Compensatory Masquerade Neuroplasticity derived from Parkinson's Disease in relation to the effects of Neural and Motor Responses within the Substantia Nigra

Shiv Parmar

EnvisionSTEM Research

Literature Review

September 28, 2025

Abstract

Parkinson's disease (PD), also referred to as idiopathic [unknown cause] parkinsonism, primary parkinsonism, and paralysis agitans, is a chronic brain disorder that causes gradual, but immense damage to the central nervous system of the brain. PD remains the second most prevalent neurodegenerative disorder within the United States, following Alzheimer's Disease (AD), while having an average diagnosis rate among individuals who are 60 years of age or older. Researchers have become attentive to the most vital and indirect effects of PD patients. In this literature review, we analyze the effects of compensatory masquerade neuroplasticity on physiological and biochemical changes within the brain, and the extent to which this affects specific motor and neural mechanisms.

Keywords: PD, neurodegenerative, compensatory masquerade, neuroplasticity, physiological changes, biochemical changes, motor mechanisms, neural mechanisms

INTRODUCTION

Researchers have been perplexed with the question: what are the most overlooked underlying causes and effects of PD patients? Compensatory masquerade is the novel allocation of a particular cognitive process to perform a task in a way that circumvents or compensates for a previous process impaired by injury. This neurological mechanism is identified to be a subset of neuroplasticity, while scientists and researchers have yet to research the in-depths of this neurological adaptivity, as it is connected to both physical and structural arrangements and how this coincides with internal and external cellular alterations, respectively [1].

At the same time, scientists have sought to investigate the cellular and molecular mechanisms that underlie the functions of motor and neural circuits within the brain, and how this is related to responses received by the brain from the environment [2]. This study particularly focuses on analyzing the loss of dopaminergic neurons, particularly the midbrain dopamine (DA) neurons, within the substantia nigra of the Basal Ganglia, which stimulates the brain's ability to account for motor circuit alterations of the contralateral nigrostriatal and basal-ganglia thalamocortical circuits (BGTC), and the neuron circuits of the major affected substantia nigra pars compacta (SNc) and minor affected adjacent ventral tegmental area (VTA) [3]. This research primarily aims to decipher the neurodegenerative patterns and signals from circuit neuroplasticity derived from compensatory masquerade, and the steps that are being taken to develop a more targeted medical therapy for PD patients [4].

MATERIAL AND METHODS

Literature for this study was gathered from a precise approach of reviewing and examining clinical experiments, peer-reviewed scientific publications, and research journals that had classifications corresponding to Parkinson's Disease (PD), neuroplasticity, compensatory masquerade, and specialized subsets of focus regarding molecular changes within the nervous system. Datasets such as ScienceDirect, Google Scholar, PubMed, and the National Center for Biotechnology Information (NCBI). In terms of inclusion, only specific studies containing peer-reviewed meta-analyses or research studies that were published in English, experiments containing patient or animal models relating to the weakening of dopaminergic neurons, the activity of the basal ganglia, and compensatory mechanisms, along with the neurochemical, genetic, and environmental factors related to the onset and continuation of PD, were selected. In

terms of exclusion, the studies that were not peer-reviewed, did not have sufficient data on neuroplasticity, and data that considered the non-motor symptoms without mentions of specific neural circuits were not considered within this literature review.

DISCUSSION

Loss of dopaminergic neurons (DA)

Research has found that PD stems from a variety of factors, such as progressive aging, along with environmental triggers and genetic associations, corresponding with damage to the DA neurons [5]. Studies have shown that an onset form of PD [Young-Onset Parkinson's Disease] has been particularly rare, with DaTSCAN data at different levels of onset, deriving that the percentage reduction of least affected putamen, most affected caudate, abnormal least affected putamen, and abnormal least affected caudate have outputted results that show a great variation of the p value [<0.05] for age of onset [>50] of PD development may also lead to PD diagnosis, This is because upon the long-term exposure of solvents such as trichloroethylene (C_2HCl_3), in an industrial workforce (i.e. detergents, dry cleaning, metal degreasing, paint thinners); as well as, the varying forms of pesticides and herbicides [2,4 dichlorophenoxyacetic acid (2,4-D), organochlorines, permethrin], which enter the body and infiltrate to cause toxicity within the dopaminergic (DA) neurons of the ventral midbrain (VM), by also initiating mitochondrial dysfunction [6]. Other environmental factors, which play a significant role in stimulating PD, are metals such as Aluminum (Al), iron (Fe), and manganese (Mn), Mercury (Hg), which can result in oxidative stress, mitochondrial dysfunction, and protein misfolding [7].

