



# *SCHIZOPHRENIA*

Understanding the Madness

## ABSTRACT

Schizophrenia remains one of the most common mental disorders affecting the world. Over the course of the last 50 years, the treatment of this disorder has advanced to the point of allowing a normal lifestyle. However, the stigmas surrounding schizophrenia have persisted despite these advances, often producing an unfair treatment of those affected with mental illness. The only effective way to combat these stigmas is to educate the population on the details of schizophrenia so that we can make educated decisions regarding the ways in which we interact with those suffering from mental illness. An instructional video that covers the basics of this research is available at <https://www.youtube.com/watch?v=LZ0dsSe9Hn4>.

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## ABSTRACT

Schizophrenia is a neurological disorder characterized by hallucinations in addition to generalized loss of normal mental function. The symptoms of schizophrenia can present as barely noticeable to completely debilitating in nature. Research into the causative mechanisms of schizophrenia has made some headway in establishing distinct relationships between both genetic and environmental factors and pathogenesis. However, much of what leads to the development of schizophrenia is still unknown. The lack of scientific knowledge is compounded by a general ignorance amongst the general public in regards to the condition itself, symptoms associated with it, causative mechanisms of those symptoms, the treatments available for these symptoms, and the general lifestyle of those affected. This lack of understanding often produces a negative disposition towards those suffering from schizophrenia that leads to a diminished level of treatment toward those suffering from it, including during employment, healthcare, and general social interaction. These biases produce additional psychological stress on schizophrenics and can often lead to exacerbation of current symptoms. Effective education on schizophrenia itself, including symptoms, treatments, and a brief overview of mechanisms of causation, in addition to the social biases that surround it provides the foundation of allowing for educated, non-biased interactions with those suffering from schizophrenia.

## INTRODUCTION

Schizophrenia remains one of the most recognizable neurological disorders in today's society, in part due to the stigma that surrounds it. That stigma, propagated in large part due to the mass exposure in media, leads to a great misunderstanding of the underlying mechanisms of schizophrenia in addition to the actual prognosis of those suffering from schizophrenia. The resulting public attitude towards those afflicted with mental illnesses and schizophrenia in particular comes to fruition as an avoidance or approach with fear, due in part to acts of violence perpetrated by those who suffer from these illnesses. However, applying judgment toward an entire community of people based on the actions of a select few people fosters an unwarranted intolerance and phobia of that group, especially given the current advances in both the pharmacological and behavioral treatments available to mental health patients. The growth in the public awareness and understanding of mental illnesses and the treatments for them would provide the foundation for an improved level of interactions between the general public and those afflicted with mental illnesses.

## GENERAL OVERVIEW OF SCHIZOPHRENIA

According to the National Institute of Mental Health, schizophrenia describes a chronic mental condition that results in an altered perception of reality that usually begins in between the ages of 16 and 30, although symptoms can present at any age. In the United

States alone, more than 200,000 cases of schizophrenia are reported every year, making it a very common disorder<sup>1</sup>. Schizophrenia is subcategorized based on the duration and severity of the symptoms experienced. Among these subcategories are paranoid, where the afflicted person experiences severe delusions or hallucinations, hebephrenic, which involves a loss of personal goals or other significant thought disorder, catatonic, which involves prolonged stupor, and simple, which involves any generalized decline in mental and social performance<sup>2</sup>.

Scientists and health professionals divide the symptoms of schizophrenia into three broad categories based on the tendencies of those unaffected with the disorder. "Positive" symptoms represent the symptoms which are additions to the normal functions of the brain. Examples of positive symptoms include hallucinations, delusions, or other abnormalities that often result with a distorted perception of reality. The hallucinations sometimes come to fruition due to mental voices being perceived as real by those affected. Often, the voices insult, belittle, or otherwise frustrate the individual. A delusion on the other hand describes a specific idea or belief of the individual that normally would be considered completely unrealistic or impossible. Often, the person holds this belief to the point that disagreement with this idea breeds frustration or anger and can affect the way in which that individual may act. One of the more frequent delusions of schizophrenics is that someone or something is watching or stalking them, leading to a dramatic general paranoia<sup>1, 3</sup>.

In contrast to the mental additions described by positive symptoms, negative symptoms describe a loss or lack of function resulting from schizophrenia. The most common negative symptoms of schizophrenia include social abnormalities in addition to problems with communication. For example, many schizophrenics find themselves unable to carry a conversation due to a lack of expression and an apparent lack of interest. This often results in a feeling of anxiousness or depression in those suffering from schizophrenia because although they are unable to portray feelings or emotions, they remain capable of the emotions and feelings that would be expected in a normal mind<sup>4</sup>.

