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Disordered Breath-Brain Lateralization: At the Core of Schizophrenia Pathogenesis

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Abstract

Index terms—

1 I. INTRODUCTION

The modern age is characterised by development, innovation, and technology, which make life full of ease, comfort, and miracles. Nevertheless, it also brings new peculiarities and complications.

Increasing rates of chronic stress, anxiety, and schizophrenia are products of overcompetition. Last century witnessed an unprecedented increase in cases of schizophrenia, and this decade of the COVID-19 pandemic has accelerated it further. However, scientists are still struggling with the core aspect: why does schizophrenia occur? Schizophrenia affects 0.3-0.7% of the global population, with a 2016 global age-standardised point prevalence of 0.28%. The median incidence is 15.2/100,000 people, with the middle 80% of estimates fluctuating by a factor of five. The 12-month prevalence is 0.33%, while the lifetime prevalence is 0.48%. However, there has been an increase in the number of cases of schizophrenia in certain areas, such as London, UK, where a doubling in the prevalence between 1965 and 1997 has been attributed to migration.

Research Domain Criteria (RDoC) is a new tool for investigation in clinical psychology (Kang 2017, Cuthbert 2022). In this self-analysis report, using empirical (introspective) findings and a review of the literature, an attempt is made to bridge the knowledge gap between three prominent theories on schizophrenia, namely neurodegeneration theory, mitochondrial dysfunction theory, and neurotransmitter deregulation theory. By using the concepts of nasal cycle rhythmic dominance, cerebral brain hemispheric lateralization, and the autonomic London Journal of Medical and Health Research nervous system's (ANS) sympathetic and parasympathetic states, the aetiology of psychopathology that leads to disordered brain hemispheric function is elaborated.

2 II. METHODS AND TOOLS

This narrative review summarises the onset of the psychopathology of schizophrenia using biological as well as behavioural constructs through the self-analysis (introspection) method. The author is a 20-year-old introspective psychologist. Google Scholar and extensive snowball searching on relevant insight points summarised the research findings. Transparent and impartial review quality is sought. Non-English articles are excluded, and only high-quality systematic reviews that address the research question are included. Schizophrenia research and knowledge are the main objectives. The objective is theoretical integration.

The author followed defined methodologies and guidelines to ensure credibility and reliability in the self-analysis approach. Among them were maintaining a clear head, being honest and straightforward, avoiding preconceptions, taking a systematic approach, and critically scrutinising information. The method proved reliable since it relied on high-quality systematic reviews and summaries from Google Scholar.

3 Oxygen Requirement for Brain Functioning

Mental and emotional states have a direct impact on the respiratory, cardiac, and digestive systems via the ANS. The ANS is divided into three parts: sympathetic, parasympathetic, and enteric.

The respiratory system has an immediate and long-lasting effect on the body's physiological and mental well-being. ANS has direct involuntary control over the mind, regulated by breath (Kang S. W., 2017).

Emotional stress is correlated with respiratory oxygen intake by the body. Stress increases brain oxygen needs, which may go unmet. Stress is correlated with an increased respiratory rate (Widjaja, Orini, et al.

2013). Increased anxiety Neurotrophin signalling is disregulated in the pathogenesis of schizophrenia, involving obstetric complications along with psychopathology. In persons with genetic susceptibility to schizophrenia, prenatal hypoxia is associated with an increased risk of developing schizophrenia later in life (Cannon, Yolken et al. 2008). In the following section, we will investigate how stress can impact the human body and mind through altered patterns of breathing and oxygen intake. In addition, genetic vulnerability can increase the probability of this psychopathology.

4 Asymmetrically Lateralized Rhythms

Biological systems are functionally lateralized in the body. These bilateral organ systems have complex functions that work through activation in a simultaneous pattern. Bilateral organs distribute workload and enhance survivability with enhanced awareness and improved movement.

Bilateral organ systems are groups of organs that work together to execute specialised tasks on one side of the body. The cerebral hemispheres are responsible for language, logical reasoning, creativity, and spatial awareness, as do the lungs London Journal of Medical and Health Research (Suess, Alexander, et al., 1980).

