Scientific Research Publishing

Open Journal of Medical Psychology, 2023, 12, 71-81
https://www.scirp.org/journal/ojmp
ISSN Online: 2165-9389
ISSN Print: 2165-9370

Genesis of Schizophrenia: An Introspective Review

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How to cite this paper: Dudi, A.K. (2023) Genesis of Schizophrenia: An Introspective Review. *Open Journal of Medical Psychology*, **12**, 71-81.
https://doi.org/10.4236/ojmp.2023.122004

Received: February 7, 2023
Accepted: April 22, 2023
Published: April 25, 2023

Abstract

Research and Results: Schizophrenia begins with nasal obstruction, disrupting supraschalemic nucleus output and lateralized ultradian body rhythms. If one nostril is blocked, vaso-choking occurs in the ipsilateral brain hemisphere cortex, which has vesicles connected to the nose. This disturbs the ultradian balance of the body and brain hemispheres causing abnormal behavior and bizarre thinking. The brain has a bidirectional connection and communication with the body via the nervous system. The Hypothalamic-Pituitary-Adrenal (HPA) axis, Autonomic Nervous System (ANS), and vagus nerve are linked. ANS lateralization can switch from parasympathetic to sympathetic due to vagus nerve changes. Schizophrenia is characterized by Basic Rest Activity Cycle (BRAC) energy balance disruption. Let's examine how a disruption in the lateralization of the nasal cycle can lead to pathology in the mind. **Purpose and Method:** A literary search is conducted in comparison with authors' introspective insights to summarize schizophrenia's genesis after curing this disease to fill the knowledge gap between a few relevant theories to build a percept of the disease through this (mini) narrative review. **Conclusion:** Nasal cycle and vagus nerve toning can play roles in mental health.

Keywords

Nasal Cycle, Lateralized Rhythms, Body Systems, Vagus Nerve

1. Introduction

Primitive man's existence was difficult but uncomplicated. Caveman's lifestyle and herb diet while progress improved people's lives, increased competition caused new problems. The man sacrificed inner calm and harmony for external tension,

conflict, and frustration. Psychiatric disorders, once unheard of, are now surprisingly common. Behavioral disorders skyrocketed in this pandemic decade.

Human understanding expanded over time, philosophy gave way to psychology as the study of the soul turned to behavior. Clinical psychology is transitioning from the Diagnostic and Statistical Manual of Mental Disorders-5-TR (DSM-5-TR) [1] to Research Domain Criteria (RDoC) [2], a newly established subfield to study schizophrenia. Uncertainty persists, scientists speculate.

Schizophrenia's onset and its possible causes. Schizophrenia is characterized by false beliefs, hostile, abnormal behavior, such as hearing voices or speaking incoherently, and a decreased ability to understand the world. It can also lead to depression, emotional apathy, indifference, laziness, and confused thinking. Clearly, schizophrenia has positive and negative symptoms [3]. If a psychiatrist is busy with the first issue, the second remains unresolved. He prescribes tranquilizers to curb delusions, hallucinations, and suspicious thinking. Emotionlessness, language delays, and psychomotor clumsiness persist. What the root cause is, though, remains an open question.

Based on the research question of the genesis of schizophrenia, an attempt is made to describe the onset of schizophrenia using introspective empiricism after curing this disease in combination with a qualitative review of the literature, with an attempt to bridge the empirical gap of knowledge between three prominent theories on schizophrenia, namely the neuro-degeneration theory, the mitochondrial dysfunction theory, and the neurotransmitter dysregulation theory. These theories, using summary, are tried to connect using concepts of nasal cycle rhythmic dominance, cerebral brain hemispheric lateralization, and ANS sympathetic and parasympathetic states to explain the etiology of schizophrenia that causes brain hemispheric dysfunction. The goal is theory integration.

The author is a psychologist with 20 years of introspection training. Using Google Scholar, along with extensive snowball searching on only the relevant insight points, the research findings were summarized. Review quality is transparent and bias-free. Only high-quality systematic reviews addressing the research question are included, and non-English articles are excluded. The overall goal is to advance schizophrenia research and knowledge. In the first section, the causes of schizophrenia symptomatology are examined, and then the enigma of curing the symptoms and the body's disorganized ultradian energy balance with its connection to the nasal cycle are discussed. Why it all happens is the core issue under discussion.

