International Journal of Science and Healthcare Research
Vol. 9; Issue: 2; April-June 2024
Website: ijshr.com
Review Article *ISSN: 2455-7587*

The Dopamine Hypothesis as a Causal Explanation of Schizophrenia

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DOI: https://doi.org/10.52403/ijshr.20240205

ABSTRACT

Schizophrenia, a severe psychiatric disorder, profoundly impacts individuals, families, and society, characterized by symptoms such as delusions, hallucinations, disorganized thinking, speech, and motor behavior, as outlined in the DSM-5 criteria. Coined by Eugen Bleuler in 1911 to emphasize fragmented cognition, the term "schizophrenia" replaced Emile Kraepelin's "dementia praecox"(1908) reflecting its chronic nature, with an estimated prevalence of 1% in the general population and a significant heritability rate of around 79%. The dopamine hypothesis, central to schizophrenia research, suggests heightened dopaminergic transmission as a primary factor in its development, supported by the efficacy of antipsychotic drugs targeting dopamine receptors. However, recent studies have revealed complexities beyond dopamine dysfunction, including the glutamate hypothesis, which proposes deficits in glutamate activity as an alternative explanation. This essay critically evaluates the dopamine hypothesis within the broader biopsychosocial framework, emphasizing the interaction of biological, psychological, and social factors in schizophrenia etiology. Despite its foundational role, the dopamine hypothesis has limitations in fully clarifying the multifaceted nature of schizophrenia, highlighting the need for comprehensive approaches integrating diverse perspectives and methodologies to enhance understanding of this complex disorder.

Keywords: Dopamine Hypothesis, Schizophrenia, Mental Illness, Psychotic Symptoms, GENE x ENVIROMENT Interaction

INTRODUCTION

Schizophrenia is a chronic and severe psychiatric disorder that has a profound impact on the individual's life, their families and on society. The formal definition of the disorder according to the 5th edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) is that schizophrenia a mental disorder characterized by abnormalities in one or more of these five domains: delusions, hallucinations, disorganized thinking (and speech), disorganized motor behavior (American Psychiatric Association [APA], 2013, p. 86). Historically though, the term however was firstly used by Paul Eugen Bleuler in 24 of April 1908 when he gave a lecture for the General Psychiatric Association in Berlin.

In 1911, a Swiss psychiatrist named Eugen Bleuler introduced the term "schizophrenia." This word, originating from the Greek roots "schizo" (meaning split) and "phrene" (related to the mind), that was chosen by Bleuler to emphasize the mental confusion and fragmented thinking that is often seen in individuals experiencing this condition. Up until that point, the illness was referred to as “dementia praecox”, a name that German psychiatrist Emile Kraepelin first used in 1899, to describe the symptoms now known as schizophrenia. Dementia praecox means "early dementia". By calling his syndrome 'early dementia', he meant to differentiate it from dementias that occur later in life such as Alzheimer's disease (Ebert & Bär, 2010). Nonetheless, it is important to be educated in schizophrenia since its genetic component is high. The prevalence of schizophrenia is estimated to be 1% in general population however it has big heritability percentages (Kahn et al. 2015). The heritability of schizophrenia is about 79% (Hilker et al., 2018).

Among the many theories given out to explain the origins of schizophrenia, the dopamine hypothesis has become well-known and resilient. It has operated as the foundation for schizophrenia research and clinical practices. The finding that antipsychotic drugs, or neuroleptics, inhibited dopamine receptors, in experiments on animals, gave rise to the dopamine hypothesis (Carlsson & Lindqvist, 1963). After that, further research was done supporting that amphetamine produced psychotic symptoms. The finding that effective antipsychotics shut dopamine receptors in the brain served as the primary basis for the initial dopamine hypothesis in schizophrenia (van Rossum, 1966). However, the hypothesis became more influential during the beginning of the 1970s, when research revealed a relationship between antipsychotics' clinical efficacy and their dopamine receptor affinity (Seeman & Lee, 1975).

Thus, the possibility that elevated dopaminergic transmission may contribute to the development of schizophrenia emerged. Unquestionably, the fact that dopamine-blocking drugs relieve the symptoms of schizophrenia is evidence. Furthermore, most schizophrenic patients blink frequently than normal, a probable symptom of excessive dopamine stimulation (Kleiman et al., 1984). Moreover, a recent metanalysis found that the underlying mechanisms of schizophrenia encompass fundamental changes in the ability to synthesize and release dopamine, along with variations in other facets of dopamine functioning (Brugger et al., 2020. p.221-222). Nonetheless, this theory still has some serious questions to answer (Jackie & Weinberger, 1992). Research has found little evidence that the brains of schizophrenic people have excessive dopamine concentrations or any excess of dopamine receptors per se. An alternate possibility opposed to the dopamine hypothesis (van Russom, 1966) is the glutamate hypothesis (Coyle, 1996). It suggested that the underlying problem of schizophrenia is not excessive dopamine but rather a deficit of glutamate activity (Coyle, 1996). Nonetheless, by integrating relevant research and theory, this essay seeks to provide a more holistic understanding of the dopamine hypothesis in the context of schizophrenia, recognizing the interplay of biological, psychological, and social factors within the broader biopsychosocial framework, a perspective pioneered by George Engel in 1977.