Mammals have only 2% brain weight in comparison to total body mass but consume about 20% of the total oxygen requirement (Sokoloff 1989). Oxygen homeostasis perturbations cause reduced oxygen availability, called hypoxia (Widjaja, Orini et al. 2013). Non-stressful attention decreases total respiratory variability, while mental load increases it (Widjaja, Orini, et al. 2013). Stress can bring about a hyperventilation reaction in the action-oriented reaction mode towards fight or flight, while feelings of defeat, depression, and being overwhelmed may produce a hypoventilation response (Suess, Alexander et al. 1980). Hypoxia impacts physiological systems through altered neuronal functions by adversely influencing neurotransmitter synthesis. Molecular oxygen is needed by rate-limiting enzymes in the fusion of many neurotransmitters for their activity (Widjaja, Orini, et al. 2013).

for breathing and the kidneys for waste filtration. The central nervous system (CNS) and autonomic nervous system (ANS) are asymmetrically

5 Nasal Cycle Dominance

Shannonhoff-Khalsa **??**1991) Reciprocal changes in the nasal airflow take place through left and right oscillators in the brain-stem region to produce an asymmetric sympathetic tone along the brain activity. Autonomic nervous fibres, through vasoconstrictor sympathetic nerves embodying large veins in turbines, supply peripheral regulation (Price and Eccles 2016).

6 Breath and Brain Inter-Relationship

Breath is interlinked with both body and mind (Werntz, Bickford, et al., 1983). Fluctuations in cerebral hemispheric activity remain associated with rhythmic variations in nasal airflow. Nostril dominance is associated with cerebral dominance.

Hence, there is a link between brain asymmetry and nasal airflow (Price and Eccles, 2016). The nasal cycle is coupled with cerebral hemispheric lateralization. Homo-lateral body-half provocation of sympathetic dominance can be accomplished through nasal airflow. Metabolism and mental states may be affected by the self-regulation of breathing (Werntz, Bickford, et al., 1983).

The nasal cycle is connected with the arousal of cerebral hemispheric lateralized rhythms (Werntz, Bickford, et al. 1983 Increased parasympathetic tone is a generalised resting position as left nostril/right brain dominance enhances parasympathetic activity and peaks healing, regeneration, and immune function (Werntz, Bickford, et al. 1983). To uphold proper homeostasis, the lateralization rhythms of ANS-CNS activity are produced for coupling mind and metabolism. Nature uses this alteration process to maximise economic efficiency.

ANS functions endure as ”ergotrophic” (energy expenditure) and ”trophotrophic” (protection and restitution of energy) functions. The active phase of BRAC correlates with the dominant status of left-brain right-nostril, while the resting phase of BRAC correlates with dominant right-brain left-nostril. Greater sympathetic activity in the right side of the physique produces the active phase of BRAC (Werntz, Bickford, et al. 1983).

7 Catecholamine Regulation through Ultradian Rhythms

The CNS and body periphery possess ANS fibres located in an uncrossed manner. The nasal cycle is coupled to the lateralized ultradian ANS-CNS rhythm in the body for plasma catecholamine level regulation (Kennedy, Ziegler et al. 1986).

Connections between cortex and hypothalamus and between periphery and hypothalamus are linked with uncrossed fibre systems of the ANS (Netter 1969

8 Werntz

(1983) demonstrated plasma catecholamine (norepinephrine, epinephrine, and dopamine) levels. These rhythms produce coupling between the CNS and ANS. BRAC has coupling with the hypothalamic-pituitary-adrenal axis (HPA), a psychological phenomenon. CRH in the hypothalamus, considered a stress peptide, co-varies with

locomotor movement. Ultradian rhythms are connected to pituitary hormone secretions such as cortisol and adrenocorticotropin (ACTH).

9 Onset of Schizophrenia

With psychological conditions shifting in ANS, lateralization episodes switch instantaneously. Immune functions are affected by states of CNS-ANS action, with distinct stressors playing an important role. Cerebral states and personality profiles can be impacted by overstimulation of one-half of the body's periphery, consisting of the CNS and ANS. Stress or overactivity combines the right sympathetic mode with excessive left-brain activity, depending on how long and how frequently a particular status is maintained. A prolonged shift towards one status is easy to imagine in the form of extended shifts and acute swings. Immune functions may be over -or under-activated with the atypical over-stimulation endeavour of one hemisphere.

