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Review Article

SCHIZOPHRENIA: A REVIEW

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ABSTRACT

Schizophrenia continues to be a mysterious disease fascinating the minds of psychiatrists, pharmacologists and neuroscientists all over the world for more than a century. The crucial welfare of the millions afflicted with schizophrenia is at stake. The cause of schizophrenia is not yet identified. However, it appears from the available reports that schizophrenia results from genetic, occupational and environmental risk factors, which act independently or combine synergistically to develop schizophrenia. In any case, schizophrenia should not be confined to split personality or multiple personality- disorder. Typically, a schizophrenic patient shows both, positive symptoms such as delusions, hallucinations or cognitive dysfunction and negative symptoms such as social withdrawal, inability to articulate or loss of emotional tone. Some psycho-active drugs such as Cocaine, Heroin, LSD, Prozac, and Ketamine produce positive symptoms of schizophrenia. Brain regions affected in schizophrenia are amygdala, ventral striatum, frontal cortex, temporal cortex, hippocampus and thalamus. The levels of neurotransmitters such as dopamine, glutamate, GABA, acetylcholine, serotonin and nor-epinephrine are significantly altered in schizophrenia. The enigma of schizophrenia has fascinated neuroscientists all over the world to develop parallel animal models in an attempt to discover new medicines for the effective management of this psychiatric disorder.

KEY WORDS: Schizophrenia, Psycho-active, Positive symptoms, Ketamine

INTRODUCTION

Schizophrenia continues to be a mysterious disease, fascinating the minds of psychiatrists, pharmacologists and neuroscientists all over the world for more than a century. The crucial welfare of the millions afflicted with schizophrenia is at stake. In 1851, it was first described as 'Folie Circulaire' or cyclical madness, and some twenty years later, it was referred to as 'Hebephrenia', or a silly, in-disciplined mind after, goddess of youth and frivolity (1871). Soon after, in 1874, it was considered both catatonic and paranoid disorders of the mind, the term catatonia describing a movement disorder characterized by a mannequin-like muscle stiffness associated with unusual postures and a pervading fear. Then in 1878, these various disorders were combined into a single disease entity, which were termed as ***dementia praecox***, or 'dementia of early onset' reflecting a decline of cognitive processes[1] marked by slow social decline concomitant with apathy and social withdrawal; *paranoid*, with its attendant fear and 'persecutory' delusions; *hebephrenic* and catatonic, characterized by a poverty of movement and expression. The inevitable inexactitudes of this emerging science continued with the dawn of the 20th Century, when in 1908 Eugen Bleuler criticized the use of the term *dementia praecox,* arguing for an absence of evidence supporting a global dementing process. It was Bleuler, who first coined the term '*schizophrenia*' in 1911. Bleuler defined schizophrenia with his four "A's", referring to the blunted *A*ffect (diminished emotional response to stimuli); loosening of *A*ssociations (by which he meant a disordered pattern of thought, inferring a cognitive deficit), *A*mbivalence (an apparent inability to make decisions, again suggesting a deficit of the integration and processing of incident and retrieved information) and *A*utism (a loss of awareness of external events, and a preoccupation with the self and one's own thoughts).[1, 2]

THE OPERATIONAL DEFINITION OF SCHIZOPHRENIA

Kurt Schneider listed his 'first rank' features of schizophrenia in 1959, which served as the inspiration for the two guides used in the operational diagnosis of schizophrenia, the ICD-10 and the Diagnostic and Statistical Manual of mental disorders (DSM). The DSM (IV) states that two or more of the following (symptoms), each present for a significant portion of time during one month period (only one symptom being required if delusions are bizarre or 'auditory' hallucinations are present).[3] A diagnosis of schizophrenia may be made if continuing signs of a disturbance have been present for at least six months, concordant with a social and occupational dysfunction for a significant period of time and the actions of substance abuse have first been ruled out.

