Journal of Advanced Pharmaceutical Technology & Research
(An official Publication of Society of Pharmaceutical Education & Research)
Home
Current issue
Instructions
Submit article

J Adv Pharm Technol Res. 2016 Oct-Dec; 7(4): 123–126.
doi: 10.4103/2231-4040.191416

PMCID: PMC5052937

Neuroanatomical changes in Parkinson's disease in relation to cognition: An update

K. G. Prakash,[1] B. M. Bannur,[2] Madhavrao D. Chavan,[3] K. Saniya,[1] Kumar Sai Sailesh,[4] and Archana Rajagopalan[5]

Address for correspondence: Dr. K. G. Prakash, Department of Anatomy, Azeezia Institute of Medical Sciences and Research Centre, Meeyyannoor, Kollam, Kerala, India. E-mail: drprakashkg@gmail.com

Abstract

INTRODUCTION

Parkinson's disease (PD) is characterized by slowness of movement, rigidity, tremor, postural instability, and often cognitive impairments.[1] Although motor features are more prominent in PD, nonmotor features also have been diagnosed in PD patients.[2] Acetylcholine, norepinephrine, and serotonin may have a role in nonmotor features of PD. Features include cognitive impairment, psychological, autonomic, and sleep disorders which decrease the quality of life further.[3,4] The pathophysiological changes underlying impairment of cognition in PD are complex and not fully understood till date.[5] Hence, understanding

the structural changes responsible for cognitive decline in PD is essential for early diagnosis and to offer effective treatment.[6,7,8] In this review, we discuss the neuroanatomical changes in major brain structures responsible for cognition in PD.

CHANGES IN BASAL GANGLIA IN PARKINSON'S DISEASE

Since changes in the morphology of basal ganglia are noticed in bipolar and unipolar disorders also, it is essential to understand the changes in basal ganglia in PD for reliable diagnosis. Basal ganglia process the signals from the cortex for accurate execution of voluntary movements.[9] Basal ganglia play a key role in cognitive functions,[10] and lesion of basal ganglia causes impairment in cognitive functions.[11] In fact, basal ganglia are the most affected brain area in PD.[12] It was reported that there were two subtypes of PD and each type will affect basal ganglia in a different fashion. The subtypes include heterogeneous clinical phenotypes such as tremor dominant (TD) and postural instability/gait difficulty (PIGD).[13] PD patients had reduced fractional anisotropy within the substantia nigra and increased mean and radial diffusivity within the substantia nigra and globus pallidus. However, microstructural changes within the substantia nigra are severely affected in PIGD patients compared to TD.[14] Reduction of the neuromelanin pigmentation, neuronal loss, and Lewy bodies are observed in the substantia nigra.[15] In PD patients, basal ganglia undergo atrophy, which depends on severity and duration of the disease.[16] In PD patients, loss of attenuation and length of the dendritic spines of medium-sized spiny neurons located in the striatum has been reported.[17] Reduction in the volumes of the caudate nucleus and thalamus and white matter is observed in PD, which may be an early sign of disease progression.[18]

CHANGES IN CEREBELLUM IN PARKINSON'S DISEASE

Increased activity of the cerebellum was observed during cognitive tasks.[19] The cerebellum has reciprocal connections with basal ganglia, and Parkinson's-related morphological changes were observed in animal models and humans.[20] These changes include significant contraction in the left cerebellum, decrease in the gray matter volume in the right quadrangular lobe.[21] These changes may be induced by degeneration of dopaminergic neurons[22] as the cerebellum receives dopaminergic projections from basal ganglia, and dopaminergic receptors were present in the cerebellum.[23]

CHANGES IN BRAIN VOLUME IN PARKINSON'S DISEASE

Strong correlation exists between brain size and cognitive functions.[24] In PD patients, atrophy of the brain was observed in many cortical and subcortical areas, which contributes in decrease in the volume of the brain.[25] Interestingly, it was reported that volume of the frontal lobe, temporoparietal junction, parietal lobe, insula, anterior cingulate cortex, basal ganglia, and thalamus increased in PD patients.[26] Prefrontal lobe plays a crucial role in cognitive functions and in PD patients; loss of gray matter has been reported.[27,28]

