MedCrave
Step into the World of Research

Journal of Neurology & Stroke

Mini Review

Open Access

CrossMark

Cerebellum in neurological disorders: a review on the role of inter–connected neural circuits

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

Volume 6 Issue 2 - 2017

Arathi G Rajendran, Chaitanya Nutakki, Hemalatha Sasidharakurup, Sandeep Bodda, Bipin Nair, Shyam Diwakar

Amrita School of Biotechnology, Amrita Vishwa Vidyapeetham (Amrita University), India

Correspondence: Shyam Diwakar, Amrita School of Biotechnology, Amrita Vishwa Vidyapeetham (Amrita University), Amritapuri campus, Clappana PO, Kollam, Kerala, 69 525, India, Email shyam@amrita.edu

Received: December 14, 2016 | **Published:** February 16, 2017

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 18th 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 simulation.[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 Tenser 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.

Acknowledgments

This work derives direction and ideas from the Chancellor of Amrita University, Sri Mata Amritanandamayi Devi. This review was inspired by The School of Brain Cells and Circuits "Camillo Golgi" 2016 organized by Egidio D'Angelo of University of Pavia (Italy), Claudia Gandini Wheeler–Kingshott of UCL (UK) and gratefully acknowledge the support for our ongoing collaborations. Authors also thank Giovanni Naldi, Thierry Nieus of University of Milan (Italy) and Sergio Solinas of CNR (Sicily, Italy). This work is supported by Grants SR/CSRI/60/2013, SR/CSRI/61/2014 from DST and BT/PR5142/MED/30/764/2012 from DBT, and by Sri Visvesvaraya Faculty Fellowship, MeitY and Government of India and by Embracing the World.

Conflicts of interests

The authors disclose no conflicts of interest.

References

1. D'Angelo E. The new challenge for Functional Neurology. *Funct Neurol.* 2015;30(4):215.
2. D'Angelo E, Galliano E, De ZeeuwCI. Editorial:The Olivo–Cerebellar System. *Front Neural Circuits.* 2016;9:66.
3. Koziol LF, Budding D, Andreasen N, et al. Consensus Paper :The Cerebellum â€TM s Role in Movement and Cognition. *Cerebellum.* 2013;13(1):151−177.
4. Berends M, Maex R, De Schutter E. A detailed three–dimensional model of the cerebellar granular layer. *Neuro computing.* 2004;58−60:587−592.
5. Dell Nave R, Ginestroni A, Giannelli M, et al. Brain structural damage in Friedreich's ataxia. *J Neurol Neurosurg Psychiatry.* 2008;79(1):82−85.
6. Bhanpuri NH, Okamura AM, Bastian AJ. Predictive Modeling by the Cerebellum Improves Proprioception. *J Neurosci.* 2013;33(36):14301−14306.
7. Piochon C, Kano M, Hansel C. LTD–like molecular pathways in developmental synaptic pruning. *Nat Neurosci.* 2016;19(10):1299−1310.
8. Flourens P. De la vie et de l'intelligence. 1st edn. Paris: Garnier Freres. 1958.
9. Albus JS. A theory of cerebellar function. *Math Biosci.* 1971;10:25−61.
10. Kawato M. Internal models for motor control and trajectory planning. *Curr Opin Neurobiol.* 1999;9(6):718−727.
11. Marr D. A theory of cerebellar cortex. *J Physiol.* 1969;202(2):437−470.

12. Wolpert DM, Miall RC, Kawato M. Internal models in the cerebellum. *Trends Cogn Sci.* 1998;2(9):338−347.

13. Kawato M. Cerebellum:*Models Encycl Neurosci.* 2009;2:757−767.

14. Bostan AC, Dum RP, Strick PL. the basal ganglia communicate with the cerebellum. Proc Natl Acad Sci U. S. A. 2010;107(18):8452−8456.

15. Stoodley CJ, Schmahmann JD. Functional topography in the human cerebellum:a meta–analysis of neuroimaging studies. *Neuroimage.* 2009;44(2):489−501.

16. D'Angelo E, Mazzarello P, Prestori F, et al. The cerebellar network:From structure to function and dynamics. *Brain Res Rev.* 2011;66(1–2):5−15.

17. Dean P, Porrill J. Evaluating the adaptive–filter model of the cerebellum. *J Physiol.* 2011;589(14):3459−3470.

18. Kawato M. Internal models for motor control and trajectory planning. *Curr Opin Neurobiol.* 1999;9(6):718−727.

19. Beaton A, Marien P. Language cognition and the cerebellum:grappling with an enigma. *Cortex.* 2010;46(7):811−820.

20. D'Angelo E, De Zeeuw CI. Timing and plasticity in the cerebellum:focus on the granular layer. *Trends Neurosci.* 2009;32(1):30−40

21. Lackner JR, Dizio P. Gravitoinertial force background level affects adaptation to coriolis force perturbations of reaching movements. *J Neurophysiol.* 1998;80(2):546−53.