In addition to this, the effects of air pollution were also found to be more prevalent within patients with PD, due to the particulate matter (PM), by impairing the neural functions of the brain, such as oxidative stress, formation of abnormal protein aggregation, and neuroinflammation [8]. With a particular focus on neuroinflammation, which occurs from PD, it results in chronic inflammation within the respiratory tract, further contributing to the decomposition of the nasal and olfactory barriers, along with the blood-brain barrier. This correlation has been shown to link an association of the neurodegeneration of dopaminergic neurological roles. Scientists have conducted valid research on the presence of Lewy bodies (LBs), which are typically found within the subcortical nuclei, such as the substantia nigra, to cause a detrimental effect as a biomarker for PD [9]. Lewy bodies, composed of cellular proteins: alpha-synuclein (α-syn), microfilaments, neurofilaments, microtubules, and synapsin III, are known to be aggregate forms of the protein α-syn.

Compensatory Masquerade in relation to the Deprivation of Lifestyle Factors

Modern scientific research has unveiled the hindrances to the central precursor of Parkinson's: loss of DA neuron functionality [5]. A loss of these primary hormones of the brain contributes to a decreased localization of neural pathways, which can lead to further chronic expansion of the condition. DA neurons are responsible for providing the brain with learning mechanisms through the N-methyl-D-aspartate (NMDA) receptors, which provide ligand-gated ion channeling allowing the sufficient influx of calcium ions into a neuron, when activated by the neurotransmitter glutamate [10]. Dopaminergic neurons are relevant to neuroplasticity through the D1 and D2 receptor subtypes, specifically linked to D2 receptor-dependent NMDA activity

reduction, resulting in a shift of the balance of synaptic plasticity from long-term potentiation (LTP) plasticity to long-term depression (LTD) plasticity [11].

Hence, the biological mechanism of compensatory masquerade within the brain shifts towards the means of an insufficient rearrangement of performing neural responses, which in turn activate motor responses, allowing for compensatory masquerade to rely on stress and adrenal glucocorticoids [12]. This corresponds to neuroplasticity being affected through changes in atrophy and configurational alterations in the hippocampus [receiving dopamine projections from the substantia nigra], further establishing minimal neurogenesis for PD patients to improve cognitive functions such as learning the control of movements: slowness of movement (bradykinesia), weakened balance, and muscle stiffness (rigidity) [13]. Studies must consider how compensatory masquerade neuroplasticity can be significantly affected by dopamine-induction, and how this can be alleviated through patient-mapping and clinical trials. While neuroplasticity is rather seen from a positive viewpoint, research must also consider how compensatory mechanisms may have associated ties with patient-based care compared to the broad spectrum of PD patients; nevertheless, this requires a detailed analysis of the variations of gene-expression biomarker profiles linked with genetic associations and environmental exposures during physiological development [14].

Motor alterations of the nigrostriatal pathway and cortico-basal-ganglia-thalamo-cortical loop (CBGTC loop)

The nigrostriatal pathway is a brain circuit that is responsible for the functions incorporating voluntary movement and body postural balance. In turn, the system functions to transmit dopaminergic signals which originate from the substantia nigra pars compacta (SNc) to the

dorsal striatum (caudate-putamen [CPu]) [15]. This pathway is involved in the control of movement, while particular abnormalities are connected to the onset of PD [12]. This is interconnected to the inclusion of structures such as the basal ganglia and its nuclei of the caudate, putamen, and globus pallidus, which are involved in circuit connections to the SN and subthalamic nucleus. Researchers have also deciphered the substantial role of the nigrostriatal pathway in influencing cognition, reward, and addiction [3].

The cortico-basal-ganglia-thalamo-cortical loop (CBGTC loop) consists of the cortex, basal ganglia, and thalamus, which corresponds to the striatum and the subthalamic nucleus (STN) [14]. The cortex with a special focus on areas of the dorsal anterior cingulate cortex (dACC) and the orbitofrontal cortex (OFC), which are primarily responsible for reward-based learning, action selection, motivation, and the monitoring of performance; from which, the cortex plays a role in connecting with the striatum through the corticostriatal pathway and the STN which contribute to motor control and the prevention of undesired movements [9]. The basal ganglia are centrally inclusive in motor control, with specific regard to the coordination of purposeful actions and inhibition of competing movements, which it receives from the cortex by way of the striatum. The modulation of movement takes place with the thalamus, which acts in accordance to a relay station of input from the globus pallidus interna/substantia nigra pars reticulata (GPi/SNR) to the cortex for the CBGTC loop to project signals within the brain [13].

CONCLUSION

Within the present society, Parkinson's disease continues to be a significant condition that affects the brain of an individual, with a wide range of effects relating to physical and structural

instability. Additionally, the overall biochemical processes of the brain are impacted by PD through the diminishment of dopamine-producing neurons, which primarily contribute to misfolded protein aggregates known as alpha-synuclein and further give rise to Lewy bodies. Research has shown that the brain tends to be adaptive and transform certain regions into holding responsibility over neural pathways and motor function, as exemplified by compensatory masquerade.