CHANGES IN THALAMUS IN PARKINSON'S DISEASE

Thalamic lesions are found to impair cognitive functions such as language, memory, and attention.[29] Thalamic stimulation was effective in enhancement of cognition through activation of neocortex and hippocampus and modulating gene expression.[30] Approximately 30%-40% loss was reported in the thalamus in PD.[31] It was reported that volume of the thalamus decreases in PD.[18] In contrast, it was reported that thalamic shape but not volume changes in PD. As specific nuclei of the thalamus are involved in PD, atrophy of the caudal intralaminar nucleus and hypertrophy of rest of the nucleus result in altered shape of the thalamus.[32] Further, changes in white matter of the mediodorsal thalamus lead to depression in most of the PD patients.[33] Significant reduction in fractional anisotropy was reported

in anterior nucleus, dorsomedial nucleus, and ventral anterior nucleus of the thalamus.[34]

CHANGES IN HYPOTHALAMUS IN PARKINSON'S DISEASE

Role of the hypothalamus in cognitive functions is well reported.[35] Impairment of hypothalamic function was reported in PD patients. Neural degeneration was observed in all 13 nuclei of the hypothalamus with predominant degeneration in tuberomamillary nucleus and the lateral and posterior hypothalamic nuclei.[36] Further, decrease in the levels of dopamine, serotonin, melanin, and hypocretin in the hypothalamus of PD patients.[37] Development of sleep, endocrine, and autonomic disorders in PD may be due to dopamine malfunction in the hypothalamus.[37] Sleep disorders may be due to loss of gray matter in hypothalamus as melatonin levels are associated with volume of gray matter.[38] As hypothalamus functioning is affected in PD, the secondary degeneration may occur to the structures directly innervated by the hypothalamus such as striatum where the dopamine synthesis occurs.[39] This further worsens the PD.

CHANGES IN LIMBIC SYSTEM IN PARKINSON'S DISEASE

Influence of limbic structures on cognition was well documented.[40] Atrophy of gray matter was observed in Parkinson's patients with dementia.[41] Dopamine dysfunction in the limbic system leads to change in the creativity and emotional dysfunction in PD patients.[42] In amygdala, accessory cortical and central nuclei are affected more by PD, and cortical, accessory basal, and granular nuclei are least affected areas.[43] Posterior cingulum is the important structure in the papez circuit which is involved in processing of episodic memory.[44] It was reported that neuronal loss, gliosis, or demyelination in the white matter and metabolic changes occurs in the cingulum of PD patients.[44,45] Change in the spontaneous resting-state neural activity is reported in prefrontal cortex, which was considered as a factor for cognitive decline

in PD.[46] Further, regional atrophy in the hippocampus contributes to impaired verbal learning memory and visuospatial processing.[47]

CHANGES IN LOCUS COERULEUS IN PARKINSON'S DISEASE

Loss of noradrenergic neuronal and Lewy bodies formation was much higher in locus coeruleus (LC) than dopaminergic neuronal loss in PD patients. Resting tremors of PD are due to neuronal loss of LC.[48,49] About 35% of PD patients were depressed, and loss of noradrenergic pathways underlies the pathophysiology of depression in PD.[50] The pathological changes in LC of PD patients are peculiar and can be differentiated from changes that occur in other neurodegenerative diseases such as schizophrenia.[50] It was reported that simultaneous lesions of dopaminergic system, and LC causes metabolic dysfunction in the cerebral cortex and impairs cognitive functions in PD.[51]

CHANGES IN GLIAL CELLS IN PARKINSON'S DISEASE

All glial cells can influence the cognitive functions.[52] Structural changes occur in astrocytes in response to physiological and pathological conditions may influence the neurons through nonsynaptic communication with neurons.[53,54,55] Altered neuroglial interaction may be the underlying cause for many neurological diseases including PD.[56] Glial response in PD offers both beneficial and hazardous effects.[57]

CONCLUSION

In this review, we have presented the neuroanatomical changes of major brain structures related to cognition in PD. We have included the key findings of various studies to provide up-to-date information for better understanding of pathophysiology of PD, which helps researchers and clinicians in planning and developing new treatment methods for the benefit of PD patients.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Eriksen JL, Wszolek Z, Petrucelli L. Molecular pathogenesis of Parkinson disease. Arch Neurol. 2005;62:353–7. [PubMed: 15767499]

2. Hughes TA, Ross HF, Mindham RH, Spokes EG. Mortality in Parkinson's disease and its association with dementia and depression. Acta Neurol Scand. 2004;110:118–23. [PubMed: 15242420]

