Galore International Journal of Health Sciences and Research
Vol. 9; Issue: 2; April-June 2024
Website: www.gijhsr.com
Review Article *P-ISSN: 2456-9321*

Understanding the Impact of the Dopamine Hypothesis on Schizophrenia

Jelena Stellakis[1], Georgios Lyrakos[2,3], Georgios Pilafas[2,4], Penelope Louka[2,5,6]

[1]Student, University of Derby (UK) at Mediterranean College campus, Athens, Greece.
[2]Accredited Lecturer, University of Derby (UK) at Mediterranean College campus, Athens, Greece.
[3]Clinical Health Psychologist, General Public Hospital of Nikaia, Piraeus, Greece.
[4]Programme Leader 'BSc (Hons) Applied Psychology', University of Derby (UK) at Mediterranean College campus, Athens, Greece.
[5]Head of School of Psychology, Mediterranean College, Greece.
[6]Deputy Head of Academic Affairs (Learning, Teaching & Assessment), Mediterranean College, Greece.

Corresponding Author: Jelena Stellakis

DOI: https://doi.org/10.52403/gijhsr.20240206

ABSTRACT

Schizophrenia is a mental disorder affecting approximately 24 million individuals worldwide, characterised by a variety of symptoms such as delusions, hallucinations, disorganised thinking, and abnormal motor behaviour. The Dopamine Hypothesis of schizophrenia suggests that an imbalance in dopamine neurotransmission plays a crucial role in the development of this disorder. Dopamine receptors and their interaction with antipsychotic medication have been extensively studied in the context of schizophrenia. Research has shown that dopamine receptor block is a key mechanism of action for neuroleptic drugs used in treating schizophrenia. Additionally, the NMDA receptor malfunction has been linked to the manifestation of schizophrenia-like symptoms, further supporting the role of neurotransmitter dysfunction in this disorder. The prevalence of schizophrenia is rising globally, particularly in low- and middle-income countries, emphasising the need for increased awareness and resources for this population. Individuals with schizophrenia often face challenges in coping with daily life and maintaining relationships, impacting their quality of life and overall well-being. Early diagnosis, appropriate treatment, and supportive services are crucial in helping individuals with schizophrenia manage their symptoms and develop coping mechanisms. The Dopamine Hypothesis provides valuable insights into the underlying mechanisms of schizophrenia, highlighting the importance of neurotransmitter dysfunction in the development of this complex disorder. Early intervention and comprehensive support services are essential in improving the outcomes and quality of life for individuals living with schizophrenia.

Keywords: Schizophrenia, Dopamine Hypothesis, Neurotransmitter Dysfunction, Antipsychotic Drugs, NMDA Receptor

Schizophrenia is a complex, chronic mental illness that can have an impact on someone's emotions, thoughts, and behaviour. It is a severe psychological condition that affects rational thinking, emotional control, and interpersonal relationships (Rahman & Lauriello, 2016). Approximately 24 million people worldwide suffer from schizophrenia (0.32%), which makes this mental disorder less prevalent than others (GBD, 2015). Charlson et al. (2018) state that the worldwide rate of schizophrenia is rising,

specifically in low - and middle - income countries, due to the larger proportion of the population living in the age group at greatest risk of schizophrenia. The American Psychiatric Association, DSM 5, diagnostic guide, characterises schizophrenia as "Schizophrenia spectrum and other psychotic disorders" (p. 87), which includes schizophrenia, schizotypal personality disorder (STPD), and other psychotic disorders such as schizoaffective disorder and delusional disorder. The symptoms associated with schizophrenia are characterised by positive symptoms such as delusions and hallucinations, while disorganised thinking and extremely disorganised or abnormal motor behaviour are examples of cognitive and negative symptoms. These can include diminished emotional expression (eye-contact, intonation of speech) and a lack of motivation (APA, 2013). People with schizophrenia might have difficulty coping with everyday life and maintaining relationships. Such challenges can have a significant impact on an individual's quality of life and overall well-being. Individuals with schizophrenia can benefit from early diagnosis, appropriate treatment, and supportive services to help them develop coping mechanisms, manage their symptoms, and build meaningful relationships (Berghofer et al., 2020; Dong et al., 2019).