22. Chen–HarrisH, Wilsim M Joiner, Vincent Ethier, et al. Adaptive Control of Saccades via Internal Feedback. *J Neurosci.* 2008;28(11):2804−2813.

23. Pizoli CE, Jinnah HA, Billingsley ML, et al. Abnormal cerebellar signaling induces dystonia in mice. *J Neurosci.* 2002;22(17):7825−7833.

24. Shadmehr R, Mussa–Ivaldi F. Adaptive representation of dynamics during learning of a motor task. *J Neurosci.* 1994;14(5):3208−3224.

25. Catalan MJ, Ishii K, Honda M, et al. A PET study of sequential finger movements of varying length in patients with Parkinson's disease. *Brain.* 1999;122(3):483−495.

26. Payoux P, Remy P, Damier P, et al. Subthalamic nucleus stimulation reduces abnormal motor cortical over activity in Parkinson disease. *Arch Neurol.* 2004;61(8):1307−1313.

27. Ghaemi M, Raethjen J, Hilker R, et al. Monosymptomatic resting tremor and Parkinson's disease:a multitracer positron emission tomographic study. *Mov Disord.* 2002;17(4):782−788.

28. Rascol O, Agid Y, Damier P. Contrasting changes in cortical activation induced by acute high–frequency stimulation within the globus pallidus in Parkinson's disease. *J Cereb Blood Flow Metab.* 2009;29(2):235−243.

29. Turner RS, Grafton ST, McIntosh AR, et al. The functional anatomy of parkinsonian bradykinesia. *Neuroimage.* 2003;19(1):163−179.

30. Wu T, Hallett M. A functional MRI study of automatic movements in patients with Parkinson's disease Brain. 2005;128(10):2250−2259.

31. Yu H, Sternad D, Corcos DM, et al. Role of hyperactive cerebellum and motor cortex in Parkinson's disease. *Neuroimage.* 2007;35(1):222−233.

32. Doya K. Complementary roles of basal ganglia and cerebellum in learning and motor control. *Curr Opin Neurobiol.* 2000;10(6):732−739.

33. Bosch–Bouju C, Hyland BI, Parr–Brownlie LC. Motor thalamus integration of cortical, cerebellar and basal ganglia information:implications for normal and parkinsonian conditions. *Front Comput Neurosci.* 2013;7:163.

34. Sherman SM, Guillery RW. the role of the thalamus in the flow of information to the cortex. *Philos Trans R Soc Lond B Biol Sci.* 2002;357(1428):1695−1708.

35. Asanuma K, Tang C, Ma Y, et al. Network modulation in the treatment of Parkinson's disease. *Brain.* 2006;129(10):2667−2678.

36. Geday J, Østergaard K, Johnsen E, et al. STN–stimulation in Parkinson's disease restores striatal inhibition of thalamocortical projection. *Hum Brain Mapp.* 2009;30(1):112−121.

37. Grafton ST, Turner RS, Desmurget M, et al. Normalizing motor–related brain activity:subthalamic nucleus stimulation in Parkinson disease. *Neurology.* 2006;66(8):1192−1199.

38. Hilker R, Voges J, Weisenbach S, et al. Subthalamic nucleus stimulation restores glucose metabolism in associative and limbic cortices and in cerebellum:evidence from a FDG–PET study in advanced Parkinson's disease. *J Cereb Blood Flow Metab.* 2004;24(1):7−16.

39. Payoux P, Remy P, Miloudi M, et al. Contrasting changes in cortical activation induced by acute high–frequency stimulation within the globus pallidus in Parkinson's disease. *J Cereb Blood Flow Metab.* 2009;29(2):235−243.

40. Krack P, Fraix V, Mendes A, et al. Postoperative management of subthalamic nucleus stimulation for Parkinson's disease. *Mov Disord.* 2002;17(3):188−197.

41. Foit NA, van Velthoven V, Schulz R, et al. Lesional cerebellar epilepsy:a review of the evidence. *J Neurol.* 2016;264(1):1−10.

42. Boop S, Wheless J, Van Poppel K, et al. Cerebellar seizures. *J Neurosurg Pediatr.* 2013;12(3):288−292.

43. Bai X, Vestal M, Berman R, et al. Dynamic Time Course of Typical Childhood Absence Seizures: EEG Behavior and Functional Magnetic Resonance Imaging. *J Neurosci.* 2010;30(17):5884−5893.

44. Casellato C, Antonietti A, Garrido J, et al. Adaptive Robotic Control Driven by a Versatile Spiking Cerebellar Network. *PLoS One.* 2014;9(11):112265.

45. Crunelli V, Cope DW, Terry JR. Transition to absence seizures and the role of GABA(A) receptors. *Epilepsy Res.* 2011;97(3):283−289.

46. D'Angelo E, Galliano E, De Zeeuw C. Editorial:The Olivo–Cerebellar System. Front. *Neural Circuits.* 2016;9:66.

47. Limousin–Dowsey P, Pollak P, Van Blercom N, et al. Thalamic subthalamic nucleus and internal pallidum stimulation in Parkinson's disease. *J Neurol.* 1999;2:II42−II45.