3. Levy G, Tang MX, Louis ED, Côté LJ, Alfaro B, Mejia H, et al. The association of incident dementia with mortality in PD. Neurology. 2002;59:1708–13. [PubMed: 12473757]

4. Goldman JG, Litvan I. Mild cognitive impairment in Parkinson's disease. Minerva Med. 2011;102:441–59. [PMCID: PMC3370887][PubMed: 22193376]

5. Yarnall AJ, Rochester L, Burn DJ. Mild cognitive impairment in Parkinson's disease. Age Ageing. 2013;42:567–76. [PubMed: 23868092]

6. Aarsland D, Bronnick K, Williams-Gray C, Weintraub D, Marder K, Kulisevsky J, et al. Mild cognitive impairment in Parkinson disease: A multicenter pooled analysis. Neurology. 2010;75:1062–9. [PMCID: PMC2942065] [PubMed: 20855849]

7. Domellöf ME, Elgh E, Forsgren L. The relation between cognition and motor dysfunction in drug-naive newly diagnosed patients with Parkinson's disease. Mov Disord. 2011;26:2183–9. [PubMed: 21661051]

8. Meireles J, Massano J. Cognitive impairment and dementia in Parkinson's disease: Clinical features, diagnosis, and management. Front Neurol. 2012;3:88. [PMCID: PMC3360424] [PubMed: 22654785]

9. Blandini F, Nappi G, Tassorelli C, Martignoni E. Functional changes of the basal ganglia circuitry in Parkinson's disease. Prog Neurobiol. 2000;62:63–88. [PubMed: 10821982]

10. Brown LL, Schneider JS, Lidsky TI. Sensory and cognitive functions of the basal ganglia. Curr Opin Neurobiol. 1997;7:157–63.[PubMed: 9142758]

11. Leisman G, Melillo R, Carrick FR. Clinical motor and cognitive neurobehavioral relationships in the basal ganglia. In: Franz E, editor. Basal Ganglia. Rijeka: InTech; 2013. pp. 1–30.

12. Obeso JA, Rodríguez-Oroz MC, Benitez-Temino B, Blesa FJ, Guridi J, Marin C, et al. Functional organization of the basal ganglia: Therapeutic implications for Parkinson's disease. Mov Disord. 2008;23(Suppl 3):S548–59. [PubMed: 18781672]

13. Jankovic J, McDermott M, Carter J, Gauthier S, Goetz C, Golbe L, et al. Variable expression of Parkinson's disease: A base-line analysis of the DATATOP cohort. The Parkinson Study Group. Neurology. 1990;40:1529–34. [PubMed: 2215943]

14. Nagae LM, Honce JM, Tanabe J, Shelton E, Sillau SH, Berman BD. Microstructural changes within the basal ganglia differ between Parkinson disease subtypes. Front Neuroanat. 2016;10:17. [PMCID: PMC4763054] [PubMed: 26941615]

15. Dickson DV. Neuropathology of movement disorders. In: Tolosa E, Jankovic JJ, editors. Parkinson's Disease and Movement Disorders. Hagerstown, MD: Lippincott Williams & Wilkins; 2007. pp. 271–83.

16. Reetz K, Gaser C, Klein C, Hagenah J, Büchel C, Gottschalk S, et al. Structural findings in the basal ganglia in genetically determined and idiopathic Parkinson's disease. Mov Disord. 2009;24:99–103. [PubMed: 18823048]

17. Stephens B, Mueller AJ, Shering AF, Hood SH, Taggart P, Arbuthnott GW, et al. Evidence of a breakdown of corticostriatal

connections in Parkinson's disease. Neuroscience. 2005;132:741–54. [PubMed: 15837135]

18. Lee SH, Kim SS, Tae WS, Lee SY, Choi JW, Koh SB, et al. Regional volume analysis of the Parkinson disease brain in early disease stage: Gray matter, white matter, striatum, and thalamus. AJNR Am J Neuroradiol. 2011;32:682–7. [PubMed: 21330396]

19. Stoodley CJ. The cerebellum and cognition: Evidence from functional imaging studies. Cerebellum. 2012;11:352–65.[PubMed: 21373864]