Depressive disorder is a common outcome of people with schizophrenia, occurring at approximately 40%; however, the exact number might vary significantly depending on the stage of the illness (chronic vs. early) and the state (acute vs. post-psychotic). In the early stages of schizophrenia, the distressing nature of the symptoms can trigger feelings of hopelessness and despair and increase the risk of depression. On the other hand, individuals with chronic schizophrenia are less likely to experience depression, possibly because they have developed coping mechanisms to manage their condition over time (Upthegrove et al., 2017). In the acute phase, individuals with schizophrenia often require immediate intervention, which may include hospitalisation, medication, and therapeutic support to manage and alleviate those symptoms. The post-psychotic phase follows when acute symptoms diminish, and the individual is in a more stable state. Treatment in this phase includes ongoing medication, psychotherapy, social support, and skill development to assist individuals in regaining functionality and improving their quality of life (Moritz, 2019).

The dopamine hypothesis, which suggests that an imbalance in dopamine signalling contributes to the onset of schizophrenia, may help explain the transition from acute to post-psychotic states. Excess dopamine signalling in certain brain regions is thought to contribute to the development of severe positive symptoms during an acute psychotic state, whereas reduced dopamine signalling may contribute to the persistence of negative symptoms during a post-psychotic state (Sonnenschein & Grace, 2020). This essay analyses relevant theories and research to evaluate the dopamine hypothesis as a causal explanation for this mental illness. Furthermore, it seeks to provide its implications for our understanding of schizophrenia by considering both supporting and opposing viewpoints (Brisch, 2014).

Dopamine (DA) is the neurotransmitter with the greatest concentration in the brain, where it regulates an extensive variety of functions, including locomotor activity, emotion, and cognition. An imbalance in dopamine activity, particularly a high level in certain brain regions, is related to the manifestation of positive symptoms such as hallucinations and delusions in schizophrenia (Juárez Olguín, 2016). Dopamine serves as the common final pathway for a wide range of predisposed factors that lead to the disease, whether environmental, genetic, or both. Other neurotransmitters, such as glutamate, may work with dopamine to create the general impression of schizophrenia (Lau et al., 2013).

The dopamine hypothesis of schizophrenia, also known as the dopamine hypothesis of psychosis, is a model that describes schizophrenia's positive symptoms of disrupted and excessive dopaminergic signalling. Jacques van Rossum was the first to recognise the importance of dopamine in the action of antipsychotic drugs. Van Rossum suggested in 1966 that dopamine receptor blockade was an acceptable explanation for the mechanism of action of this type of drug. He referred to neuroleptics as the first dopamine antagonists that were available. Overstimulation of dopamine receptors could then be a contributing factor (Seeman, 2021).

The dopamine hypothesis aims to prove dopamine activity to be too high in certain parts of the brain. A combination of factors contributes to schizophrenia, including environment, brain chemistry, and genetics. Studies on neuroimaging reveal structural variations in the central nervous system and the brain in individuals with schizophrenia. Inconsistencies that occur naturally in the biochemistry of the brain, such as the neurotransmitters glutamate and dopamine, may be the leading cause of schizophrenia (Tsuang, 2000; Sawa, 2002). The dopamine hypothesis was initially developed based on the discovery that medications used to treat schizophrenia decrease dopamine activity, whereas other dopamine-increasing treatments can cause psychosis by blocking dopamine D2 receptors (Seeman, 2009).

Several studies on the dopamine hypothesis functioning as supporting evidence for a better understanding of the relationship between dopamine and schizophrenia can be explained using PET imaging, antipsychotic medications, amphetamine-induced psychosis, and genetic as well as neurochemical material. Studies employing brain tissue analysis or imaging technologies, such as PET and SPECT scans, have revealed abnormalities in dopamine receptors in people with schizophrenia. For example, Seeman et al. (1987) discovered elevated levels of dopamine D2 receptors in the brains of people with schizophrenia, lending support to the theory of increased dopamine sensitivity in the disorder. Furthermore, PET imaging studies have shown increased dopamine receptor occupation in different parts of the brain in schizophrenia patients when compared to healthy control subjects. These findings support the idea that dopamine receptor changes are an essential characteristic of schizophrenia (Abi-Dargham et al., 2000; Weinstein, 2017).