2. Positive Symptom Physiopathology

Dopamine overactivation is a target of tranquilizer chemotherapy. Pain and shock hyperactivate dopamine projections from the prefrontal cortex to the amygdale, hippocampus, nucleus accumbens, and hypothalamus [4].

In schizophrenia, the right cerebral hemispheric cortex is less active than the left [5]. Under the influence of a dysfunctional DLPFC, the mesolimbic dopamine system in the midbrain overactivates. Prefrontal degeneration reduces dopamine

terminals. Dopaminergic function attempts to increase DLPFC activity [4].

As schizophrenia's clinical status improves, metabolic activity shifts from the left to the right hemisphere [5]. Degenerative changes in the prefrontal cortex affect dopamine neurons as schizophrenia progresses. Right hemisphere brain function is deficient. Brain mechanisms try to boost DLPFC physiology [6] [7]. As a compensatory mechanism, the right hemisphere's hypoactivity boosts the left hemisphere's dopaminergic system, causing hyperactivity [8]. The right hemisphere has no additional arousal, but the left does. Hypoactivation of the brain may result from a right-hemisphere strategy mode of thought, causing inadequacy during challenging tasks requiring additional arousal. Left hemisphere hyperarouses in threat and danger [9]. As a compensatory mechanism, the brain transfers its energy, albeit inefficiently, from the right to the left hemisphere to maintain performance. Positive symptoms result.

3. Negative Symptomatology

Hemispheric dysfunction characterizes schizophrenia [10]. This psychopathology affects the right hemisphere [8] [11]. Right DLPFC hypometabolism affects emotional processing, expression, social affiliation, and cognition, causing aberrant emotional behavior and social withdrawal [12]. Frontal hypofrontality causes decreased Cerebral Blood Flow (rCBF) in schizophrenia [13]. Hypofrontality in the prefrontal lobe causes negative schizophrenia symptoms [10].

Murray (1987) [14] promoted hypo-frontality and blamed schizophrenia's negative symptoms and attention-cognitive deficits on frontal lobe dysfunction. Apoptosis in the right hemisphere's Dorsolateral Prefrontal Cortex (DLPFC) causes neurodegeneration and "hypo-frontality" of prefrontal areas. Murray calls schizophrenia a connectivity disorder. Schizophrenia alters the neuronal activity baseline, the Default Mode Network. Apoptosis can cause brain gliosis and cell injury. Prefrontal cortex activity is imbalanced. This imbalance reduces formation and excessively shortens this inhibitory and excitatory process, which may cause brain gray matter loss. Small atopsis in dendrites and synapses causes neuropil loss in neuroplasticity. Atopsis-induced neuropil loss, retention, and degeneration without cell death cause synaptic degeneration and neuron size reduction [14]. Neurodegeneration causes negative symptoms and hypofrontality [15].

Rotenberg (1984) [9] found many similarities between right hemisphere damaged patients (due to accident) and schizophrenia patients, including apathy, indifference, inability to show emotions, poor appraisal of negative emotions, impaired fear and anger perception, affect process deficits, and general cognitive deficits [9]. The chirmic faces test in schizophrenia shows left-hemisphere bias [16] [17]. This is the reality underlying schizophrenia's symptoms; however, how can it be healed?

4. Vagus Nerve in Mental Health Well-Being

The vagus nerve is extremely important to a person's mental health and overall

well-being. The brainstem connects various systems in psychopathological disorders like schizophrenia. The vagus nerve, originating in the brainstem, traverses the neck, thymus, and abdomen. Left and right brainstem nodes sprout vagus nerve trunks. Each vagus has multiple functions. The vagus nerve is in the Hypothalamic-Pituitary-Adrenal (HPA) axis, Autonomic Nervous System (ANS), and Central Nervous System (CNS); it has sympathetic, parasympathetic, and Enteric Nervous System (ENS) branches [18]. Multiple regions of the brain generate a family of neural pathways, which, when combined, constitute the vagus nerve. The two lateralized vagus nerve trunks, however, have different vagi that originate from brainstem nuclei and control visceral function [19].