The third type of symptoms that plague schizophrenics are cognitive symptoms. Unlike positive and negative symptoms which are characterized by a marked gain or loss of function, cognitive symptoms take the form of abnormalities in other areas of brain function, such as affecting memory, attention, and poor problem solving. All of these examples contribute to a hindrance in regards to employment. This trouble brings a great amount of distress to those suffering from schizophrenia and unfortunately, cognitive symptoms are often the most difficult to recognize and treat<sup>1</sup>.

## CAUSATIVE MECHANISMS AND RISK FACTORS

The fact that schizophrenic disorders have some hereditary mechanism of development or risk has long been established within the scientific community, primarily

using studies that feature twins. These studies show a pattern of inheritance of schizophrenia amongst twins, both monozygotic and dizygotic, as well as the heritability estimate of schizophrenia in twins. These studies must then be reconciled with studies focusing on adoption and environmental aspects to generate a clear correlation between factors and the emergence of schizophrenia<sup>5</sup>. Despite the success of twin studies in establishing a genetic aspect of the emergence of this disorder, the specific causative mechanisms that lead to schizophrenia remain the subject of much debate, despite it being one of the most common mental disorders in the world and thus one of the more well studied. As with most mental disorders, a great deal of focus lies in specific genetic factors or genes that can give rise to schizophrenia. However, this research has only found limited success as no singular gene or gene group has been isolated and determined to be the sole cause of the development of schizophrenia. Rather, numerous “emergence genes”, in addition to other psychological factors, specifically the neurotransmitters glutamate and dopamine, have been linked to the development of schizophrenia<sup>6</sup>.

A vast number of genes have been thought to play a role in the pathogenesis of schizophrenia. Despite modern studies, no gene has been isolated as the main causative factor behind pathogenesis. However, numerous genes have been shown to be candidate genes for causation and none have been linked with assurance to schizophrenia. This paper will highlight three of the better understood of these genes. The first is a gene that codes for a growth factor that acts on ErbB family receptor tyrosine kinases (RTKs) called neuregulin-1 (NRG1). Although the exact mechanism of causation remains unclear, examinations of brain tissue from deceased schizophrenia patients shows a substantially altered NRG1 expression, either hyperactive or hypoactive. In mice studies, disruption of NRG1 expression produces glutamatergic disruption in the hippocampus, which is associated with memory in humans, and amygdala, associated with memory and emotions. In addition, in mutant mice deficient in NRG1 production, a general hypoactivity was noted in addition to a substantial decrease in fear conditioned learning. Also of note was that hyperactive NRG1 expression resulted in an increase in inhibitory neurotransmission and a disruption of hippocampal synaptic plasticity, or the ability for synapses to grow stronger or weaker over time, which is extremely important in learning and memory<sup>7</sup>.

The second major gene associated with schizophrenia pathogenesis, DTNBP1, is located on the sixth chromosome in humans and codes for dysbindin, a protein that is necessary for the formation of dendritic spines and, thus, proper neural communication in the brain. These dendrites play a crucial role in ensuring that connections between neurons are fully functional and effective. Research has shown that these connections between neurons are severely hindered in patients with schizophrenia. Specifically, the number of dendritic spines formed by those suffering with schizophrenia is significantly lower, leading to impaired mental function. These subjects have markedly low levels of both dysbindin RNA and functional protein, leading researchers to believe that this gene plays a crucial role in the development of schizophrenia. Also of interest is a significantly

increased amount of D2 dopaminergic receptors in mice that fail to express DTNBP1. These D2 receptors are frequently targeted in the treatment of schizophrenia<sup>8</sup>.

A recent article published in January 2016 has proposed a new gene that could possibly play a crucial role in the altered mental function characteristic of schizophrenia. Complement component 4 (C4), also located on chromosome 6, codes for a protein that is thought to localize in synapses, dendrites, and axons and play a crucial role in overall synapse function. C4 protein was found to mediate the termination of synapses in mice. In individuals suffering from schizophrenia, the expression of C4 protein was measured to be, on average, 1.4 times higher than normal individuals. This correlation serves to explain a dramatic decrease in the number of functioning synapses in individuals suffering from schizophrenia vs. unaffected individuals, although more research into this correlation is necessary before establishing distinct causation<sup>9</sup>.