Antipsychotic drugs, particularly those that focus mainly on dopamine receptors, often show effectiveness in reducing positive symptoms associated with schizophrenia and enhancing the role of dopamine in schizophrenia. Recent studies have demonstrated the efficacy of dopamine-blocking antipsychotic medications in reducing hallucinations and delusions in people with schizophrenia (Jones et al., 2020; Lally, 2015). Kane et al. (1988) support the assumption that medications targeting dopamine receptors effectively reduce positive symptoms, emphasising the importance of dopamine dysregulation in schizophrenia symptoms.

Amphetamines, known for their ability to increase dopamine release, have been associated with psychotic symptoms like those seen in people with schizophrenia. Vollenweider et al. (2000) conducted a study that specifically investigated the relationship between amphetamine-induced psychosis and dopamine dysregulation. The study suggested a possible link between elevated dopamine levels after amphetamine consumption and the development of temporary psychosis. This study provides insight into how amphetamine-induced changes in dopamine levels can cause transient psychotic experiences, similar to some aspects of schizophrenia symptoms.

Genetic studies on dopamine function variations have revealed connections to an increased risk of developing schizophrenia. The relationship between dopamine synapse density and schizophrenia provides significant evidence supporting the involvement of dopamine in the

neurochemical aspects of the disorder. Genetic variations that affect dopamine-related processes, as well as changes in the density of dopamine synapses, may have a significant impact on the development or progression of schizophrenia. This emphasises the complex relationship between genetic elements that influence dopamine function and the underlying neurochemical aspects associated with schizophrenia (Howes et al., 2013). Novak and Seeman (2022) argue that environmental exposures, stress, prenatal complications, and drug abuse may affect gene expression patterns, potentially increasing the risk of developing schizophrenia. Disruptive pregnancy events, such as infections or malnutrition, may alter foetal brain development, while chronic stress can alter gene expression in brain regions associated with emotional regulation. Substance abuse, especially during critical developmental periods, has been linked to disruptions in normal brain development and gene expression. These environmental factors can have an impact on epigenetic mechanisms such as DNA methylation, affecting brain function and increasing susceptibility to schizophrenia (Wahbeh and Avramopoulos, 2021; Kundakovic and Jaric, 2021). Understanding the relationship between inheritance and environmental influences using epigenetic mechanisms is crucial to understanding the complex nature of schizophrenia's aetiology.

On the other hand, several neuroimaging studies raised doubt on the possible attribution of dopamine irregularities in schizophrenia, implying potential roles for other neurotransmitters. While disruptions in dopamine function may exist, they may not be exclusively associated with schizophrenia, according to some PET imaging techniques. Studies that proposed similar changes in dopamine signalling were observed in other psychiatric disorders, arguing against the idea that dopamine dysregulation is unique to schizophrenia. It is suggested that dopamine systems have a wider effect across various psychiatric conditions, indicating the need for a deeper understanding of neurotransmitter involvement in the context of mental health disorders that go beyond dopamine (Laruelle et al., 1999; Kesby, 2018). Many symptoms, however, cannot be explained by dopamine imbalances alone. Glutamate abnormalities, such as dysfunctional glutamine receptors, also occur in schizophrenia. These abnormalities may be responsible for some negative and cognitive symptoms (Abi-Dargham, 2000).