Nucleus Ambiguous (NA), Dorsal Motor Nucleus of Vagus (DMV), and Nucleus Tractus Solitaries (NTSs) are three medulla neural systems that regulate the vagal system. NA and DMV have distinct central projections and operate independently. Both vagus nuclei receive input from the amygdala, hypothalamus, and NTS [20] [21]; vagal pathways originate in the cortex and project to the limbic system and medullary nuclei. This regulates autonomic and facial striate muscles. Two vagus origin nuclei project to peripheral structures [22].

The vagus nerve's length earns it the nickname "Wanderer Nerve". The vagus nerve connects the ENS to the CNS, forming the "Brain Gut Axis". Due to structural, functional, and chemical coding similarities with the brain, it is called "Brain in the Gut" and "Second Brain". It involves the endocrine, immune, humoral, gut microbiota, and Sympathetic Nervous Systems (SNSs). It is a high-resuscitation mass of nerve cells in the intestinal wall [23] [24].

The vagus nerve regulates behavior via afferent and efferent nerves. Afferent nerve cell communication from the intestine to the brain lets the brain know where the intestine, liver, heart, lungs, and other organs are. Efferent nerve cells monitor flight-or-fight and vegetative activities. Parasympathetic nerves regulate bowel motility and glandular secretion.

ENS is an intestinal nerve plexus. The "brain-gut axis" sends bidirectional sensory messages through the gut [25]. Neuroendocrine and metabolic systems influence gastrointestinal homeostasis at the HPA-Vagus junction under the control of brain and intestinal functional effector cells and gut microbiota. The gut microbiome affects anxiety and depression [26].

5. Vagus Nerve's Social Behavioral Role

The vagus nerve regulates socially desirable behavior. The ANS promotes social commitment behavior via facial expressions and vocalizations via its neuroanatomical channel with the carnitine nerves. SNS restricts physiologic status to support positive social engagement [27].

An animal's vagal tone temporarily decreases in response to environmental challenges. Fight-or-flight increases metabolic output. Vagal tone is greatest in uncontrolled conditions (like sleep), but it's reduced by stress, exercise, attention, information processing, and other metabolically demanding states [28]. During

life-threatening states like rage and panic, humans have no NA vagal tone. In all stress states, metabolic demands reduce NA vagal tone. Hypoxia reduces vagal efferent activity, causing bradycardia. Massive neurogenic bradycardia is caused by reflexive vagal activity, which damages the oxygen-hungry cortex and myocardium [20].

A healthy vagus shifts lateralization from left to right and *vice versa* with each breath. Oxygen deprivation of the right hemisphere cortex causes ipsilateral vagus nerve dysfunction. Disordered breath lateralization may affect vagus lateralization shifts, disrupting ANS balance regulation and causing psychopathology. Reduced oxygen causes CNS depression to reduce behavioral complications [22]. In usual conditions, the ANS regulatory process is balanced. Unbalanced ANS neural control causes behavioral and psychiatric problems. Unbalanced sympathetic and parasympathetic ANS functioning, excess sympathetic outflow, and decreased parasympathetic outflow produce dysfunctional mental states and uncontrolled emotional behavior [22].

6. Disruption of the Body's Energy Equilibrium

As breathing patterns change, vagus' lateralized rhythms can switch from left to right *and conversely*. Alterations in the vagus nerve can switch ANS lateralization from parasympathetic to sympathetic and *vice versa*. This causes a change in the ANS's ergotrophic and trophotrophic states. Nevertheless, schizophrenia is characterized by a disruption in the Basic Rest and Activity Cycle (BRAC) energy balance. SNS affects cerebral hemispheric activity and nasal airflow [29]. Where CNS-ANS lateralized neural activities fulfill bodily needs via ultradian rhythms (work, rest, eating, etc.), Kleitman calls them BRAC [30] [31] [32]. Higher right-sided sympathetic tone is associated with ergotrophic states, sympathetic arousal, and BRAC activity [33].

Nonetheless, BARC is linked to CNS and ANS rhythms. ANS and CNS lateralized neural rhythms cause ultradian rhythms. Ultradian rhythms help the body expend and restore energy efficiently. Stress or overactivity causes right sympathetic dominance. The lateralized rhythms of ANS-CNS activity act pendulum-like to maintain homeostasis by altering brain and metabolic rhythms. This modification mechanism is employed by nature to maximize economic efficiency.

