

# Cerebellum in Neurological Disorders: A Review on the Role of Inter-Connected Neural Circuits

## Mini Review

### Abstract

Recent studies have indicated the additional role of cerebellum beyond motor coordination non-motor and socio-cognitive tasks. Exploration of cerebellar roles in timing and plasticity have been attributed specific roles in neurological conditions such as ataxia, severe disorders such as Parkinson's and epilepsy. Cerebellar dysfunctions elaborate the need of research on cerebellar circuitry and physiology to better understand neurological functions and dysfunctions. Structural and functional studies of cerebellum also implicate the connection between cerebellum with inter-connected circuits such as thalamo cortical and basal ganglia networks during motor and non-motor functions. In this review, we list some of recently perceived roles of cerebellum in information processing, neurological conditions in disorders.

**Keywords:** Cerebellum; Ataxia; Parkinson 's disease; Epilepsy; Neurological Disorders

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## Introduction

Recent advances in neuroscience encouraging the development of new technologies including anatomical explorations of 100 billion nerve cells, decoded activity patterns in neural circuits provided new information to understand the neurological conditions and their mechanistic basis [1,2]. Although until the end of 18<sup>th</sup> century, the role of cerebellum was co-involved solely with motor coordination its role in motor function has been further explored [3] and has led to experiments and theories that now include cerebellum's contributions to cognitive processing and emotional control. Cerebellum receives sensory information as an input from the spinal cord and other parts of the brain and generates a motor movements as output. Cerebellar cortex inhibits and excites the motor control actions that are generated elsewhere in the brain [4] and have been associated to help maintain posture and balance, speech and movement coordination resulting from smooth muscle activity. Mossy fiber inputs have been known to carry information on the goal of a movement, sensory feedback about the states of the body and the sensory representations of external world, and the efferent copy of motor commands to granule cells [5]. Purkinje cells, mainly activated by parallel fiber inputs from granule cells, project to deep cerebellar nuclei, which further transmit information to downstream motor systems such as the ocular motor system, spinal cord and cerebral cortex via the thalamus.

## Prediction and correction using cerebellar internal models for ataxia

Cerebellar damage results in uncoordinated, inconstant and dissymmetric movements known as ataxia causes mismatch between dynamics modeled by the brain and actual body dynamics resulting in ataxia condition. A study [6], It used both behavioral and computational approaches to demonstrate cerebellar patient movement deficits from the biased internal models. Mathematical

modeling suggests bias in ataxic movements to be an internal misestimate of arm inertia. Another study [6] emphasized that an undamaged cerebellum is critical for maintaining accurate internal model of dynamics. In the case of Friedreich's ataxia, cerebellum was observed with significant loss of grey matter and white matter using voxel-based morphometry [7]. Studies on abnormalities related to brain connectivity and functions were reported earlier [8].

Structural and functional relationship of the major components of central nervous system includes coordination of loco motor movements in cerebellum [9] is one among five properties. More than a century later, a study [10] explained electro physiological properties of cerebellar learning behavior neural circuit and predicted that synaptic efficacy decreases when the parallel fibers and climbing fibers are activated. Some studies focus on cerebellar function as a sensory motor control system modeled as embedded forward controllers and internal structures for error prediction and learning [11-15] based on the connection statistics of the circuit, the geometry and the connectivity of the circuit [16].

Recent imaging studies have shown that the cerebellar outputs to a vast area of neocortex and have reciprocal connections with the basal ganglia [17,18]. Cerebellar cortex models [19,20]. helps to understand the structure function relationship between neurons, impact of the membrane properties on spikes, and the role of synaptic plasticity and synaptic dynamics during spike-time dependent plasticity [21,22] as well as impacting various input parameters on computing signals and transferring information [10,23,24] which depend on the position and orientation of the robotic manipulator [25-28]. Understanding the cellular mechanisms of the encoding information by the cerebellum ideally includes identifying what the properties of synaptic inputs to the nuclei are, how the excitability of neurons is affected by these stimuli, and which patterns of activity modify synaptic inputs and spike outputs to yield motor coordination and learning

[29]. Associated with physiological roles, cerebellar cortex, deep cerebellar nuclei and the inferior olive are the three main hubs of the cerebellar circuit. Each of these circuits involves a relatively modest number of cell types with synaptic connectivity between the hubs being highly parallel and modular. Cerebellum has an important role in movement disorders in association with basal ganglia (BG) since, the functions of both sub cortical structures are almost same. Recent findings have associated cerebellum with neurological disorders and conditions such as Parkinson's disorder, ataxia, dyskinesia and degradation of movement and increased tremors.