Neuroscientist Dr. Joseph T. Coyle and his colleagues were early supporters of the glutamate hypothesis. The recently proposed Glutamate Hypothesis proposes that glutamate system dysfunctions, specifically those involving the NMDA receptor of glutamate, play a critical role in the pathology of schizophrenia (Coyle, 2019). Javitt (2004, 2007) and Krystal et al. (2017) investigated this hypothesis, looking into the relationship between NMDA receptor hypofunction and the manifestation of schizophrenia-like symptoms. Their findings point to a broader neurochemical perspective that goes beyond the traditional focus on dopamine in understanding the complexities of schizophrenia. This study emphasises the significance of studying glutamate dysregulation, particularly NMDA receptor abnormalities, as a key factor in the neurobiology of schizophrenia.

Beyond the traditional focus on dopamine and glutamate, studies show that other neurotransmitters play an important role in the pathophysiology of schizophrenia (Pourhamzeh, 2021; Bansal & Chatterjee, 2021). These studies highlight the roles that serotonin, gamma-aminobutyric acid (GABA), and other neurotransmitter systems play in the complex mechanisms that underpin schizophrenia. Recent research has shown the complicated interaction and dysregulation of serotonin, a neurotransmitter known for its impact on mood and cognition, as well as gamma-aminobutyric acid (GABA), an important neurotransmitter in controlling active

signals in the brain (Carhart-Harris et al., 2017; Quednow et al., 2020). These new findings add to our developing understanding of the roles of serotonin and GABA, among other neurotransmitters, in the complex neural mechanisms of schizophrenia. These neurotransmitters, among others, are recognised as important players in the neural circuits implicated in schizophrenia, broadening our understanding beyond dopamine and glutamate and emphasising the multifaceted nature of the disorder (Bansal & Chatterjee, 2021).

Therapies that are still in development and do not directly target dopamine receptors could represent an important change in schizophrenia treatment. These new compounds may provide renewed hope for more effective treatment, allowing psychiatrists to confidently switch or augment medications, addressing a broader range of symptoms in patients (Kantrowitz et al., 2023). According to Kantrowitz et al. (2023), these novel medications may offer disease modification, potentially preventing relapses, and may benefit groups of patients who are resistant to current treatments, including those who are unresponsive to clozapine.

The commonly held view of schizophrenia as being merely related to dopamine reduces the disorder's complexity. However, there are some studies that argue the opposite. Associating schizophrenia with dopamine dysfunction, emphasising the need for a more comprehensive understanding of its underlying causes. By raising doubts about the narrow focus on dopamine while arguing for a broader investigation of the disorder's aetiology, some studies emphasise the importance of considering multiple factors other than dopamine in order to gain a comprehensive understanding of schizophrenia (Howes & Murray, 2014; Howes et al., 2012). They conducted meta-analyses that show that while some patients have increased dopamine activity, others do not, therefore suggesting that dopamine dysregulation across all cases of schizophrenia is not consistent (McCutcheon, Merritt, & Howes, 2021). These studies indicate the diverse nature of dopamine alterations in schizophrenia patients, implying that not all cases of the disorder exhibit the same patterns of dopamine dysregulation. The glutamate hypothesis, which focuses on disruptions within the glutamate system, particularly those involving NMDA receptors, provides an intriguing alternative viewpoint. Studies on NMDA receptor malfunction suggest that glutamate neurotransmission plays a significant role in schizophrenia. This hypothesis expands the neurochemical framework beyond dopamine, implying that irregularities in glutamate signalling could play a significant role in the disorder.

To conclude the discussion on the dopamine hypothesis as a causal explanation for schizophrenia, it is important to recognise the disorder's complex nature. While the dopamine hypothesis has long been considered an important element in understanding the neurobiology of schizophrenia, this essay's examination of relevant theories and research has revealed both supporting and opposing views. However, the theory has evolved to include a broader range of neurotransmitters, genetic factors, brain structures, and environmental influences, examining the oversimplified view of dopamine as the single cause of schizophrenia.

When the dopamine hypothesis is evaluated, it becomes clear that, while dopamine dysfunction is important, it is not the only determinant in the disorder's complex aetiology. This realisation emphasises the importance of considering multiple factors in the pathophysiology of schizophrenia, such as glutamate, serotonin, GABA, genetic predispositions, and environmental stressors. By recognising the interplay of these separate components, we develop a more comprehensive understanding of schizophrenia.