20. Rolland AS, Herrero MT, Garcia-Martinez V, Ruberg M, Hirsch EC, François C. Metabolic activity of cerebellar and basal ganglia-thalamic neurons is reduced in Parkinsonism. Brain. 2007;130(Pt 1):265–75. [PubMed: 17148469]

21. Borghammer P, Østergaard K, Cumming P, Gjedde A, Rodell A, Hall N, et al. A deformation-based morphometry study of patients with early-stage Parkinson's disease. Eur J Neurol. 2010;17:314–20. [PubMed: 19912319]

22. Wu T, Hallett M. The cerebellum in Parkinson's disease. Brain. 2013;136(Pt 3):696–709. [PubMed: 23404337]

23. Giompres P, Delis F. Dopamine transporters in the cerebellum of mutant mice. Cerebellum. 2005;4:105–11. [PubMed: 16035192]

24. Rushton JP, Ankney CD. Whole brain size and general mental ability: A review. Int J Neurosci. 2009;119:691–731.[PMCID: PMC2668913] [PubMed: 19283594]

25. Watts RL, Standaertt DG, Obeso JA, editors. Movement Disorders. 3rd ed. New York: McGraw Hill; 2011.

26. Cerasa A, Messina D, Pugliese P, Morelli M, Lanza P, Salsone M, et al. Increased prefrontal volume in PD with levodopa-induced dyskinesias: A voxel-based morphometry study. Mov Disord. 2011;26:807–12. [PubMed: 21384430]

27. Siddiqui SV, Chatterjee U, Kumar D, Siddiqui A, Goyal N. Neuropsychology of prefrontal cortex. Indian J Psychiatry. 2008;50:202–8.[PMCID: PMC2738354] [PubMed: 19742233]

28. Biundo R, Formento-Dojot P, Facchini S, Vallelunga A, Ghezzo L, Foscolo L, et al. Brain volume changes in Parkinson's disease and their relationship with cognitive and behavioural abnormalities. J Neurol Sci. 2011;310:64–9. [PubMed: 21862438]

29. Aglioti S. The role of the thalamus and basal ganglia in human cognition. J Neurolinguistics. 1997;10:255–65.

30. Shirvalkar P, Seth M, Schiff ND, Herrera DG. Cognitive enhancement with central thalamic electrical stimulation. Proc Natl Acad Sci U S A. 2006;103:17007–12. [PMCID: PMC1622923] [PubMed: 17065322]

31. Halliday GM. Thalamic changes in Parkinson's disease. Parkinsonism Relat Disord. 2009;15(Suppl 3):S152–5. [PubMed: 20082979]

32. McKeown MJ, Uthama A, Abugharbieh R, Palmer S, Lewis M, Huang X. Shape (but not volume) changes in the thalami in Parkinson disease. BMC Neurol. 2008;8:8. [PMCID: PMC2386499] [PubMed: 18412976]

33. Li W, Liu J, Skidmore F, Liu Y, Tian J, Li K. White matter microstructure changes in the thalamus in Parkinson disease with depression: A diffusion tensor MR imaging study. AJNR Am J Neuroradiol. 2010;31:1861–6. [PubMed: 20705702]

34. Planetta PJ, Schulze ET, Geary EK, Corcos DM, Goldman JG, Little DM, et al. Thalamic projection fiber integrity in de novo Parkinson disease. AJNR Am J Neuroradiol. 2013;34:74–9. [PMCID: PMC3669594] [PubMed: 22766668]

35. Zimmerman D. Thinking with your hypothalamus. Philos Phenomenol Res. 2001;63:521–41.

36. Langston JW, Forno LS. The hypothalamus in Parkinson disease. Ann Neurol. 1978;3:129–33. [PubMed: 350130]

37. Politis M, Piccini P, Pavese N, Koh SB, Brooks DJ. Evidence of dopamine dysfunction in the hypothalamus of patients with Parkinson's disease: An *in vivo* 11C-raclopride PET study. Exp Neurol. 2008;214:112–6. [PubMed: 18723016]

38. Breen DP, Nombela C, Vuono R, Jones PS, Fisher K, Burn DJ, et al. Hypothalamic volume loss is associated with reduced melatonin output in Parkinson's disease. Mov Disord. 2016;31:1062–6. [PMCID: PMC5025727] [PubMed: 26971528]

39. Sandyk R, Iacono RP, Bamford CR. The hypothalamus in Parkinson disease. Ital J Neurol Sci. 1987;8:227–34. [PubMed: 2887537]

