintaining a similar anatomic organization in all its parts, the cerebellum could organize and modulate cognition and emotion in the same way as it organizes and modulates motor coordination and control. Accordingly, cerebellar alterations affecting the cerebello-cortical loops may lead not only to motor abnormalities but also to behavioral, cognitive and affective alterations, which may be manifested as severe psychiatric and developmental disorders. The cerebellum is fundamental for contextualizing specific stimuli and coordinating their spatio-temporal evolution, generating coherent ensemble activities (14-16). Therefore, dysfunction of the cerebellar circuits and of information reentry toward the frontal and parietal cortex may contribute to preventing the formation of coherent and contextualized behaviors. Additionally, the cerebellum is critical for revealing differences (either error or novelty) between predictions elaborated by the cortex and the reality

[1] Meeting abstracts can be found at: http://www.frontiersin.org/events/The_Cerebellum_from_neurons_t_1/1095/cellular_neuroscience

conveyed by experience through the senses and motor interactions. Thus, dysfunction of the cortico-cerebellar circuits may prevent the detection of novelty and impair attention switching (4,5,14-18).

Cerebellar ataxia and the cerebellar cognitive affective syndrome (CCAS)

Ataxia (from the Greek α–$\tau\acute{\alpha}\xi\iota\varsigma$, meaning "lack of order") is a neuropathological state that consists of gross lack of coordination of muscle movements. Ataxia is caused by dysfunction of those parts of the nervous system that coordinate movement and includes forms of cerebellar, sensory and vestibular origin. *Cerebellar ataxia* is expressed through a variety of elementary neurological deficits, such as antagonist hypotonia, asynergy, dysmetria, dyschronometria, and dysdiadochokinesia. How and where these abnormalities manifest themselves depends on which cerebellar structures have been damaged and whether the lesion is bilateral or unilateral. In very general terms, 1) dysfunction of the vestibulo-cerebellum impairs body balance (Romberg test) and the control of eye movements (saccade alterations, nystagmus), 2) dysfunction of the spino-cerebellum impairs gait (wide-based "drunken sailor" gait, characterized by uncertain start and stop, lateral deviations, and unequal steps), 3) dysfunction of the cerebro-cerebellum causes disturbances in carrying out voluntary, planned movements. These disturbances include intention tremor (coarse trembling, accentuated on the execution of voluntary movements, possibly involving the head and eyes as well as the limbs and torso), peculiar writing abnormalities (large, unequal letters, irregular underlining), and a peculiar pattern of dysarthria (slurred speech, sometimes characterized by explosive variations in voice intensity despite a regular rhythm). Finally, a less known but important sign is so-called *dysmetria of thought*, which arises as a consequence of damage to the cortico-cerebellar connections linking the cerebellum to prefrontal and limbic areas. This disturbance configures the *cerebellar cognitive affective syndrome* (CCAS) (6,19-22). CCAS is characterized by: 1) disturbances of executive functions, which include deficient planning, set-shifting, abstract reasoning, working memory, and decreased verbal fluency; 2) impaired spatial cognition, including visual-spatial disorganization and impaired visual-spatial memory; 3) personality change characterized by flattening or blunting of affect and disinhibited or inappropriate behavior; 4) linguistic difficulties, including dysprosody, agrammatism and mild anomia. The net effect of these cognitive disturbances is a general lowering of overall intellectual performance resembling a prefrontal syndrome.

The various components of ataxia have overlapping causes, and therefore can either coexist or occur in isolation. They include the following.

1) Focal lesions (associated with stroke, brain tumors, multiple sclerosis).

2) Exogenous substances with depressant, dissociative or toxic effects on central nervous system function (e.g. ethanol, cannabis, ketamine, PCP, dextromethorphan, most antiepileptic drugs, methylmercury).

3) Metabolic disorders (such as vitamin B12 deficiency).

4) Non-hereditary cerebellar degeneration (including chronic ethanol abuse, paraneoplastic cerebellar degeneration, high altitude cerebral edema, celiac disease, normal pressure hydrocephalus, cerebellitis, prion disease).

5) Hereditary ataxias caused by several forms of degeneration of the cerebellum and/or of the spinal cord – the autosomal dominant disorders include spinocerebellar ataxia (SCA), episodic ataxia (EA), olivo-cerebellar ataxia and dentatorubropallidoluysian atrophy; the autosomal recessive disorders include Friedreich's ataxia and Niemann Pick disease, ataxia-telangiectasia, and abetalipoproteinemia; the X-linked ataxic condition is the fragile X-associated tremor/ataxia syndrome.

6) Arnold-Chiari malformation.

7) Recently, several indications suggest that cerebellar alterations are involved in the pathogenesis of autism (8,21).

The relationship between neurons, networks and cerebellar functions

Besides the complex nature and pathogenesis of ataxia in humans, several related forms of cerebellar disturbances can be revealed in the laboratory animal. In several cases it is possible to associate ataxic symptoms or milder motor learning deficits with ionic channel mutations or other genetic alterations. This provides scope for developing animal models, which can help in determining the nature of cerebellar circuit function and dysfunction. Moreover, some of these animal models can be reconnected to channelopathies or other mutations causing forms of hereditary cerebellar ataxia (e.g. EA and SCA).

Mutations affecting granule cell synaptic currents and ionic channels can cause various ataxic symptoms and motor learning deficits (23-27), although the impact of cell-specific mutations has not yet been reported. Investigation in Purkinje cells is much more advanced and is reviewed here. Mutation in Purkinje cell calcium-dependent potassium channels can cause motor performance deficits (Libster et al., Empson et al.), while several mutations in synaptic transmission and long-term synaptic plasticity cause motor learning deficits (Le Guen and De Zeeuw; Rinaldo and Hansel). These results have to be considered in view of two recent cellular theories on cerebellar functioning addressing the role of the granular layer (28-31) and of the inferior olive-Purkinje cell circuit (32-35).

Once the critical cellular mechanisms are identified, one main problem that remains to be solved is how the cerebellar circuitry generates the computations required to control learning and coordinate spatio-temporal sequences. Current theoretical approaches are summarized (Dean and Porrill) and compared to most recent computational models

of the cerebellar circuit (36). These investigations aim to identify the general algorithm subtending the various sensory-motor and cognitive operations performed by the cerebellum.
Finally, the recent development and application of repetitive TMS (rTMS) to the cortico-cerebellar circuits is reviewed here both for limb and eye-movement studies. rTMS makes it possible to influence cerebellar long-term synaptic plasticity (Colnaghi et al., Koch) using patterns similar to those used in animal models *in vitro,* providing a bridge between cellular physiology and human behavior. The ability of rTMS to elicit long-term synaptic plasticity in the human cerebellum carries potential implications for neurological rehabilitation.

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