Neurotransmitters also play a crucial role in overall brain function by the activation of receptors specific to each neurotransmitter. This activation causes either an excitatory or inhibitory response and is heavily regulated in the brain. Dopaminergic receptor antagonists have been shown to cause a state of catalepsy, or a trance or seizure accompanied by a loss of sensation or consciousness and a disruption of normal musculoskeletal movements. This finding led to the notion that dopamine could play a crucial role in a number of neurological disorders. Dopamine lies at the foundation of the discussion of neurotransmitter causation of schizophrenia. Dopamine belongs to the catecholamine family of neurotransmitters, along with norepinephrine and epinephrine (adrenaline), and can be either inhibitory or excitatory in nature, depending on the type of receptors are present at the target site. Dopamine can be found in numerous brain regions, such as the substantia nigra (motor function), ventral tegmental area (reward system), and arcuate nucleus (inhibits prolactin release). Most noteworthy in regards to pathogenesis of mental illness, dopamine performs the essential function of coordinating our body movements by interacting with dopaminergic receptors, which are G-protein coupled receptors (GPCRs). These GPCRs act by either inhibiting or activating an enzyme called adenylate cyclase, which catalyzes the conversion of adenosine triphosphate (ATP) to 3', 5'-cyclic AMP (cAMP). This conversion or lack thereof alters protein kinases downstream, altering phosphorylation events of a number of targets. Besides movement, scientists also attribute some mechanisms of drug dependency, motivation, and reinforcement to dopamine signaling<sup>10</sup>.

Initial research into the role of dopamine in schizophrenia pathogenesis suggested that hyperactive transmission, either by increased release of dopamine, increased receptor activation, or an inefficiency in dopamine reuptake would produce the symptoms characteristic of those suffering from schizophrenia. However, this assumption was made when psychiatry as a whole was in its infant stages. As our understanding of both schizophrenia and the brain advanced, research has expanded this approach to examine the roles of each type of dopamine receptor and how these receptors play a role in causing positive, negative, and cognitive symptoms of schizophrenia. Positive symptoms, which

include hallucinations, were shown to involve an excess release of dopamine in the subcortical areas of the brain, specifically the hippocampus (associated with memories) and amygdala (associated with memories and emotions), leading to over-activation of D<sub>2</sub> receptors. However, negative symptoms were linked to a decrease in activation of D<sub>1</sub> receptors of the prefrontal cortex<sup>11</sup>. Recent research has refined the original dopamine hypothesis even further. By examining the roles of different dopaminergic receptors in different areas of the brain, researchers have been able to isolate differing levels of dopamine in different areas of the brain between subjects suffering from schizophrenia and control subjects. Dysregulation of dopaminergic transmission in the prefrontal cortex, which plays a crucial role in personality and the higher order functioning, the cingulate cortex, which is a part of the limbic system and plays a part in the formation of emotions, or the hippocampus, which is involved in memory development, can all give rise to the symptoms characteristic of schizophrenia. In addition to these findings, serotonin, glutamate, and  $\gamma$ -aminobutyric acid (GABA) have been shown to play a crucial role in regulating dopaminergic transmission via feedback mechanisms and thus, also play a role in schizophrenia pathogenesis<sup>12</sup>.

While biological factors play a key role in the development of psychosis in patients suffering from schizophrenia, the environmental conditions under which these factors are expressed are often required to supplement the pathogenesis of schizophrenia. This finding is supported by the fact that identical twins of schizophrenics have a greater than 50% chance of having normal mental function. Such a finding supports the role of environmental factors aiding in pathogenesis. These environmental factors combine with the aforementioned emergence genes to create many of the symptoms characteristic of schizophrenia. Causative environmental factors can be found both prenatally, during infancy, during childhood, and later in life, and are various in both occurrence and mechanism<sup>13</sup>.

Early studies in neurodevelopment postulated that schizophrenia may be a neurodevelopmental disorder, originating from prenatal conditions that lead to psychosis. Specifically, neurological damage incurred during prenatal development or during early infancy has been linked to an increase in development of schizophrenia in addition to other psychoses. Some conditions that can lead to increased risk of psychosis development are blunt head trauma, infection, and abuse of alcohol. Other developmental conditions have also been implicated. Schizophrenia in men tends to come to fruition ten years earlier than in women, and more schizophrenics are born in winter months than other times of the year. In addition, schizophrenics are more likely to be left handed. The exact mechanisms behind these observances are currently unknown. Researchers postulate that the proper development and termination of neuronal synapses lies at the heart of these findings, with each individual circumstance posing its own unique threat to neurodevelopment. However, no direct correlations have been proven<sup>14</sup>.