Finally, this investigation of the dopamine hypothesis leads to a shift towards a more integrative understanding of schizophrenia.

Rather than viewing it through a single neurotransmitter lens, taking into account the intricate interactions between various biological, genetic, and environmental factors provides a richer framework for understanding the complexity of this mental illness. This broader perspective not only broadens our understanding of schizophrenia but also sets the way for more targeted and personalised interventions that consider the complexities inherent in the disorder's origins and manifestations.

Declaration by Authors

Ethical Approval: Not Applicable
Acknowledgement: None
Source of Funding: None
Conflict of Interest: The authors declare no conflict of interest.

REFERENCES

1. Abi-Dargham A., Rodenhiser J., Printz D., Zea-Ponce Y., Gil R., Kegeles L. S., Weiss R., Cooper T. B., Mann J. J., Van Heertum R. L., Gorman J. M., & Laruelle M., (2000). Increased baseline occupancy of D2 receptors by dopamine in schizophrenia. *Proceedings of the National Academy of Sciences of the United States of America,* 97 (14): 8104–9. doi:10.1073/pnas.97.14.8104
2. American Psychiatric Association (2013). *Cautionary statement for forensic use of DSM-5. In Diagnostic and statistical Manual of Mental Disorders (5th ed.)*. Washington, DC http://dx.doi.org/10.1176/appi.books.9780890425596
3. Bansal, V., & Chatterjee, I. (2021). Role of neurotransmitters in schizophrenia: a comprehensive study. *Kuwait J.Sci.*, vol.48(2), pp. (1-27), https://journalskuwait.org/kjs/index.php/KJS/article/view/9264
4. Berghofer, A., Martin, L., Hense, S. et al. (2020), Quality of life in patients with severe mental illness: a cross-sectional survey in an integrated outpatient health care model. *Qual Life Res* 29, 2073–2087. https://doi.org/10.1007/s11136-020-02470-0
5. Brisch, R., Saniotis, A., Wolf, R., Bielau, H., Bernstein, H.-G., Steiner, J., … Gos, T. (2014). The Role of Dopamine in Schizophrenia from a Neurobiological and Evolutionary Perspective: Old Fashioned, but Still in Vogue. *Frontiers in Psychiatry, 5.* doi:10.3389/fpsyt.2014.00047
6. Carhart-Harris, R., & Nutt, D. (2017). Serotonin and brain function: a tale of two receptors. *Journal of Psychopharmacology, 31(9), 1091–1120.* doi:10.1177/0269881117725915
7. Coyle, J. T., & Uno, Y. (2019). Glutamate Hypothesis in Schizophrenia. *Psychiatry and Clinical Neurosciences.* doi:10.1111/pcn.12823
8. Charlson, F. J., Ferrari, A. J., Santomauro, D. F., Diminic, S., Stockings, E., Scott, J. G., … Whiteford, H. A. (2018). Global Epidemiology and Burden of Schizophrenia: Findings From the Global Burden of Disease Study. *Schizophrenia Bulletin.* doi:10.1093/schbul/sby058
9. Dean, B., Crossland, N., Boer, S., & Scarr, E. (2008). Evidence for altered post-receptor modulation of the serotonin 2a receptor in schizophrenia. *Schizophrenia Research, 104(1-3), 185–197.* doi:10.1016/j.schres.2008.06.011
10. Dong, M., Lu, L., Zhang, L., et al. (2019), Quality of Life in Schizophrenia: A Meta-Analysis of Comparative Studies. *Psychiatr Q* 90, 519–532. https://doi.org/10.1007/s11126-019-09633-4
11. Howes, O. D., & Murray, R. M. (2014). Schizophrenia: an integrated sociodevelopmental-cognitive model. *The Lancet, 383(9929), 1677–1687.* doi:10.1016/s0140-6736(13)62036-x
12. Howes, O. D., Kambeitz, J., Kim, E., Stahl, D., Slifstein, M., Abi-Dargham, A., & Kapur, S. (2012). The Nature of Dopamine Dysfunction in Schizophrenia and What This Means for Treatment. *Archives of General Psychiatry, 69(8).* doi:10.1001/archgenpsychiatry.201
13. Institute for Health Metrics and Evaluation (IHME). *GBD Compare. Seattle, WA: IHME,* University of Washington, 2015. http://vizhub.healthdata.org/gbd-compare.
14. Javitt, D. C. (2004). Glutamate as a therapeutic target in psychiatric disorders. *Molecular Psychiatry, 9(11), 984–997.* doi:10.1038/sj.mp.4001551
15. Javitt, D. C. (2007). Glutamate and Schizophrenia: Phencyclidine, N-Methyl-d-Aspartate Receptors, and Dopamine–Glutamate Interactions. *Integrating the Neurobiology of*