Table 1: Symptoms of Schizophrenia

Positive symptoms	Negative symptoms
• *Psychotic episode* (displacement from reality, inability to separate real and unreal experiences) inclusive of	• Social and occupational dysfunction
• *Delusions* (false beliefs/judgment)	• Lack of motivation, loss of concentration
• *Hallucinations* (strong subjective perceptions of an object, voice or event, which is non-existent that may affect any or all sensory perceptions)	• Social withdrawal
• Cognitive dysfunction *(disorganized speech/ behavior/ thought)*	• Blunted, apathetic or flat affect (loss of emotional tone or reaction)
	• Inability to articulate

It may be instructive to derive the core features inferred from this operational definition of schizophrenia. Extreme distortions of sensory processing are apparent, with attendant difficulties in screening out various unwanted sensory stimuli or ideations (leading to delusions or hallucinations) which is suggestive of a decreased capacity to filter and process information. The resulting disorganized thought and display of behaviors that do not meet with social expectation are often associated with the development of poor memory and a shortened attention span. The apparent decline in cognitive

processing is often reflected in disorganized speech, further suggestive of a deficit in information processing. A decrease in emotional tone and of reaction to social and other external stimuli may parallel a decline in social functioning, emphasizing the importance of the integrity of higher cortical circuits in mediating receptive, productive and appropriate social interaction, or 'successful' human social 'behavior'. This reductionism and generalization leading to the definition of 'schizophrenia' as one or more related disorders resulting in a disruption of cortical processing and filtering, permits us to correlate these human behaviors with those of animal models from which the putative existence of a biochemical basis for schizophrenia might be tested.

Table 2: Subtypes of Schizophrenia

Subtype of Schizophrenia	Characteristics
Paranoid	Preoccupation with one or more delusions or frequent auditory hallucinations
Disorganized	Disorganized speech and behavior, a flat or inappropriate affect, apathy or indifferent attitude are all conspicuous
Catatonic	Two of the following must be present: Lack of motor response to a stimulus, excessive motor activity, an absence of speech, echolalia (repetitions of words and phrases, peculiar mouth movements or echopraxia (repetitions of another's motor movements)
Undifferentiated	Symptoms of schizophrenia are present but conditions for other three types are not met
Residual	Absence of prominent delusions, hallucinations, disorganized speech, and grossly disorganized and catatonic behavior despite continuing evidence of a disturbance

THE MUCH MALIGNED AND MISUNDERSTOOD SCHIZOPHRENIC

Schizophrenia does not infer, from the literal translation 'split mind', to a dissociation of personality or multiple personality disorder. Rather Bleuler intended it to refer to a split between subjective feeling, or affect, and the thought being experienced.[1] Most schizophrenics have not, contrary to widespread belief, been shown to be unusually prone to violence either normally or following substance abuse. Diagnosed schizophrenics receive discrimination in seeking employment, housing, health care and insurance. Thus, schizophrenia is a dysfunction with often severe social consequence.

Consumption of Psycho-active drugs produce Schizophrenia like features
• Crack (purified *cocaine*) and ice or crystal (pure methamphetamine) cause the positive symptoms of schizophrenia, and dysphoria upon withdrawal
• Anti-depressants and serotonin reuptake blockers, such as ecstacy, Prozac & LSD create hallucinations and false memory
• Chronic alcoholics suffer loss of gray matter, cognitive dysfunction, disorganization of thought and memory loss
• Special K, otherwise known as *ketamine*, causes a schizophrenia-like psychosis in healthy individuals and exacerbates the psychotic symptoms in schizophrenic patients, decreasing sensitivity to environmental stimuli
• PCP, or *phencyclidine* otherwise known as 'Angel Dust', causes both the positive and negative symptoms of schizophrenia conditions, which produce Schizophrenia like Symptoms
• Schizophrenia-like psychosis of epilepsy (SLPE), resulting from temporal lobe epilepsy of the left (dominant) superior temporal gyrus, have similar symptoms to schizophrenics, but the predominant cause is temporal rather than in the anterior cingulate or frontal lobes, as in schizophrenia
• Prior to this century, 10-30% of schizophrenia-like patients had neurosyphilis
• Post-traumatic stress disorder also produce schizophrenia-like symptoms
• Sleep deprivation impairs cognitive performance and causes activity shifts from temporal to parietal cortex on verbal learning tasks.

IN WHAT WAY ARE THE BRAINS OF SCHIZOPHRENICS DIFFERENT?

As schizophrenia is believed by many to reflect a disturbance in information processing, and specifically a failure to correlate and integrate contextually appropriate stored material (memory) as a function of sensory input, in other words an inability to effectively relate stored experience to current circumstance. Indeed 'paranoid' and 'non-paranoid' schizophrenic subjects exhibit equivalent performances in tests related to cognitive and intellectual functioning.[5] The general concept of a fundamental cognitive deficit in schizophrenia is unifying and takes into account a broad diversity of symptoms and possible causes by describing a functional consequence rather than defining a specific causality.

WHAT REGIONS OF THE BRAIN MAY BE AFFECTED IN SCHIZOPHRENIA?