Other health factors have been isolated that could also play a role in schizophrenia development. The bulk of these factors again highlight early development, although they

are often non-infectious or traumatic in nature. Examples include maternal diabetes, improper prenatal nourishment, stressful pregnancy, and tobacco use. Generally, the consensus is that mothers who suffer a stressful pregnancy are more likely to give birth to a child that will suffer from a psychotic disorder. In one study, it was shown that when the father died during the pregnancy, the chance of developing schizophrenia in the child climbed six fold. In addition, the risk in children who suffer from malnourishment during childhood or are victims of abuse is substantially higher. Later in life, head injury, drug abuse, and social setting have all been tentatively linked to pathogenesis. However, despite these noted trends, specific mechanisms are still poorly understood<sup>13</sup>.

## TREATMENTS

The treatment of schizophrenia constitutes a broad spectrum of medication, psychosocial treatment, and educational services. Medication remains the initial course of treatment, to decrease symptoms as much as possible before attempting to provide psychosocial treatment in order to mediate the social symptoms often associated with the illness. These drugs are generally categorized into two groups, first generation or “typical” antipsychotics and second generation, “atypical” antipsychotics, which are more modern. More common first generation antipsychotics include Chlorpromazine, Haloperidol, Perphenazine, Fluphenazine, Loxapine, and Droperidol<sup>15</sup>. Among these and most other antipsychotics, Chlorpromazine remains the benchmark for performance. Chlorpromazine was the first antipsychotic, and remains a vastly important medication in the treatment of psychoses. Chlorpromazine, in addition to the overwhelming majority of all other antipsychotics, act as D<sub>2</sub> antagonists, due to the prevalence of the dopamine hypothesis mentioned earlier<sup>16</sup>.

While first generation antipsychotics, particularly Chlorpromazine, have long been used for the treatment of not only schizophrenia but a wide assortment of other psychoses, the advent of modern pharmacology has produced a new wave of second generation drugs that have quickly replaced some of their older progenitors. The reason behind this transition is that first generation antipsychotic drugs tend to have more adverse side effects, due to their lack of selectivity in the D<sub>2</sub> receptors upon which they act. Second generation antipsychotics, which include Clozapine and Risperidone, have a dramatically decreased level of adverse side effects. This decrease is the result of an alternate mechanism of action. Atypical antipsychotics bind with a greater affinity to dopamine rather than the dopamine receptor. Also, in comparison with first generation antipsychotics, second generation medications dissociate much more rapidly than their ancestors, resulting in a much greater quality of life for those being treated for schizophrenia<sup>17</sup>.

Although in many mental illnesses medication is sufficient in controlling symptoms, those suffering with schizophrenia often receive treatment beyond the front line treatment in medication in the form of psychotherapy. The goal of psychotherapy is to aid those suffering from a mental disorder in understanding their illness, the challenges associated,

and ways in which they can combat the symptoms and live a normal life. One major technique in psychotherapy is cognitive behavioral therapy, or CBT. Often times CBT is used as the primary method of treatment in psychoses. However, in schizophrenics, it must be used as an add-on to initial medication. This therapy arms schizophrenics with various coping mechanisms with which they handle their symptoms, specifically auditory and visual hallucinations. They also learn what circumstances tend to trigger symptoms and general ways to reduce the stress associated with everyday challenges and problems. Dialectical behavior therapy, a subcategory of CBT, is also used to establish normal reasoning in those suffering from psychosis. In DBT, two opposing extreme views are presented by the therapist, who proceeds to help the patient establish a “middle ground”. This viewpoint helps to establish a tendency of moderation that often aids in problem solving and temperament. Interpersonal therapy (IPT) is a much more personal type of counseling that aims to treat depression but can also aid in other psychoses. This is a one-on-one therapy that helps to provide an outlet for emotions that a person may be feeling, aid in analysis of these emotions, and develop ways in which to cope with these emotions in a healthy and productive manner. In schizophrenics, these therapies must be combined with initial pharmacological treatment to aid in treatment<sup>18</sup>.

