An Exploration into the Psychotic Symptoms Associated with Schizophrenia and Major Depressive Disorder

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AN EXPLORATION INTO THE PSYCHOTIC SYMPTOMS ASSOCIATED WITH SCHIZOPHRENIA AND MAJOR DEPRESSIVE DISORDER

by

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ABSTRACT

This research focuses on examining the neurological similarities between schizophrenia and major depressive disorder with psychotic features in order to compare the manifestations of psychosis in each disorder. Both disorders often involve symptoms of psychosis, although the overall disorders are very different from each other. The hypothesis for this research is that the neurological similarities between schizophrenia and major depressive disorder with psychotic features will provide researchers with the strategies needed to develop a treatment for psychotic symptoms. In order to test this hypothesis, five related studies were gathered for each disorder, and three studies were gathered for psychosis. These studies were then analyzed to pinpoint any similarities among factors for psychosis, and this analysis allowed for the determination of whether or not the hypothesis would be rejected. The results indicated that a lot of the similarities between the two disorders cannot be verified because of the lack of substantial research.

Keywords: psychosis, schizophrenia, major depressive disorder with psychotic features

DEDICATION

To the kindhearted educators who want nothing more than to help their students succeed. And to those who struggle with psychological disorders in any form, know that you are not alone.

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INTRODUCTION

Schizophrenia and major depressive disorder with psychotic features (MDD-PF) are psychological disorders in which patients experience psychotic symptoms, also called psychosis. These symptoms include delusions, hallucinations, and in some cases incoherent speech or inappropriate behavior. Psychosis can be a scary experience, seeing as it involves what is often described as a "loss of touch" with reality. It can be difficult for a person experiencing psychosis to recognize when their experiences are not consistent with reality. If left untreated, psychosis can lead to social decline, paranoia, and neurological damage. Therefore, early treatment is important as it can lead to a better prognosis. If the possible causes for psychosis are pinpointed, this could lead to the development of a treatment for psychosis, potentially improving prognosis at all stages of development.

OBJECTIVE

The purpose of this research is to identify similarities between schizophrenia and MDD-PF. These disorders were chosen due to the fact that they are distinct enough from each other that any similarities may offer significance for potential causes. Other psychotic disorders such as schizoaffective disorder and bipolar disorder share a greater number of similarities with schizophrenia compared to MDD-PF. The vast difference between disorders is important because any factors that are shared may be directly related to psychosis, which is the most prominent feature that the disorders share. Factors that are compared include epidemiology, symptoms, treatment mechanisms, and prognosis. Any similarities between the two disorders may have significant implications for the treatment of psychotic symptoms, considering that psychosis is present in both disorders. The disorders are different enough from each other that any similarities may offer insight into potential diagnoses and treatments. It is likely that the causes for psychosis will be observable when examining the molecular backgrounds and neurological manifestations for each disorder. Psychosis is a symptom in which patients often experience a disconnection from reality (e.g., delusions or hallucinations). The causes for psychosis are not known, although there are theories that will be explored throughout this research. Because psychosis is displayed in the psychiatric disorders described, it is likely that the causes for psychosis will manifest in these disorders. Ideally, the potential causes for psychosis will be observable when the disorders are being analyzed. The hypothesis for this research is that the neurological similarities between schizophrenia and MDD-PF will provide researchers with strategies to develop a treatment for psychotic symptoms.

BACKGROUND

Psychosis is said to represent the "severe" end of schizophrenia [1], seeing as schizophrenia is often thought to encompass some of the most damaging aspects of psychosis. Schizophrenia can be described as a transient disconnection from reality. MDD-PF is a form of major depression in which psychotic symptoms are often present. While thought to not be as "severe" as schizophrenia, it can also have some damaging effects. In both cases, it is important that symptoms are managed and treatment is ongoing. With proper treatment and emotional support, patients are able to live healthy and successful lives.