48. Kalanovic VD, Popovic D, Skaug NT. Feedback error learning neural network for trans–femoral prosthesis. IEEE Trans. *Rehabil Eng.* 2000;8(1):71−80.

49. Jayakar PB, Seshia SS. Involuntary movements with cerebellar tumour. *Can J Neurol Sci.* 1987;14(3):306−308.

50. Koh KN, Lim BC, Hwang H, et al. Cerebellum Can Be a Possible Generator of Progressive Myoclonus. *J Child Neurol.* 2010;25(6):728−731.

51. Mink JW, Caruso PA, Pomeroy SL. Progressive myoclonus in a child with a deep cerebellar mass. *Neurology.* 2003;61(16):829−831.

52. Strazzer S, Zucca C, Fiocchi I, et al. Epilepsy and neuropsychologic deficit in a child with cerebellar astrocytoma. *J Child Neurol.* 2006;21(9):817−820.

53. Zamponi N, Passamonti C, Luzi M, et al. Fourth ventricle hamartoma presenting with progressive myoclonus and hemifacial spasms:case report and review of literature. *Child's Nerv Syst.* 2011;27(6):1001−1005.

54. Shen G, Nan G, Shin CW, et al. Combined focal myoclonus and dystonia secondary to a cerebellar hemorrhage:a case report. *BMC Neurol.* 2016;16:228.

55. Popa D, Spolidoro M, Proville RD, et al. Functional Role of the Cerebellum in Gamma–Band Synchronization of the Sensory and Motor Cortices. *J Neurosc.* 2013;33(15):6552−6556.

56. Proville RD, Spolidoro M, Guyon N, et al. Cerebellum involvement in cortical sensorimotor circuits for the control of voluntary movements. *Nat Neurosci.* 2014;17(9):1233−1239.

57. Neychev VK, Fan X, Mitev VI, et al. The basal ganglia and cerebellum interact in the expression of dystonic movement. *Brain*. 2008;131(9):2499−2509.

58. Hamandi K, Salek–Haddadi A, LaufsH, et al. EEG–fMRI of idiopathic and secondarily generalized epilepsies. *Neuroimage.* 2006;31(14):1700−1710.

59. Holmes MD, Brown M, Tucker DM. Are & quot; Generalized & quot; Seizures truly generalized? evidence of localized mesial frontal and frontopolar discharges in absence. *Epilepsia.* 2004;45(12):1568−1579.

60. Szaflarski JP, DiFrancesco M, Hirschauer T, et al. Cortical and subcortical contributions to absence seizure onset examined with EEG/fMRI. *Epilepsy Behav.* 2010;18(4):404−413.

61. Westmijse I, Ossenblok P, Gunning B, et al. Onset and propagation of spike and slow wave discharges in human absence epilepsy: *A MEG study Epilepsia.* 2009;50(12):2538−2548.

62. Rossi MA. Deep white matter track record of functional integrity in childhood absence epilepsy. *Epilepsy Curr.* 2012;12(6):234−235.

63. Qiu W, Gao Y, Yu C, et al. Structural abnormalities in childhood absence epilepsy: voxel–based analysis using diffusion tensor imaging. *Front Hum Neurosci.* 2016;10:483.

64. Krook–Magnuson E, Szabo GG, Armstrong C, et al. Cerebellar directed optogenetic intervention inhibits spontaneous hippocampal seizures in a mouse model of temporal lobe epilepsy. *e Neuro.* 2014;1(1).

65. Eccles JC, Ito M, Szentágothai J. The Cerebellum as a Neuronal Machine. Springer Berlin Heidelberg, Germany,1967.

66. Ito M. Control of mental activities by internal models in the cerebellum. *Nat Rev Neurosci.* 2008;9(4):304−313.

67. Lackner JR, Dizio P. Rapid adaptation to Coriolis force perturbations of arm trajectory. *J Neurophysiol.* 1994;72(1):299−313.

68. Marr D. A theory of cerebellar cortex. *J Physiol.* 1969;202(2):437−470.

69. Nave RD, Ginestroni A, Giannelli M, et al. Brain structural damage in Friedreich's ataxia. J. Neurol. Neurosurg. *Psychiatry.* 2008;79(1):82−85.

70. Rascol O, Sabatini U, Fabre N, et al. The ipsilateral cerebellar hemisphere is overactive during hand movements in akinetic parkinsonian patients. *Brain.* 1997;120(1):103−110.

71. Schmahmann JD, Caplan D. Cognition, emotion and the cerebellum. *Brain.* 2006;129(2):290−290.

Citation: Rajendran AG, Nutakki C, Sasidharakurup H, et al. Cerebellum in neurological disorders: a review on the role of inter–connected neural circuits. *J Neurol Stroke.* 2017;6(2):1–6. DOI: 10.15406/jnsk.2017.06.00196