In humans, when there is no alternative to fight or flight or no control of circumstances, they are forced towards a passive state for an extremely long time, which makes them inclined to depression, a right cerebral disorder. This is a determinant disease condition due to unequalised lateralization action in the form of uneven metabolic shifts with a negative psychological and physiological impact. This occurs because of the environmental condition that is responsible for excessive use of the cerebral state (Selye 1946). Stress or overactivity contributes to right sympathetic dominance as a result of too much brain activity (Werntz, Bickford et al. 1983). These produce diseases of adaptation or stress-induced mental disorders.

Prolonged stress may induce a condition of hypoactivity in the brain, which, if not restored to its normal resting phase within its normal rhythmic cycle time, may continue for a prolonged period. This over-work of one hemisphere may exhaust the brain's (impulse) energy resources and disturb homeostatic adaptation between brain hemisphere and nostril dominance; both may start working in a contrary to normal (opposite) dominant position.

London Journal of Medical and Health Research Ultradian rhythms possess lateralized autonomic dominance. (Kleitman 1967;Kleitman 1982) The ultradian BRAC hypothesis, in its extended form, explains the lateralized ultradian ANS-CNS coupling alteration. To maintain homeostasis, together with adaptation in the structural and temporal elements, these rhythms must persist and be organised economically.

In the extended continuance attributed to the "active phase" of BRAC, sudden neurodegeneration into one (right) brain hemisphere's A choked right nostril produces a lack of oxygen supply to the active hemisphere, creating hypoxia in the neuro-cells and impacting cortical stimulation. Literally speaking, the right brain stops breathing, which may create neurodegeneration and hypo-frontality in a particular (right) hemisphere, leading to the psychopathological disorder of schizophrenia.

This creates lateralized cerebral dysfunction. Hence, schizophrenia and similar lateralization diseases may occur due to the cortical connection of nasal airflow asymmetry (Price and Eccles 2016).

Physiological malfunctions are connected with nasal cycle dysfunctions such as schizophrenia, autism, Kallmann's syndrome, Parkinson's disease, etc.

10 Mitochondrial Dysfunction

Dysfunction in the mitochondria leading to cell death (due to apoptotic cell death or neurosis) is caused by the formation of reactive oxygen species (ROS) and reactive nitrogen species (RNS). Lack of oxygen, or hypoxia, produces oxidative stress (OxS). Moreover, a high influx of sodium and calcium in the glutamate-dependent N-methyl-D-aspartate (NMDA) channels also causes overproduction of free radicals, which finally leads to OxS. This OxS may decrease the respiratory complex's activities, which in turn cause defective mitochondrial respiratory chain complexes. Due to excessive oxidants or reduced antioxidants, an imbalance in oxidants and antioxidants is created, causing oxidative damage to the cell. This increases free iron levels or generates free radicals, causing ROS. Neural membranes rich in polyunsaturated fatty acids are particularly susceptible to the formation of ROS.

Nicotinamide adenine dinucleotide phosphate (NADPH) oxydase, which oxidises NADPH by donating electrons to an oxygen molecule (O 2) to produce superoxide (O2), may also lead to reactive oxygen species (ROS) formation.

Inefficient oxidative phosphorylation (OXPHOS) in cells may also lead to ROS, which in turn leads to impaired energy metabolism due to a low adenosine triphosphate (ATP) supply. Energy metabolism is responsible for the oxidation of mitochondrial proteins, lipids, and DNA (

Defective energy metabolism leads to compromised viability of mitochondria and, hence, mitochondrial dysfunction. Necrosis, or apoptotic cell death, is caused by mitochondrial dysfunction, leading to neurodegeneration and neuroinflammation.