40. Rajmohan V, Mohandas E. The limbic system. Indian J Psychiatry. 2007;49:132–9. [PMCID: PMC2917081] [PubMed: 20711399]

41. Xia J, Miu J, Ding H, Wang X, Chen H, Wang J, et al. Changes of brain gray matter structure in Parkinson's disease patients with dementia. Neural Regen Res. 2013;8:1276–85. [PMCID: PMC4107646] [PubMed: 25206422]

42. Kulisevsky J, Pagonabarraga J, Martinez-Corral M. Changes in artistic style and behaviour in Parkinson's disease: Dopamine and creativity. J Neurol. 2009;256:816–9. [PubMed: 19240966]

43. Braak H, Braak E, Yilmazer D, de Vos RA, Jansen EN, Bohl J, et al. Amygdala pathology in Parkinson's disease. Acta Neuropathol. 1994;88:493–500. [PubMed: 7879596]

44. Kamagata K, Motoi Y, Abe O, Shimoji K, Hori M, Nakanishi A, et al. White matter alteration of the cingulum in Parkinson disease with and without dementia: Evaluation by diffusion tensor tract-specific analysis. AJNR Am J Neuroradiol. 2012;33:890–5. [PubMed: 22241380]

45. Camicioli RM, Korzan JR, Foster SL, Fisher NJ, Emery DJ, Bastos AC, et al. Posterior cingulate metabolic changes occur in Parkinson's disease patients without dementia. Neurosci Lett. 2004;354:177–80. [PubMed: 14700725]

46. De-Zhi K, Fu-Xiang C, Fu-Yong C, Ying L, Gang W, Liang-Hong Y, et al. Altered regional homogeneity of prefrontal cortex in Parkinson's disease with mild cognitive impairment. Chin Neurosurg J. 2016;2:1–7.

47. Duncan GW, Firbank MJ, O'Brien JT, Burn DJ. Magnetic resonance imaging: a biomarker for cognitive impairment in Parkinson's disease? Mov Disord. 2013;28:425–38. [PubMed: 23450518]

48. Isaias IU, Marzegan A, Pezzoli G, Marotta G, Canesi M, Biella GE, et al. A role for locus coeruleus in Parkinson tremor. Front Hum Neurosci. 2012;5:179. [PMCID: PMC3250076] [PubMed: 22287946]

49. Bertrand E, Lechowicz W, Szpak GM, Dymecki J. Qualitative and quantitative analysis of locus coeruleus neurons in Parkinson's disease. Folia Neuropathol. 1997;35:80–6. [PubMed: 9377080]

50. Ferreira D, Guerra A. Depression and Parkinson's disease: Role of the locus coeruleus. Eur Psychiatry. 2015;30:641.

51. Schwartz WJ, Sharp FR, Gunn RH, Evarts EV. Lesions of ascending dopaminergic pathways decrease forebrain glucose uptake. Nature. 1976;261:155–7. [PubMed: 1272385]

52. Fields RD, Araque A, Johansen-Berg H, Soo-Siang L, Lynch G, Klaus-Armin N, et al. Glial biology in learning and cognition. Neuroscientist. 2014;20:426–31. [PMCID: PMC4161624] [PubMed: 24122821]

53. Theodosis DT, MacVicar B. Neurone-glia interactions in the hypothalamus and pituitary. Trends Neurosci. 1996;19:363–7.[PubMed: 8843607]

54. Theodosis DT, Poulain DA, Oliet SH. Activity-dependent structural and functional plasticity of astrocyte-neuron interactions. Physiol Rev. 2008;88:983–1008. [PubMed: 18626065]

55. Villalba RM, Smith Y. Neuroglial plasticity at striatal glutamatergic synapses in Parkinson's disease. Front Syst Neurosci. 2011;5:68.[PMCID: PMC3159891] [PubMed: 21897810]

56. Voronkov DN, Khudoerkov RM, Dovedova EL. Changes in neuroglial interactions in nigrostriatal brain structures on modeling of dopamine system dysfunction. Neurosci Behav Physiol. 2014;44:1073–7.

57. Vila M, Jackson-Lewis V, Guégan C, Wu DC, Teismann P, Choi DK, et al. The role of glial cells in Parkinson's disease. Curr Opin Neurol. 2001;14:483–9. [PubMed: 11470965]