Mesolimbic areas including the amygdala and ventral striatum, believed to be important in imparting emotional 'coloring' to external stimuli, have been shown to be unusually active in schizophrenia, whilst the prefrontal cortex is unusually hypoactive during hallucinations, a symptom of the so-called 'active phase of schizophrenia. In fact, these patterns of differential activity may be seen by **PET** imaging even without stimulation, suggesting a constitute state of arousal typically observed in response to threat. Brain imaging of responses to non-threatening, negative expressions such as disgust, or threatening facial expressions, such as fear or anger, suggest that a region called the amygdala specifically responds to threatening facial expressions, an area known to be important in the integration of the cognitive and emotional aspects of human behavior. The amygdala has since been shown to have an enormous influence on dopamine release, thereby emotionally and motivationally 'coloring' a wide range of behaviors. It is suspected by some that the amygdala plays a role in mediating some of the symptoms of schizophrenia. There is agreement that an area known as the associative frontal (including left dorso-lateral pre-frontal) cortex has both, reduced blood flow and metabolic activity in 'never-been' medicated schizophrenics, as do the unfolding (gyri) of the parietal and temporal cortex, all association areas essential in governing the high level cognitive functions implicit in social interaction and language. Further the prefrontal cortex has been shown to be an area consistently associated with the altered cognitive activity and attentional deficits in schizophrenics, consistent with an area involved in mediating transient working memory and processing information involved in thought, which is impoverished or disorganized in schizophrenics. However, the thalamic and cingulate cortical areas are hyperactive in schizophrenics, regions that are thought to be important in perception and communication. The hippocampus serves as a thoroughfare for information arriving from sensory areas en route to higher cortical areas

for further association and encoding, a seeming crucial junction box both in information processing and learning. In particular the hippocampus has been implicated as central in the formation of memory and learned behaviors, and in particular spatial memory for places and resources. Rats with lesions introduced into their ventral hippocampus showed less time spent in interaction and an enhanced aggression, which was not attributable to anxiety. This effect however occurred only in young rats and not in those lesioned after weaning, indicating that damage to cortical integrative circuits sustained before or during the period of learned social behaviors can result in schizophrenic social withdrawal. Furthermore lesioning of the hippocampus, which processes auditory information, results in a loss of filtering of auditory information presented in the form of paired clicks, as the electrical signal produced by the second click was not substantially attenuated in the lesioned animals. As with the **PPI** test, this suggests that filtering of auditory information is deficient, and may occur at the level of the hippocampus, which mediates, at least in part, the selective filtering of sensory information. The brain functions, as do its individual units of information processing (neurons), as difference detectors, comparing two inputs, for example sensory input with stored memory, and subtracting the current (sensory) input from the past (stored) experience (which may for example be a recent or evoked memory), and projecting the difference in the form of a (non-linear) output. If there is no difference between a present stimulus and a past stimulus then the pattern may be said to be 'expected' and that there is relatively little that is new to report and thus little information processing capacity is devoted (energy) within higher cortical centers (attention) as the information may not be projected as extensively to higher centers for processing. By this means, only changes in environment 'perceived as significant' are passed forward and unwanted background information is filtered out, although in schizophrenia, **it is this filtering that is apparently impaired**. It was postulated that the diverse symptoms of schizophrenia the cortical-thalamic-cerebellar-cortical (CCTCC) circuit, which is critical in the synchronous firing of neuronal centers involved in the smooth co-ordination of mental processes. It was proposed when the synchrony of the CCTCC circuit is impaired the patient suffers from cognitive dysmetria, are due to a single disorder involving the misconnection of neural circuitry within and it is this impairment of basic cognitive processes which defines the hallmark of schizophrenia. Hence many different disruptions of this circuit may produce a common phenotype, just as many different ways in which cells may fail to regulate their growth and survival might result in a cancer. It has argued that there is connectivity between nodes (or clusters of neurons involved in processing) in the pre-frontal cortex, the thalamic nuclei and the cerebellum. Any fundamental disruption in the CCTCC circuit may result in a cognitive impairment or dysmetria, associated with a difficulty in prioritizing, processing, co-ordinating, and responding to sensory information. This, as has been long since demonstrated for the visual system, shows that the brain is not comprised of a series of clearly defined and discrete functional centers ascribed to specific functions such as memory or logical thought, but rather is comprised of diffuse aggregates of functionally associated neuronal clusters, or nuclei, which distribute and dynamically process information in parallel. Thus damage to the delicate microelectronic circuitry of the brain can readily disrupt the highest level brain functions such as language, intelligence and social behavior. Difficulties in isolating a cognitive deficit to any one receptor or part of a circuit is difficult, as function is thus devolved, and all neurons are ultimately interconnected. Further, any given neuron may express upon its receiving surface receptors for as many as six or more different neurotransmitters. From these basic observations there is an implicit divergence of information flow, and the consequences of disrupting signaling via any one type of neurotransmitter has widespread consequences for information processing across and between many circuits.