The form of neuroplasticity that compensatory masquerade enhances consists of the brain finding new techniques in order to activate and utilize certain neural pathways. This contrasts with methods such as homologous area adaptation, which consists of the opposite hemisphere of the brain having control over the performance of tasks. Yet, compensatory masquerade in correspondence to the substantia nigra must correlate to the specific needs of the patients, such as the development of molecular biomarkers and cognitive psychology, which aid in the development of medications that can improve the functional response of the nigrostriatal pathway and cortico-basal-ganglia-thalamo-cortical loop (CBGTC loop).

References

[1] A. Ho, Y. Khan, G. Fischberg, and D. Mahato, “Clinical Application of Brain Plasticity in Neurosurgery,” World Neurosurgery, vol. 146, pp. 31–39, Feb. 2021, doi: https://doi.org/10.1016/j.wneu.2020.09.021.

[2] J. Kumar et al., “Innovative Approaches and Therapies to Enhance Neuroplasticity and Promote Recovery in Patients with Neurological disorders: a Narrative Review,” Cureus, vol. 15, no. 7, Jul. 2023, doi: https://doi.org/10.7759/cureus.41914.

[3] “How Are Dopaminergic Circuits Established?,” Harvard Brain Science Initiative. https://brain.harvard.edu/hbi_news/how-are-dopaminergic-circuits-established/

[4] H. Sauer and W. H. Oertel, “Progressive degeneration of nigrostriatal dopamine neurons following intrastriatal terminal lesions with 6-hydroxydopamine: A combined retrograde tracing and immunocytochemical study in the rat,” Neuroscience, vol. 59, no. 2, pp. 401–415, Mar. 1994, doi: https://doi.org/10.1016/0306-4522(94)90605-x.

[5] P. Damier, E. C. Hirsch, Y. Agid, and A. M. Graybiel, “The substantia nigra of the human brain,” Brain, vol. 122, no. 8, pp. 1437–1448, Aug. 1999, doi: https://doi.org/10.1093/brain/122.8.1437.

[6] E. Ghanavati, M. A. Salehinejad, L. De Melo, M. A. Nitsche, and M.-F. Kuo, “NMDA receptor–related mechanisms of dopaminergic modulation of tDCS-induced neuroplasticity,” Cerebral Cortex, Feb. 2022, doi: https://doi.org/10.1093/cercor/bhac028.

[7] S. Srinivasan, M. Shariff, and S. E. Bartlett, “The Role of the Glucocorticoids in Developing Resilience to Stress and Addiction,” Frontiers in Psychiatry, vol. 4, 2013, doi: https://doi.org/10.3389/fpsyt.2013.00068.

[8] M. M. G. H. van de Veerdonk, T. A. M. Bouwens van der Vlis, L. Ackermans, K. R. J. Schruers, Y. Temel, and A. F. G. Leentjens, “The role of the dorsal anterior cingulate cortex in obsessive-compulsive disorder,” Deep Brain Stimulation, vol. 3, pp. 1–7, Oct. 2023, doi: https://doi.org/10.1016/j.jdbs.2023.07.001.

[9] J. L. Lanciego, N. Luquin, and J. A. Obeso, “Functional Neuroanatomy of the Basal Ganglia,” Cold Spring Harbor Perspectives in Medicine, vol. 2, no. 12, pp. a009621–a009621, Oct. 2012, doi: https://doi.org/10.1101/cshperspect.a009621.

[10] C. Finsterwald and C. M. Alberini, “Stress and glucocorticoid receptor-dependent mechanisms in long-term memory: From adaptive responses to psychopathologies,” Neurobiology of Learning and Memory, vol. 112, pp. 17–29, Jul. 2014, doi: https://doi.org/10.1016/j.nlm.2013.09.017.

[11] C. Pittenger and R. S. Duman, “Stress, Depression, and Neuroplasticity: A Convergence of Mechanisms,” Neuropsychopharmacology, vol. 33, no. 1, pp. 88–109, Sep. 2007, doi: https://doi.org/10.1038/sj.npp.1301574.

[12] “Nigrostriatal Pathway - an overview | ScienceDirect Topics,” www.sciencedirect.com. https://www.sciencedirect.com/topics/neuroscience/nigrostriatal-pathway

[13] T. V. Maia, R. E. Cooney, and B. S. Peterson, “The neural bases of obsessive–compulsive disorder in children and adults,” Development and Psychopathology, vol. 20, no. 4, pp. 1251–1283, 2011, doi: https://doi.org/10.1017/s0954579408000606.

[14] A. Tewari, R. Jog, and M. S. Jog, “The Striatum and Subthalamic Nucleus as Independent and Collaborative Structures in Motor Control,” Frontiers in Systems Neuroscience, vol. 10, Mar. 2016, doi: https://doi.org/10.3389/fnsys.2016.00017.

[15] J. Blesa, “Inter-hemispheric asymmetry of nigrostriatal dopaminergic lesion: a possible compensatory mechanism in Parkinson’s disease,” Frontiers in Systems Neuroscience, vol. 5, 2011, doi: https://doi.org/10.3389/fnsys.2011.00092.