## LIFESTYLE TENDENCIES

While the mental health of schizophrenics obviously poses some concern, their physical health is also noteworthy. In fact, when compared to those without schizophrenia, schizophrenics die significantly earlier, often times greater than ten years<sup>19</sup>. The reasons behind this pronounced difference are various in nature. However, modern research has highlighted numerous lifestyle tendencies among schizophrenics that could play into the increased mortality rate among them. Generally, dietary tendencies among schizophrenics tend to be less healthy than recommended, with less fruit and vegetable consumption of particular prevalence. Physical activity among schizophrenics is often limited, partially due to the nature of some antipsychotics. The combination of dietary and exercise tendencies produce an increased rate of obesity in schizophrenics, which then leads to a myriad of other health problems, such as diabetes, hypertension, congestive heart failure, stroke, and respiratory problems. Perhaps the most pronounced lifestyle tendency among schizophrenics, however, is a drastically increased prevalence of smoking. In the general populace, 30 – 40 percent of the population smokes. Among schizophrenics, that number rises to 75 percent and has been estimated to be as high as 92 percent. In addition to the general detrimental health effects associated with smoking, smoking increases the rate at which antipsychotic drugs are metabolized, resulting in the need for greater medication among smoking schizophrenics. Also, while breaking nicotine addiction poses problems to all smokers, success rates among schizophrenics tend to be even lower<sup>20</sup>.

## PUBLIC PERCEPTION

Perhaps the greatest challenge facing schizophrenics in today's society is the residual stigma that surrounds their illness. This stigma was birthed out of a generation before modern antipsychotic measures were implemented and furthered by popular portrayal of schizophrenics as dangerous, harmful, eccentric, etc. A study published in 2014 compared perceptions of schizophrenics in 2008, 2003, and 1998 while also comparing them to perceptions of depression and anxiety. When presented with negative statements, study participants were asked whether they agreed or disagreed with the statement. 63% of the people surveyed agreed that schizophrenics were a danger to others, 70% agreed they were unpredictable, and 50% agreed that they were hard to talk to. Also noteworthy is that 44% of participants stated that schizophrenics never fully recover. In contrast, only 21% felt those suffering from depression were a danger to others, and only 20% felt such about those suffering from anxiety. Only 50% felt that depression led to unpredictability, and only 43% for anxiety. Across all categories, the level of agreement with negative statements was significantly higher when asked about schizophrenia than both anxiety and depression. However, in comparison with perception in 1998 and 2003, agreement with negative statements has decreased in several categories, namely danger to others and unpredictability<sup>21</sup>.

When schizophrenics were surveyed to find if and how they experienced discrimination in their everyday lives, the results agree with what would be expected given the previously mentioned survey results. 47% of schizophrenics surveyed said they had personally experienced negative discrimination in regards to friendships, 43% from family members, 23% when attempting to gain employment, and 27% in regards to intimate relations. In addition, nearly none of those surveyed reported experiencing positive discrimination. Moreover, a vast majority (72%) were compelled to hide their medical condition due to the discrimination that they anticipated<sup>22</sup>.

While predetermined biases are present in today's society regarding the safety of schizophrenics in the general population, statistics have shown that, while schizophrenics are more likely to commit crime than the general population, the number of schizophrenics committing violent crimes poses no urgent threat to the safety of the public. The proportionality of crime in schizophrenics vs. crime in the general public is comparable. In societies that have higher crime rates, more schizophrenics commit crimes. Likewise, in societies with lower crime rates, fewer crimes are committed by those suffering from schizophrenia. Also worth noting is the fact that drug use and homelessness are very prevalent among the schizophrenic population, which could lead to an increase in violent crime. As a result, most violent schizophrenics are institutionalized or incarcerated for much of their lives<sup>23</sup>. In contrast, victimization rates of both violent and non-violent crimes were found to be significantly higher among those suffering from severe mental illness, including schizophrenia. This highlights a high prevalence of prejudice towards those suffering from mental illness<sup>24</sup>.

## CONCLUSION

The treatment of mental illness has been revolutionized over the last century with the advent of more advanced pharmacological and psychosocial treatments. Often times, those suffering from mental illness, specifically schizophrenia, are able to acclimate to society and live full and healthy lives as productive members of society. However, despite the changing landscape of psychological medicine, stigmas established well before our knowledge of psychiatry grew into what it is now are still in place. These views on schizophrenia lead to a generally misguided conception of schizophrenics as dangerous, unstable, or otherwise unable to live a normal life. This negative attitude towards schizophrenics often leads to a much more difficult and stressful livelihood for them. To combat these stigmas, the general population must be educated on schizophrenia, including the symptoms, causative mechanisms, and treatments, so that we can effectively discern how to interact with someone suffering from mental illness in a fair, encouraging, and proactive way.

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