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Asymmetry in Parkinson's Disease: Exploring the Role of Hemispheric Specialization in Treatment Success

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Parkinson's disease (PD) is a severe and irreversible neurodegenerative disorder, characterized primarily by motor symptoms that are unilateral at onset in over 85% of patients. (1) This lateralization arises from asymmetric neurodegeneration in the brain, where the hemisphere contralateral to the predominant motor symptoms shows greater neuronal and synaptic dysfunction in both the nigrostriatal system and cortical structures. (2) Such asymmetries emerge early, even during preclinical stages, and remain directionally stable throughout disease progression, affecting motor and cognitive functions differently based on the hemisphere involved. (3) Importantly, the asymmetric presentation of motor symptoms correlates with disease progression rates and cognitive outcomes, influencing visuospatial tasks, language, verbal memory, and susceptibility to psychosis. Despite these well-documented patterns, the underlying factors that make neurons in one hemisphere more vulnerable than the other remain poorly understood. This asymmetry in PD reflects a broader principle of brain organization: hemispheric specialization. In humans, handedness exemplifies this phenomenon, with the left hemisphere typically supporting language and the right hemisphere excelling in visuospatial processing. Similarly, in animal models, paw preference serves as an indicator of hemispheric dominance. (4) This specialization may also extend to how the brain responds to neurodegeneration and therapeutic interventions. Previous studies in PD rat models have shown that cell transplantation into the dominant hemisphere's striatum results in superior motor recovery compared to the non-dominant hemisphere. (5) However, the biological mechanisms behind this discrepancy are unclear. This study aims to address this gap by investigating whether intrinsic differences in brain structure and function between the dominant and non-dominant hemispheres could account for variations in therapeutic outcomes. Here we tested the hypothesis that the dominant hemisphere exhibits a variation of dopaminergic neurons and structural differences in the substantia nigra pars compacta (SNpc) and striatum compared to the non-dominant hemisphere. (n=113) Sprague Dawley rats underwent the Collins paw preference test to determine hemispheric dominance where 50, 43, and 20 were found to be right paw preference, left paw preference, and ambidextrous, respectively. Fifteen brains were then analyzed using Cresyl violet staining and Tyrosine hydroxylase (TH) immunohistochemistry. The Optical fractionator stereological method was precisely used to quantify neuronal populations in SNpc. Cavalieri Volumetry was used to make volume estimates of SNpc and

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the striatum. Our preliminary data does not show any significant difference in the number of dopaminergic neurons between dominant and non-dominant hemispheres (P=0.7). Furthermore, our data does not reveal a significant difference in the volumes of SNpc (P=0.39) and striatum (P=0.9) between dominant and non-dominant hemispheres. The immunoblot analysis (n=2) did not show any significant difference in the expression of TH between the left and right hemispheres. However, the protein expression analysis of other dopaminergic factors: dopamine transporter (DAT), dopa-decarboxylase (DDC) and vesicular monoamine transporter-2 (VMAT2), is ongoing. If we can find any difference between the two hemispheres, that could explain why neurons in one hemisphere are more vulnerable to degeneration and how integrating hemispheric dominance might improve the success of cell transplantation therapies. Ultimately, this work could contribute to more personalized, hemisphere-specific treatment strategies for Parkinson's disease, paving the way for more effective clinical interventions.

Keywords: Limb Dominance, Hemisperic Dominance, Hemisperic Lateralization, Parkinson's Disease, Hemispheric Specialization, Handedness, Pawedness

References

1. Li, P., Ensink, E., Lang, S., Marshall, L., Schilthuis, M., Lamp, J., Vega, I., & Labrie, V. Hemispheric asymmetry in the human brain and in Parkinson's disease is linked to divergent epigenetic patterns in neurons. Genome biology, 2020. 21(1), p. 61. doi:10.1186/s13059-020-01960-1

2. Pagano, G., Ferrara, N., Brooks, D. J., & Pavese, N. Age at onset and Parkinson's disease phenotype. Neurology, 2016. 86(15), pp. 1400-1407. doi:10.1212/WNL.0000000000002461

3. Wang, J., Yang, Q. X., Sun, X., Vesek, J., Mosher, Z., Vasavada, M., Chu, J., Kanekar, S., Shivkumar, V., Venkiteswaran, K., & Subramanian, T. MRI evaluation of asymmetry of nigrostriatal damage in the early stage of early-onset Parkinson's disease. Parkinsonism & related disorders, 2015. 21(6), pp. 590-596. doi:10.1016/j.parkreldis.2015.03.012

4. Pençe S. Paw preference in rats. Journal of basic and clinical physiology and pharmacology, 2002. 13(1), pp. 41–49. doi:10.1515/jbcpp.2002.13.1.41

5. Nikkhah, G., Falkenstein, G., & Rosenthal, C. Restorative plasticity of dopamine neuronal transplants depends on the degree of hemispheric dominance. The Journal of neuroscience: the official journal of the Society for Neuroscience, 2001. 21(16), pp. 6252–6263. doi:10.1523/JNEUROSCI.21-16-06252.2001