SYMPTOMS, EPIDEMIOLOGY, AND DIAGNOSIS

Schizophrenia

Patients with schizophrenia experience two types of symptoms: positive and negative. Positive symptoms are perceptions that are not normally present in the general population, such as hallucinations and delusions. Negative symptoms occur when perceptions that are normally present in the general population are absent. This can include reduced emotional expression (i.e., constricted/flat affect), and reduced motivation (i.e., avolition) [11]. According to the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5), individuals must experience symptoms for a period of at least six months in order to be diagnosed with schizophrenia.

Causes for this disorder are still being researched, although there are believed to be genetic and environmental risk factors. It is, however, difficult to determine whether specific environmental factors can lead to the development of schizophrenia or if these factors simply co-occur with the disorder. For this reason, it is practical to think of environmental factors as potential risk factors rather than causes. There are three different "levels" of risks: highest-level risk,

intermediate risk, and lower-level risk [14]. The highest-level risk factors can involve having a direct relative with schizophrenia or having a parent who is an immigrant from a certain country. These factors appear to have more significance in the development of schizophrenia compared to intermediate and lower level risks. Intermediate risks can involve being born or raised in an urban area, having had a father over the age of fifty-five at the time of birth, and having minor physical abnormalities [2]. Lower-level environmental risk factors include the exposure to certain harmful agents prior to birth. For example, studies show that if a woman smokes while she is pregnant, there is an increased risk that the child will suffer from schizophrenia. This is similarly the case when a fetus is exposed to maternal stress. Interestingly, studies indicate that children born during the winter or early spring seasons experience a 10% increase in risk for developing schizophrenia [3]. Additionally, there is a strong association between maternal herpes simplex virus type 2 antibodies and development of psychotic symptoms later in life. Children who are at risk for schizophrenia may have an increased risk if exposed to influenza during the mother's first trimester of pregnancy. One important thing to note is that a lot of these factors are simply correlated with the disorder; they do not indicate direct causes.

Some potential risk factors can occur after birth, such as childhood sexual abuse and traumatic brain injury. Ongoing use of cannabis in the early adolescent years (prior to age 16) is shown to accelerate one's risk of experiencing psychosis, as this leads to increased levels of dopamine [12]. In some cases, those who are susceptible develop marijuana-induced psychosis. The regular use of marijuana during early adolescence can therefore be thought of as a potential risk factor for schizophrenia. Another factor that may increase one’s risk for developing this disorder is withdrawal from social interaction. Studies show that those who isolate themselves are

at a higher risk for developing the disorder. In order to reduce one's risk of developing schizophrenia, individuals should avoid social isolation and seek psychological intervention if initial signs begin to occur, such as behavioral changes and fragmented psychotic symptoms [13]. This is especially important if there is a family history of schizophrenia, as this is shown to be correlated with higher-level risk. It is not certain whether a person must be genetically predisposed in order to develop the disorder.

Childhood environment also plays an important role in the development of psychotic symptoms. In an Israeli study that examined childhood-rearing and its links to psychiatric disorders, researchers concluded that at-risk children who were raised in family environments were less likely to develop a psychiatric disorder compared to children who were raised in kibbutz environments. Children who have atypical interactions with their mothers also experience a greater risk for developing schizophrenia later in life. Psychotic symptoms are likely to be experienced by individuals who have grown up in unstable or abusive homes [14]. This does not indicate that childhood abuse causes psychotic symptoms, but the correlation indicates that certain environments can play a role in whether or not psychotic symptoms develop. Head injury is also a potential risk factor for psychotic symptoms. In the case of a head injury, because the brain is affected, a type of psychosis known as organic psychosis may occur. This is also true for cases of infections or illnesses that affect the brain [14].

In order to be diagnosed with schizophrenia, patients can undergo physical examinations, screenings to rule out conditions with similar symptoms, and psychiatric evaluation [7]. Individuals should also meet the diagnostic criteria listed in the Diagnostic and Statistical Manual of Mental Disorders (DSM-5).