Schizophrenia, 69–108. doi:10.1016/s0074-7742(06)78003-5

16. Jones, R., MacCabe, J. H., Price, M. J., Xiangxin, L., & Upthegrove, R. (2020). Effect of age on the relative efficacy of clozapine in schizophrenia. *Acta Psychiatrica Scandinavica.* doi:10.1111/acps.13156
17. Juárez Olguín, H., Calderón Guzmán, D., Hernández García, E., & Barragán Mejía, G., 2016. The Role of Dopamine and Its Dysfunction as a Consequence of Oxidative Stress. *Oxidative Medicine and Cellular Longevity, 2016, 1–13.* doi:10.1155/2016/9730467
18. Kane, J. (1988). Clozapine for the Treatment-Resistant Schizophrenic. *Archives of General Psychiatry*, 45(9), 789–799. doi:10.1001/archpsyc.1988.01800330013001
19. Kantrowitz J. T., Correll C. U., Jain R., Cutler A. J. (2023). New Developments in the Treatment of Schizophrenia: An Expert Roundtable. *Int J Neuropsychopharmacol*. 31;26(5):322-330. doi: 10.1093/ijnp/pyad011
20. Kesby, J., Eyles, D., McGrath, J., & Scott, J. (2018). Dopamine, psychosis and schizophrenia: the widening gap between basic and clinical neuroscience. *Translational Psychiatry*, 8(1). doi:10.1038/s41398-017-0071-9
21. Krystal, J. H., Murray, J. D., Chekroud, A. M., Corlett, P. R., Yang, G., Wang, X.-J., & Anticevic, A. (2017). Computational Psychiatry and the Challenge of Schizophrenia. *Schizophrenia Bulletin*, 43(3), 473–475. doi:10.1093/schbul/sbx025
22. Kundakovic M, & Jaric I. (2021) The Epigenetic Link between Prenatal Adverse Environments and Neurodevelopmental Disorders. *Genes (Basel)*. 2017 Mar 18;8(3):104. doi: 10.3390/genes8030104. PMID: 28335457; PMCID: PMC5368708.
23. Lally, J., & MacCabe, J. H. (2015). Antipsychotic medication in schizophrenia: a review. *British Medical Bulletin, 114(1), 169–179.* doi:10.1093/bmb/ldv017
24. Laruelle, M., Abi-Dargham, A., Gil, R., Kegeles, L., & Innis, R. (1999). Increased dopamine transmission in schizophrenia: relationship to illness phases. *Biological Psychiatry*, 46(1), 56–72. doi:10.1016/s0006-3223(99)00067-0
25. Lau, C. I., Wang, H. C., Hsu, J. L., & Liu, M. E. (2013). Does the dopamine hypothesis explain schizophrenia? *Reviews in the Neurosciences*, 24(4). doi:10.1515/revneuro-2013-0011
26. McCutcheon, R. A., Merritt, K., & Howes, O. D. (2021). Dopamine and glutamate in individuals at high risk for psychosis: a meta-analysis of in vivo imaging findings and their variability compared to controls. *World Psychiatry, 20(3), 405–416.* doi:10.1002/wps.20893
27. Moritz, S., Schmidt, S. J., Lüdtke, T., Braunschneider, L.-E., Manske, A., Schneider, B. C., & Veckstenstedt, R. (2019). Post-psychotic depression: Paranoia and the damage done. *Schizophrenia Research.* doi:10.1016/j.schres.2019.06.022
28. Novak G., & Seeman M. V. (2022). Dopamine, Psychosis, and Symptom Fluctuation: A Narrative Review. *Healthcare (Basel)*. 10(9):1713. doi: 10.3390/healthcare10091713
29. Pourhamzeh, M., Moravej, F. G., Arabi, M., Shahriari, E., Mehrabi, S., Ward, R., … Joghataei, M. T. (2021). The Roles of Serotonin in Neuropsychiatric Disorders. *Cellular and Molecular Neurobiology*. doi:10.1007/s10571-021-01064-9
30. Rahman, T., & Lauriello, J. (2016). Schizophrenia: An Overview. *FOCUS, (Am Psychiatr Publ), 14(3), 300–307.* doi:10.1176/appi.focus.20160006
31. Sawa, A. (2002). Schizophrenia: Diverse Approaches to a Complex Disease. *Science*, 296(5568), 692–695. doi:10.1126/science.1070532
32. Seeman, P. (1987). Dopamine receptors and the dopamine hypothesis of schizophrenia. *Synapse, 1(2), 133–152.* doi:10.1002/syn.890010203
33. Seeman, P. (2009). Dopamine Receptors and Antipsychotic Drugs in Health and Disease. *Encyclopedia of Neuroscience, 579–596.* doi:10.1016/b978-008045046-9.01144-x
34. Seeman, M. V. (2021). History of the dopamine hypothesis of antipsychotic action. *World J Psychiatry.* ;11(7):355-364. doi: 10.5498/wjp.v11.i7.355.
35. Sonnenschein, S. F., & Grace, A. A. (2020). Emerging therapeutic targets for schizophrenia: a framework for novel treatment strategies for psychosis. *Expert*