The autonomic dominance of ultradian rhythms is lateralized. This dominance is either left sympathetic and right parasympathetic (left nasal dominance) or the opposite. The ANS functions are ergotrophic (energy expenditure) and tropotrophic (energy conservation and restoration) [34]. An increase in parasympathetic tone has the opposite effect of stress, which is relative calm due to right brain dominance over the left nostril. Right brain dominance with left nasal dominance boosts healing, regeneration, and immune function. During the BRAC active phase, the ultradian rhythm of CRH, which regulates "fight or flight", is amplified in the right nostril, where left-brain dominance exists. Left-nasal breathing causes BRAC's resting phase, which is parasympathetic [29].

Humans can be forced into a prolonged state of passivity when they cannot fight, flee, or retain control of the situation; this may cause a cerebral disorder. Unbalanced lateralization activity and metabolic shifts cause a negative psychophysiological effect. The environment may force excessive single-hemisphere lateralized use.

Catecholamine secretion, however, is also asymmetrically lateralized and controlled by rhythmic variations, resulting in unbalanced neuroendocrine gland secretion that affects human health and behavior [35]. This circulation affects adrenal function through rapid metabolism. Due to excess corticoids and catecholamines, the adrenal glands may secrete unbalanced hormones (pro- and anti-phlogistic). Adaptation diseases or stress-induced mental disorders result [33]. Plasma catecholamine (norepinephrine, epinephrine, and dopamine) levels in both arms co-vary with nasal cycle variation on both lateralized sides [29].

7. Schizophrenia's Origins

The brainstem is involved in psychopathology, including schizophrenia. The vagus nerve connects the brain stem to the cerebral cortex and hypothalamus Supraschalemic Nucleus (SCN). The suprachiasmatic nucleus produces circadian rhythms to adapt to the time of day and specific needs. SCN projects to the ANS and CNS, which have neural networks that regulate outputs [29] [36].

Single-cell circadian oscillators cause clock genes to oscillate. Clock genes are expressed in nearly all body tissues, including SCN neurons. SCN regulates glucose in the liver, glucocorticoids in the adrenal gland, Adrenocorticotropic Hormone (ACTH) in the pituitary gland, and CRH, AVP, and oxytocin in Paraventricular Nucleus (PVN) neurons. The Hypothalamic-Pituitary-Adrenal (HPA) axis connects the hypothalamus to the adrenal glands. The SCN controls circadian HPA activity. Stress-induced ACTH controls glucocorticoid release. The adrenal clock and ANS control the HPA axis's circadian rhythms. Disrupting the circadian rhythm can cause metabolic diseases [29].

SCN regulates lateralization along with other body rhythms, including lateralized breathing. Nasal cycle disturbance is linked to schizophrenia, autism, Parkinson's disease, and Kallmann's syndrome. Self-regulation aids development through lateralized breathing patterns. It affects cerebral and CNS-ANS rhythms. The nasal cycle is the most prominent ANS rhythm. Erectile tissue temporarily obstructs the nasal passage, resulting in asymmetric airflow. This alternation is called the nasal cycle. Additionally, differential nasal congestion affects lateral lung response. The dominant nostril on one side has a homolateral lung to increase sympathetic tone. Asymmetrical blood flow swells the nasal septum (front) and inferior turbine of each nostril [37].

Left and right oscillators in the brainstem cause asymmetric sympathetic tone and brain activity. The hypothalamus regulates nasal airflow rhythm. The hypothalamus controls oscillators, sympathetic neurons that regulate sympathetic tone centrally, to regulate rhythmic nasal cycles. Nasal airflow affects brain activity. Nasal

and brain hemisphere asymmetries are linked. Nostril and brain dominance are related. Rhythmic nasal airflow fluctuations correlate with cerebral activity [38]. Each hemisphere's arousal peak correlates with nasal dominance. Contralateral nasal dominance is correlated with each hemisphere's arousal peak. Laterality of contraction has emotional repercussions [37].