11 Right Prefrontal-Cortex Neurodegeneration

Murray (1987) advocated hypo-frontality and said that negative symptoms and attention-cognitive deficits in schizophrenia are due to dysfunctional frontal lobes. Neuro-degeneration is found to occur in the dorso-lateral prefrontal cortex (DLPFC) of the right hemisphere through apoptosis, which leads to slow activation of frontal and prefrontal lobe regions and is called "hypo -frontality" of prefrontal areas. According to Murray, schizophrenia is a disorder of connectivity. Default Mode Network (DNM), which is a baseline for neuron activity, is severely altered

in schizophrenia; this alteration may occur due to varied causes. Neural injury occurring to London Journal of Medical and Health Research prefrontal cortex (PFC) may occur because of acute or prolonged imbalance comprising lateralized autonomic arousal in the brain. Deep into the right nasal path, the inferior turbine nasal septum is engorged with erectile tissue obstruction due to greater blood flow into the ipsilateral hemisphere. A higher sympathetic state of arousal (Ergotrophic state) is correlated with a higher right-sided sympathetic tone. Greater sympathetic activity is produced in the right side of the physique (Selye 1946) during this arousal phase, and it may activate right adrenal action through quick metabolic change. Plasma catecholamine levels, such as norepinephrine, epinephrine, and dopamine, may become disordered and imbalanced, and immune functions may get disturbed (with over-or underaactivation) due to overstimulation generated in one single hemisphere. cells is called "brain gliosis and may occur due to apoptosis in the brain. There are two types of brain gliosis due to apoptosis: astroistosis and microgliosis. Oligodendrocytes perform the 2.10 Hypo-Active Right Brain Hemisphere Gur (1978) showed that people with schizophrenia overactivate their left hemisphere, which gets dysfunctional to a greater degree than typical humans. Chaotic use of the left (dysfunctional) hemisphere creates malfunctioning logic and a lack of affect (Gur 1978). Right dorsolateral prefrontal cortex hypometabolism influences emotion expression, with social affiliation leading to abnormal emotional behaviour. Hypo-frontality enjoys a positive correlation with chronic schizophrenia, which in turn is associated with negative symptoms.

12 Hyper-Active Left Brain Hemisphere

The left brain hemisphere gets hyper-active due to right hemispheric hypo-frontality. **??**ur (Feb. 1987a) showed this in patients with the left as compared to the right sub-cortex. Due to hypo-frontality in schizophrenia, frontal regions, as compared to posterior ones, have reduced metabolic rates in addition to glucose metabolism. Kucharska-Pietura (2006) has noted similarities between right-sided brain-damaged people and people with schizophrenia. There is righthemisphere impairment in schizophrenia (Kucharska-Pietura 2006). Right hemisphere damage patients (due to an accident) and schizophrenia patients share a number of characteristics, according to Rotenberg (1994), including apathy, indifference, an inability to express emotions, a poor assessment of negative emotions, impaired perception of fear and anger, deficits in the affective process, and general cognitive deficits (Rotenberg 1994). Schizophrenia patients who take the chirmic faces test exhibit left-hemisphere bias (Levy, Heller et al. 1983).

13 Hypo -to Hyper-Brain Activation: A Compensatory Effort

Rotenberg (1984) stated that the right hemisphere performs imagination and information processing, while the left one performs arithmetic tasks and numerical counting. The right hemisphere is "entropic" of image thinking (polysemantic context). To limit the interconnections of things and phenomena and for probability forecasting, the left hemisphere requires additional activation.

Brain "hypo-activation" is due to the right London Journal of Medical and Health Research Myelination leads to the loss of white matter in the prefrontal cortex. This white matter works to join the frontal and temporal lobes. The imbalance in the inhabitation and excitation processes in the prefrontal cortex leads to reduced formation and excessive shortening of this inhibitory and excitatory process, which may cause loss of grey matter in the brain. Diminished neuroplasticity leads to loss of neuropil due to small apoptosis in dendrites and individual synapses. Due to loss of neuropil by apoptosis, excess neuropil excretion, retention, and degeneration, without causing cell death, leads to synaptic degeneration (disappearance of synapses) and a reduction in neuron size (Murray and Foerster 1987). Hence, neurodegeneration is the cause of negative symptoms and hypofrontality.

Also, the left temporal lobe shows higher activity, and the left basal ganglia receives reduced metabolism. They possess left hemispheric over-activation **??**Gur, Resnick et al. 1987).

More severely disturbed patients showed greater left-hemispheric metabolism. **??**ur (Feb. 1987b) showed that hemispheric arousal is atypical in the right cerebral hemispheric cortex as compared to the left one. The dopaminergic system in schizophrenia contains greater left-hemispheric involvement **??**Gur, Resnick et al. 1987).