Opinion on Therapeutic Targets. doi:10.1080/14728222.2021.1849144
36. Tsuang, M. (2000). Schizophrenia: genes and environment. *Biological Psychiatry, 47(3), 210–220.* doi:10.1016/s0006-3223(99)00289-9
37. van Rossum, J. M. (1966). The significance of dopamine-receptor blockade for the mechanism of action of neuroleptic drugs. *Arch Int Pharmacodyn Ther.* ;160:492–494.
38. Upthegrove, R., Marwaha, S., Birchwood, M., 2017, Depression and Schizophrenia: Cause, Consequence, or Trans-diagnostic Issue?, *Schizophrenia Bulletin*, Volume 43, Issue 2, Pages 240–244, https://doi.org/10.1093/schbul/sbw097
39. Vollenweider, F. X., Vontobel, P., Øye, I., Hell, D., & Leenders, K. L. (2000). Effects of (S)-ketamine on striatal dopamine: a [11C]raclopride PET study of a model psychosis in humans. *Journal of Psychiatric Research, 34(1), 35–43.* doi:10.1016/s0022-3956(99)00031-x
40. Wahbeh M. H. & Avramopoulos D. (2021). Gene-Environment Interactions in Schizophrenia: A Literature Review. *Genes (Basel).*;12(12):1850. doi: 10.3390/genes12121850. PMID: 34946799; PMCID: PMC8702084.
41. Weinstein, J. J., van de Giessen, E., Rosengard, R. J., Xu, X., Ojeil, N., Brucato, G., … Abi-Dargham, A. (2017). PET imaging of dopamine-D2 receptor internalization in schizophrenia. *Molecular Psychiatry, 23(6), 1506–1511.* doi:10.1038/mp.2017.107

How to cite this article: Jelena Stellakis, Georgios Lyrakos, Georgios Pilafas, Penelope Louka. Understanding the impact of the dopamine hypothesis on schizophrenia. *Gal Int J Health Sci Res*. 2024; 9(2): 41-48. *DOI: https://doi.org/10.52403/gijhsr.20240206*

******