If unresolved stress is combined with a weak genetic foundation, the brain's immune system may be compromised. Simultaneously, infection with neurotrophic viruses (possibly herpes simplex virus 1) can cause chronic obstruction of the right nostril [39]. SCN is severely affected by the altered blood oxygen level-dependent signal response [40]. This is the onset of schizophrenia. The nasal cycle is associated with cerebral hemispheric lateralization, which may lead to functional hemispheric imbalance. The ANS, which regulates cognition, tightly couples the cerebral rhythm and ultradian rhythm (the nasal cycle) [38]. According to Price and Eccles (2016) [37], nasal airflow asymmetry may cause schizophrenia and other lateralization disorders. With vaso-choking of the right nostril, the ipsilateral brain hemisphere vesicles that supply oxygen-rich blood to the right hemisphere become chocked, affecting its function.

8. Mitochondrial Dysfunction

Reactive Oxygen Species (ROS) and Reactive Nitrogen Species (RNS) cause mitochondrial dysfunction and cell death (apoptosis or necrosis) in the brain. Hypoxia causes Oxidative Stress (OxS). High sodium and calcium in glutamate-dependent N-Methyl-D-Aspartate (NMDA) channels cause overproduction of free radicals, which leads to OxS. Oxidative OxS may reduce respiratory complex activity and damage the mitochondrial respiratory chain complex. An imbalance in oxidants and antioxidants causes cell oxidative damage. Free iron or free radicals increase ROS. Polyunsaturated fatty acid-rich neural membranes synthesize reactive ROS easily. Nicotinamide Adenine Dinucleotide Phosphate (NADPH) oxydase oxidizes NADPH to produce superoxide (O_2) and Reactive Oxygen Species (ROS). Cells with inefficient Oxidative Phosphorylation (OXPHOS) produce ROS, which lowers Adenosine Triphosphate (ATP) levels and impairs energy metabolism. Energy metabolism oxidizes mitochondrial proteins, lipids, and DNA. Mitochondria, neurocells' powerhouses, will also harm them [41].

Mitochondrial dysfunction is caused by poor energy metabolism. Mitochondrial dysfunction causes cell necrosis and neuroinflammation.

Right nostril obstruction marks the onset of schizophrenia, disrupting SCN output and lateralized ultradian body rhythms. This symptom is similar to the common cold symptom of nasal congestion; however, it is permanent. The brain has a large, oxygen-sensitive neocortex [42]. Autonomic mechanisms optimize cortical oxygenation. In extreme stress, the left hemisphere may over-activate, which requires an increased oxygen supply to the brain neurons and, if unmet, may cause hypoxia in the contralateral right hemisphere of the brain. In the right Prefrontal Cortex (PFC), hypoxia may cause mitochondrial dysfunction and neu-

rodegeneration. If the right nostril is blocked, the ipsilateral brain hemisphere cortex, which has vesicles connected to the nose, also experiences neuronal vaso-choking. Without oxygen-rich blood, the right prefrontal cortex may degenerate. Due to an infection (possibly Herpes Simplex Virus type 1 (HSV-1) or any other similar viral infection), the nose is chocked [39]. Right hemisphere PFC neurons may die from hypoxia or apoptosis. Apoptosis involves mitochondrial dysfunction. Hypoxia kills neuronal mitochondria, which produce energy with oxygen. Nonetheless, it is evident that all of this is preceded by a long history of chronic stress and conflict, which may have likely weakened the brain's physiology and immunity.

9. Study Limitations

This research has limitations. As an introspective psychologist, the author's background in the humanities may limit his biological descriptions. Reference citations are from initial research and may be less recent. Introspection methodology may be biased despite care. Moreover, this methodology lacks repeatability.

10. Conclusion

Schizophrenia causes rhythmic brain and body lateralization disorders. The SCN, which generates rhythms in asymmetrically lateralized organ systems, is disrupted, causing abnormal behavior in the nasal cycle, brain hemispheres, autonomic sympathetic and parasympathetic states, the Basic Rest Activity Cycle (BRAC)—ergo trophic and trophotropic states—neuroendocrine regulation, the vagus, and numerous other lateralized systems of the body. The objective of future research should be to regenerate defunct neural cells.

About the Author

The author is a psychologist at a vocational rehabilitation center for differently abled people with 20 years of experience in guidance, counseling, and rehabilitation (which includes persons with mental illness). His introspective findings describe this self-analysis report after he was cured of schizophrenia.

Acknowledgements

Dr. Bhagyashree Kar, Director, *BRAIN DYNAMICS, "Because Mental Health Matters"*, helped with proofreading.

Conflicts of Interest

The author declares no conflicts of interest regarding the publication of this paper.

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