Unilateral forced nostril breathing yields clinical effects for the treatment of a variety of disorders. Differential stimulation of cognitive efficiency can be produced by altering cerebral activity through breathing, which is used as a remedy for psychopathologies connected with lateralized cerebral dysfunctions (Shannahoff-Khalsa, Boyle et al. 1991).

hemisphere's thinking manner leading to functional inadequacy during task resolution, which activates "hyper-arousal" of the left Rotenberg (1994) explained that the left hemisphere undertakes additional compensatory physiological and psychological activation because of right hemisphere functional insufficiency. The left hemisphere makes effort as compensatory hyper-activation (due to the weakness of right hemisphere skills) in the realms of logical thinking and decision-making in non-verbal tasks that are accomplished by right hemisphere competence.

Although unsuccessful and inefficient, the brain attempts to transfer all its resources to perform at its best. Search activity, in addition to brain catecholamines, upholds the appositive feedback loop mechanism, which is entirely performed by hyperbolic left hemisphere functions. Dopamine pathways support higher action in the left hemisphere over the right one.

The left sub-cortical structure has an additional number of dopamine receptors as compared to the right one (Rotenberg 1994).

14 Neurotransmitter Deregulation

With respect to schizophrenia, Weinberger (1987) described that defects in the DLPFC myelination process may cause dysfunction in the mesolimbic dopamine system by making it functionally overactive. Degenerative changes in the prefrontal cortex affect dopamine neurons by diminishing activity at their terminals. The mesocortical system stretches from the prefrontal cortex to the midbrain up to the amygdale, nucleus accumbens, and other areas such as the hypothalamus and hippocampus. To enhance physiological activity in the prefrontal cortex, dopamine function attempts an up-regulation of post-synaptic receptors, and increased dopamine turnover, such as homovanillic acid concentration and chronic caused as a result of enhanced dopamine (Weinberger 1987).

Oxygen supply can limit the synthesis of a few neurotransmitters in the brain. Under limited oxygen supply, catecholamine and serotonin synthesis get restricted, and "transmission failure" occurs because of decreased biosynthesis of neurotransmitters under hypoxic conditions (Feinsilver, Wong et al. 1987).

Molecular oxygen is needed by rate-limiting enzymes for the synthesis of many neurotransmitters and their activity. Hypoxia impacts neuronal functions by adversely influencing neurotransmitter synthesis. Biogenic amines, amino acids, acetylcholine, and bio-active peptides, together with gas transmitter synthesis, are impacted by hypoxia (Kumar 2011).

This study has some limitations that must be considered. The author's humanities background as a self-analysis (introspecting) reporting psychologist may be limiting in his descriptions of biological concepts. References may be less recent because they come from their original sources. Introspection can be biassed, even with care. Additionally, this method is unrepeatable.

15 III. CONCLUSION

Disturbed nasal cycle rhythms may be considered reasons behind the onset of schizophrenia. A chronically chocked right nostril creates hypoxia in the ipsilateral right hemisphere, causing neurodegeneration in the right PFC, making it hypofrontal. As a compensatory mechanism, the left brain attempts hyper-activation, producing neurotransmitter dysregulation. Hence, cerebral hemispheric lateralization and ANS functioning get disordered, leading to abnormal behaviour. In schizophrenia, right-hemisphere functioning is disordered (David and Cutting 1990). Kucharska-Pietura (2006) stated that there is a functional deficiency and inadequacy or an anatomical abnormality of subtle brain impairment in the right cerebral cortex in schizophrenia. dopamine hyperactivity, develops. Hallucinations, delusions, and other positive symptoms are