A plethora of theories have arisen to explain the deficits associated with schizophrenia including specific or 'global' changes in neurotransmission involving significant changes in the levels of a given neurotransmitter (such as dopamine, glutamate, GABA, Ach, 5-HT or NE,) cell type or receptor, and a host of changes in brain function elicited by agents as diverse as stress, developmental aberrations and viral infection. The four 'S" namely Stress, Steroids, Solitude and Sensory deprivation have all been held culprits for developing Schizophrenia.

POPULAR THEORIES OF **SCHIZOPHRENIA**
• Miswiring of the brain during development
• An inherited disorder exacerbated by stress and hormonal changes
• A viral infection
• Perinatal hypoxia
• Auto-immune damage
• A neurodegenerative disorder (such as Alzheimer, Parkinson's)
• Genetic predisposition interacting with an overload of dietary proteins
• The neurotoxic effects due to excessive nerve transmission
• Social stressors in urban settings
• Depletion of certain fatty acids in cell membranes
• Dietary Exorphins from milk

SCHIZOPHRENIA: A CONTEMPORARY EPIDEMIC?

Schizophrenia is a disabling condition with an age of onset, which is earlier for men (15-25 yrs.) than for women (25-35yrs), with a lifetime prevalence of 1.3% within the U.S. population. About half of all schizophrenics will attempt suicide at least once, 10-15% of whom will be successful. Schizophrenia has an attributed, estimated annual direct and indirect cost to U.S. economy of $30-48 billion, and there are related costs due to the high prevalence of substance abuse and cigarette smoking amongst schizophrenics. More intriguing and indicative for the possible role of environmental factors in the etiology of schizophrenia, is the epidemiology of the disease. Specifically the question is whether the incidence of schizophrenia is rising (or falling) as a consequence of changes in lifestyle and work practices? Surprisingly there is little evidence available in the literature to reveal any such patterns.

WHO CONSTITUTE HIGH-RISK GROUPS FOR SCHIZOPHRENIA?

Low socio-economic status has NOT consistently been shown to be a risk factor for schizophrenia although this remains contentious. Several high risk groups have been identified however, in addition to late adolescent males, especially blacks and women during menopause, childbirth and pregnancy. Against a background prevalence of 1.3% for the general U.S. population (and approximately 1% in the U.K.), a recent follow-up study of mental health amongst non-German speaking immigrants indicated that 38.7% were schizophrenic, whilst only 8.3% were diagnosed as impaired at the time of entry, although this was admittedly seen as an

over estimate due to language difficulties. Studies amongst the homeless in Germany have indicated that schizophrenia is significantly over-represented amongst both women and men.[6] Intriguingly, whilst the rates for effective psychoses were low among men in Greenland, a possible model for 'social' isolation in comparison to the Danish mainland, rates for schizophrenia and suicide were found to be very high.

CONCLUSION

Schizophrenia is a serious brain disorder showing neuro-anatomical and neuro-physiological abnormalities. Typically, a schizophrenic patient shows both, positive symptoms such as delusions, hallucinations or cognitive dysfunction and negative symptoms such as social withdrawal, inability to articulate or loss of emotional tone. The cause of schizophrenia is not yet identified. However, it appears from the available reports that schizophrenia results from genetic, occupational and environmental risk factors, which act independently or combine synergistically to develop schizophrenia. Non-genetic causes of schizophrenia can be attributed to obstetric complications, stress, steroids, solitude, sensory deprivation, viral infection during pregnancy and substance abuse. In any case, schizophrenia should not be confined to split personality or multiple personality-disorder. Brain regions affected in schizophrenia are amygdala, ventral striatum, frontal cortex, temporal cortex, hippocampus and thalamus. The levels of neurotransmitters such as dopamine, glutamate, GABA, acetylcholine, serotonin and norepinephrine are significantly altered in schizophrenia. The enigma of schizophrenia has fascinated neuroscientists all over the world to develop parallel animal models in an attempt to discover new medicines for the effective management of this psychiatric disorder.

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