MAIN PART

As mentioned earlier, according to DSM-5 schizophrenia is a complex disorder typically characterized by multiple types of emotional, behavioral, and cognitive dysfunctions (APA, 2013, p.87). Positive and negative symptoms are frequently used to classify symptoms of schizophrenia. Positive symptoms include abnormal behaviors that are not usually observed in the general population, such as sensory perceptions without the need for external stimuli, delusions, and fixed false beliefs.

On the other hand, negative symptoms, such as lowered emotional expression, avolition (lack of determination), and anhedonia (reduced ability to experience pleasure), these symptoms signify deficiencies in normal functioning (Mäkinen, et al. 2008; Waters et al., 2017). The heterogeneity of the symptoms is very clear, every person experiences the disorder differently, however their cause has changed a lot throughout the years. If you asked any researcher for the past 50 years what their explanation for schizophrenia and its symptoms you would most likely be lectured about the dopamine hypothesis (Meltzer et al., 1976, p. 19–76).

However, what exactly is this so called "dopamine hypothesis" and what does it explicate? As mentioned earlier the hypothesis emerged when Carlsson and Lindqvist (1963) observed that, without changing the concentration of dopamine, the newly approved antipsychotic haloperidol and chlorpromazine enhance the concentration of dopamine metabolites in the mouse brain. Thus, supporting the theory that psychotic symptoms can be relieved by blocking dopamine neurotransmission. This established a basis for the theory that the primary feature of schizophrenia is excessive dopamine transmission (Van Rossum, 1966). The initial articulation of the dopamine hypothesis was inherently focused on dopaminergic signaling within the basal ganglia. However, a contemporary interpretation expands upon this framework, associating the positive symptoms of schizophrenia with heightened dopamine transmission in subcortical brain regions, particularly in the striatum. Concurrently, negative symptoms and cognitive deficits are linked to dopaminergic dysfunction within the prefrontal cortex, as discussed by Davis et al. (1991) and Weinberger (1987). However, the confirmation of dopaminergic irregularities in schizophrenia initially faced obstacles due to a lack of neurochemical data. Postmortem examinations did not show noteworthy variations in cerebral concentrations of dopamine or its metabolites when comparing controls to individuals who passed away with schizophrenia (Winblad et al., 1979).

Nevertheless, some studies reported elevated dopamine levels in certain areas of the striatum (Crow et al., 1979). Gründer and Cumming (2016) propose that new molecular imaging studies, supporting a dopamine model of schizophrenia, face challenges like small sample sizes in PET/SPECT literature and the possibility of normal markers in a proportion of patients, highlighting the need for larger, multicenter studies to address heterogeneity in populations meeting the diagnostic criteria for schizophrenia. A recent metanalysis by McCutcheon et. al. (2018) concluded that individuals with schizophrenia have a severe dopamine dysfunction in their dorsal striatum (p.1304). The dopamine hypothesis can explain specific elements of schizophrenia's psychopathology, particularly its positive symptoms (Yui et al., 2000). However, except for clozapine, antipsychotics have minimal impact on negative and cognitive symptoms, which are key indicators of disability in schizophrenia (Im et al., 2016). The fundamental features of schizophrenia, which substantially contribute to persistent impairment, are linked to extensive cortical abnormalities, notwithstanding the improbability that they stem solely from dopamine dysfunction (Coyle et al., 2018).

Considerable evidence has been amassed, pointing to the involvement of the glutamate system in the development of schizophrenia. Unlike dopamine neurons, which have localized cell bodies, glutamatergic neurons, being the primary excitatory neurotransmitter in the central nervous system, are widely distributed across the brain (Goff,1997; Haaf et al., 2023). Widely acknowledged as the predominant excitatory amino acid neurotransmitter in the brain, glutamate activates both ionotropic receptors and G protein-coupled metabotropic (mGlu) receptors (Fonnum, 1984). The initial substantiation for the

implication of glutamate in the pathophysiological mechanisms of schizophrenia emanated from observations of psychotomimetic effects associated with NMDA antagonists (Coyle, 1996). While alignment between preclinical and post-mortem investigations and this hypothesis is discernible, empirical backing from imaging studies remains constrained. Nevertheless, recent genetic revelations, diverging from the dopamine hypothesis, substantiate the proposition that abnormalities in glutamatergic function potentially have an influence on the pathophysiological dynamic of schizophrenia (Haaf et al., 2023). For over 50 years, schizophrenia pharmacotherapy has revolved around inhibiting dopamine D2 receptors (D2R), a fundamental aspect in all antipsychotics since the discovery of chlorpromazine. The advent of antipsychotics significantly decreased schizophrenia cases in mental hospitals. A second generation of antipsychotics (SGA) emerged by incorporating 5-hydroxytryptamine2 (5-HT2)-receptor blocking activity, effectively minimizing the risk of extrapyramidal neurological side effects (Uno & Coyle, 2019). Meta-analyses indicate that clozapine, characterized as a mild D2R antagonist, consistently demonstrates superior efficacy compared to all other antipsychotics and exhibits an influence on negative symptoms (Girgis et al., 2011).