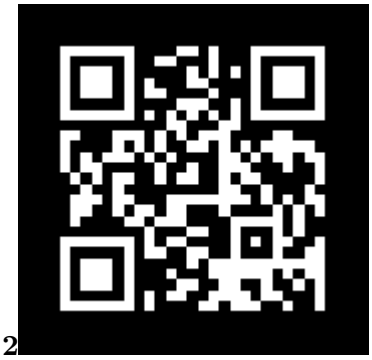

Figure 1: 2 ©

4

Figure 2: 4 ©

asymmetrical blood flow. A rhythmic shift of nasal dominance delivers engorgement of nasal mucosa for 25-200 minutes in each nostril (Schiff and Rump 1995). Vasoconstriction (and decongestion) in one nasal passage is connected to unilateral sympathetic dominance, while simultaneous vasodilation (and congestion) in another is connected to parasympathetic dominance. In this way, the ANS is connected to the nasal cycle, and ANS asymmetry is due to nasal asymmetry. The nose and hypothalamus are linked through autonomic nerve fibres, and nasal airflow affects brain activity. Rhythmic nasal cycles are produced by hypothalamic regulation. Brain stem oscillators, collections of sympathetic neurons, function as central regulators of sympathetic tone.

Differential nasal congestion influences the half-sided response to the lungs. The dominant nostril involves the homolateral lung to generate sympathetic tone (Shannahoff-Khalsa 1991). Alternating congestion and decongestion of the nostrils is called the nasal cycle (Shannahoff-Khalsa, Boyle et al. 1991). The concept of "nasal cycle" referred to the interchanges in nostril breathing efficiency. Erectile tissue causes transient blockage in the nasal passage, producing an asymmetry of higher airflow in one nostril over the other, with the mechanism of physical blockage in the air by asymmetrically increased tissue. The anterior nasal septum with the inferior turbine of the nostril achieves engorgement of erectile tissue alternatively

Figure 3: worked extensively on the nasal cycle study. The nasal cycle is the most important rhythmic lateralization of the ANS.

The sympathetic nervous system (SNS) has a

correlation with cerebral hemispheric action and nasal airflow. The brain-stem area reticular formation involved in arousal and consciousness enhances arousal by air insufflations. The sensation of nasal airflow entering the trigeminal nerve stimulates the nasal mucosa's intense cold receptors. Nasal airflow stimulation increases arousal, activates reticular formation, and improves cognitive performance. Unilateral nasal airflow stimulation generates contralateral and ipsilateral effects on the hemispheres, with greater effects on the contralateral side. Lower cortical stimulation (with nasal airflow) is effective in the ipsilateral hemisphere (Price and Eccles 2016).
The dominant nostril leads to the arousal of the contralateral brain hemisphere through relative nostril effectiveness (Schiff and Rump 1995). The cerebral hemisphere gets vasoconstricted because of ipsilateral vasoconstriction in the nasal vessels (with unilateral forced nostril breathing), inducing ipsilaterally diminished cerebral blood flow with a contralateral increase. This enhances blood flow contralaterally and improves cognitive performance. Nasal airflow stimulation creates arousal of the cerebral cortex using the medium of reticular formation (Price and Eccles 2016).
The dominant nostril with the contralateral hemisphere has increased blood flow due to cerebral parasympathetic dominance. The ipsilateral hemisphere has decreased blood flow due to cerebral sympathetic activity. Increased sympathetic activity reduces cerebral circulation. The hemisphere contralateral to the dominant nostril has increased mental activity and metabolic rates. Due to dilated cortical arteries and increased parasympathetic tone, cognitive performance efficiency is increased in the contralateral cerebral hemisphere of the

dominant (greater airflow) nostril (Shannahoff-

Khalsa, Boyle et al., 1991; Shannahoff-Khalsa,

Kennedy et al., 1996; Shannahoff-Khalsa, Shannahoff-Khalsa 2007). Vasoconstriction and decongestion of the nostril are caused by unilateral sympathetic dominance, concurrent vasodilation and congestion of the opposite nostril are caused by parasympathetic

dominance.

2.5 Basic Rest and Activity Cycle
Each hemisphere functions independently. The ANS regulates cognition. Cerebral and ultradia rhythms (nasal cycle) are tightly coupled and controlled by the ANS (Shannahoff-Khalsa, Boy et al. 1991). Werntz, Bickford, et al. (1983) supported the idea that the ultradian rhythms the nasal cycle are tightly coupled to the alternating lateralization of cerebral activity.

lateral

hemisphere aroused generates unilateral

cerebral, and functional states. The paired Central Nervous System (CNS)-ANS is asymmetrically organised in a lateralized body, possessing asymmetrical activity in the form of rhythmic lateralization to complement each other's functions indepen-

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