### **Cerebellum as target in Parkinson's disease**

Parkinson's disease (PD) is a neurodegenerative disorder that affects motor and cognitive behavior through cerebello-thalamo-cortical circuits. Multiple functional neuro imaging studies demonstrated hyper activation in the cerebellum in patients with Parkinson's disease [30-35]. From a computational angle, it has been suggested that the cerebellum is specialized for supervised learning based on the error signal encoding whereas basal ganglia are specialized for reinforcement learning (RL) based on the reward signal encoded in the dopaminergic fibers from the substantianigra and cerebral cortex is specialized for unsupervised learning based on plasticity between cortical areas. Damage to the basal ganglia or cerebellar components of circuits with motor areas of cortex have been known to lead to motor symptoms, whereas damage of the sub cortical components of circuits with non-motor areas of cortex has been known to cause higher-order deficits [36].

In animal models of PD, oscillatory activity at tremor frequencies have been recorded in motor thalamus along with this hyper activations in some other regions such as motor cortex and striatum and weak striato-thalamo-cortical and striato-cerebellar connectivity. Previous studies have shown that disynaptic connections transmit STN activity to cerebellar cortex [37,38]. The motor signs and cerebellar activation have been known to be improved by normalizing the functions of cerebellum through various treatment methods including surgical treatment and deep brain stimulation [39-42]. Deep brain stimulation of the STN is also an effective treatment for the movement symptoms of PD [43,44]. Deep brain stimulation may alter STN activity and reduce STN abnormal output to the cerebellum.

### **Lesional cerebellar Epilepsy**

Over the last decades, advances in knowledge on epileptogenicity and seizure spread have led to better understanding of the role of sub cortical structures during epilepsy [45] myoclonic seizure is most common in lesional Cerebellar Epilepsy, which has been reported in patients [46-50]. A study [51] suggested that propagation of epileptic activity from cerebellar hematoma may cause myoclonus. This epileptic nature of myoclonic 'seizures' is further braced by evidences from invasive EEG studies. Myoclonic seizures occurs with dystonia, which causes sustained muscle contraction, repetitive movements and abnormal postures [52]. Though there have been extensive reports of dystonia associated with cerebellar lesions, the pathophysiology is not clear. However the structural and functional interactions between the

cerebellum and basal ganglia circuits plays a major role [53,54] In this movement disorder dystonic, movement disorder has been associated to both basal ganglia and cerebellar circuits, which forms multi synaptic loops with cerebral cortex [55].

Absence seizures are kinds of epileptic seizures which lasts for few seconds and characterized by unconsciousness or absent state and appear to be initiated in a putative control initiation site with expression of 5-9Hz due to decreased GABAA receptor function [45]. Absence seizures have been associated to abnormal electric activity in reciprocally connected thalamo-cortical areas [52-56].

The abnormalities related to white matter reflects in increased cortical excitability and cause cognitive, linguistic and behavioral/emotional deficit in both during and between seizures [57]. Related work has been done by [58], using this Diffusion Tensor Imaging (DTI) to quantify structural abnormalities of Default Mode Network (DMN) region in CAE patients indicated structural impairments in DMN regions in CAE patients experiments [59]. This will be indicated that the cerebellum is a powerful modulator of temporal lobe epilepsy. The study based on mouse models used online seizure detection and responsive opt genetic interventions to understand the role of cerebellum in spontaneous temporal lobe seizures indicated that the cerebellum inhibited spontaneous temporal lobe seizures.

### **Conclusion**

Recent advances in cerebellum research has helped augment understanding functions related to both motor and cognitive domains allowing evaluating the effectiveness of certain treatments for neuro-disorders. Possibility that the cerebellum having the feedback internal models (forward and inverse) retain and integrate the system exploiting mechanisms of motor learning and control.

Cerebellar neuronal disorders are being treated using transcranial direct current stimulation (tDCS), deep brain stimulation and surgical interventions promising solutions towards Parkinson's, dystonia, essential tremor and cerebellar ataxia. Such methods also influence study of non-motor functions like pain experiences, nociceptive perceptions and cognitive functions. It implicates studies of inter-connected circuits and the need of explorations of roles of cerebellum in timing and plasticity.

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