However, the cause of schizophrenia is not only due to chemical imbalances in the brain. Systematic reviews and meta-analyses suggest that there are increased rates of schizophrenia and related psychoses are also a consequence of environmental factors (Stilo & Murray, 2019; Wahbeh & Avramopoulos, 2021). A substantial amount of literature connects anomalies during pregnancy, delivery, and the neonatal period to an elevated risk of neurological and psychiatric disorders, manifesting in both childhood and adulthood (Mas et al., 2020). This study adulthood (Mas et al., 2020) explained not only the effect a complication at birth can have on schizophrenia but also the interaction between gene-environment by using an ERS. Besides birth, severe trauma can cause the development of psychosis. A metanalysis conducted by Varese et al. (2012) found a connection between experiences of childhood adversity (sexual abuse, physical abuse, emotional/psychological abuse, neglect, parental death, and bullying) and an elevated likelihood of developing psychosis in adulthood (with an OF= 2.78). Studies and systematic reviews have consistently shown higher occurrences of schizophrenia and related psychotic disorders among both first- and second-generation migrants (Henssler et al., 2019). To be precise, in their subgroup analysis they found among first-generation immigrants, relative risk of incidence was 1.81 (95% CI 1.59, 2.07) (I 2=97.6%) compared to the native population, and 1.82 (95% CI 1.66, 1.99) (I 2=90.5%) among second-generation immigrants (Henssler et al., 2019, p.327). Also, cannabis use has been found to play a role in the development of schizophrenia (Godin & Shehata, 2022). A systematic review done by Godin and Shehata (2022) showed that both high- and low-frequency marijuana use were corelated with a significantly increased risk of schizophrenia. The frequency of use among high- and low- frequency users is similar in both, demonstrating statistically significant increased risk in the development of schizophrenia. All the previous listed research emphasizes the impact environment and social situations can negatively impact symptoms of psychosis and schizophrenia.

Nonetheless it can be clear from the analysis provided so far that schizophrenia is a complex issue. It cannot be defined or explained only by biology nor social/environmental factors (Stilo, & Murray, 2019), mostly due to the heterogeneity of the disorder (Brugger et. al, 2020). The primary support for the impact of Gene-Environment interaction on psychosis has been derived indirectly through studies involving twins, adoptions,

and various naturalistic approaches that assess general genetic influences (Van Os et al., 2008). More recently, researchers have gained insights into the ways in which variations in specifically measured genes interact with measured environmental factors (Moffitt TE et. al, 2005). Moreover a recent study by Musci et al. (2019) explained the way GENE x ENVIROMENT work together. Their findings concluded that occurs when an individual's genetic constitution impacts or is associated with a particular environmental exposure. In simpler terms, a person's genetic makeup can influence the likelihood of them encountering specific environmental factors (Musci et al., 2019, p.81). Thus, the hypothesis of a dopamine disfunction (van Rossum, 1966) as a casual explanation of schizophrenia is not entirely incorrect, perhaps not the only explanation of the disorder, especially since it lacks context.

CONCLUSION

On the whole, the dopamine hypothesis is still important for helping us understand schizophrenia, but it needs to be recognized at the context of a larger body of research. Therefore, the notion that dopamine hypothesis can explain the development of schizophrenia is not accepted (Moncrieff, 2009). Moreover, dopamine has rather a causal role in psychosis or schizophrenia (Moncrieff, 2009). Although positive symptoms of schizophrenia can be effectively reduced with antipsychotic medications, numerous patients experience incomplete response to treatment, leading to permanent suffering. These drugs frequently have serious negative effects as well. The psychotherapeutic method has a lengthy history of treating schizophrenia and is best viewed as an adjunct to medication (Ruffalo, 2023). It is clear from these limitations and criticism that the dopamine hypothesis, valuable though it is, falls short in offering a thorough explanation for the genesis of schizophrenia. The glutamate hypothesis being a more widely accepted hypothesis it still lacks to deepen the complexity of schizophrenia.

Lastly, research through Genome-Wide Association Studies (GWAS) has shown that psychiatric disorders, including schizophrenia, have a polygenic nature. This means that hundreds or even thousands of variants play a role in the likelihood of developing schizophrenia. Studies on rare variants associated with schizophrenia have also made important progress by identifying shared genes and gene sets with other neurodevelopmental disorders. This concept of pleiotropy adds complexity to the overall understanding emerging from these studies (Sullivan & Geschwind, 2019). Thus, to further the understanding of this complex psychiatric disorder, future research should strive to integrate multiple perspectives, examine unique methods, and consider the dynamic interplay of various neurobiological, heterogeneity and environmental/social factors (Mas et. al, 2020).

Declaration by Authors

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

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How to cite this article: Maria Chanioti, Georgios Lyrakos, Georgios Pilafas, Penelope Louka. The dopamine hypothesis as a causal explanation of schizophrenia. *International Journal of Science & Healthcare Research.* 2024; 9(2): 27-34. DOI: *https://doi.org/10.52403/ijshr.20240205*

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