MDD-PF

MDD, commonly called clinical depression, is a mood disorder in which patients experience constant sadness that interferes with normal functioning. MDD-PF, also known as psychotic depression, is considered a subset of MDD in which patients sometimes experience psychosis during a depressive episode. Some symptoms for the disorder include fatigue or loss of energy, social isolation, difficulty concentrating, and insomnia or hypersomnia [15]. Symptoms may differ slightly depending on the age of the patient. The epidemiology is variable, since it is not known exactly what causes psychotic depression. Biological changes in one's brain, neurochemistry, and genetics are thought to play a role. Certain symptoms for MDD-PF may be associated with neurotransmitter imbalance. Researchers believe that imbalances in dopamine and glutamate may be present in both MDD-PF and schizophrenia, although further testing is required in order to confirm this. Genetic factors play an important role in the disorder, as studies have shown that genetic offspring are more likely to suffer from MDD-PF, as opposed to adopted children with no family history of depression. Twin studies have indicated that twins have a heritability of approximately 40-50% [5]. Poor physical health and traumatic life events are associated with MDD-PF, indicating that environmental factors can play a minor role. However, based on existing research, genetics appear to have the largest influence over whether or not an individual will develop the disorder.

As mentioned previously, the use of cannabis during adolescence has been correlated with an increased risk of psychotic symptoms due to higher concentrations of dopamine being secreted. However, depression is typically associated with decreased levels of dopamine, so it is difficult to say whether cannabis use during the early teenage years can lead to the development of psychosis

in MDD-PF. Environmental factors are limited in cases of MDD-PF, mainly due to the lack of substantial research on the disorder. Psychosocial factors have been shown to play a role. One's social environment can have an effect on the development of psychosis in MDD-PF, as social isolation is generally sh own to increase risk [8]. Some other factors that can lead to the development of psychosis mirror the environmental risk factors for schizophrenia. Child abuse and maternal separation can lead to the development of psychosis in individuals who are susceptible. Demographics indicate that MDD-PF is more common in older women and in African and Caribbean migrants [8].

According to the DSM-5, patients must experience a minimum of five of the listed symptoms for a period of at least two weeks in order to be diagnosed with MDD. Because depression tends to co-occur with chronic diseases, physicians may run lab tests or do physical examinations on patients who show symptoms. For example, in the case of hypothyroidism, an underactive thyroid may cause patients to feel depressed and fatigued [16]. It is common for doctors to fail to diagnose hypothyroidism due to depressive symptoms being present, so it is important that a blood test is done in order to rule out this possibility. Physical examinations may also be conducted in order to rule out underlying physical health issues (i.e., diabetes or high blood pressure). A psychiatric evaluation may be used to diagnose the disorder.

BIOLOGICAL FACTORS

As is the case with most psychiatric disorders, there are biological factors that affect the development and manifestation of both disorders. Schizophrenia and MDD-PF are believed to be influenced by both genetics and environment, although the extent to which they are influenced by

these factors is not known. Because genetics have an influence on each disorder, it is important to examine the biological factors that are involved.

Schizophrenia

Schizophrenia may include an imbalance in certain neurotransmitters. Some of these neurotransmitters include dopamine, which is responsible for motivation and reward, and glutamate, the primary excitatory neurotransmitter [4]. Neuroimaging can provide information about how the disorders relate to differences in the brain structure and/or function and can assist researchers with understanding the neurobiology behind each disorder. This aids in the development of treatments and in diagnostic procedures. A MRI study of monozygotic twins in which one was affected by schizophrenia and one was not showed that those affected by schizophrenia have larger ventricles. This is also true of those who are unaffected carriers [4]. Studies have also shown that those who suffer from schizophrenia have smaller hippocampal volumes. Change in hippocampal structure is associated with early stress, as the hippocampus is responsible for stress regulation [4]. Additionally, reduced white and gray matter are structural characteristics for schizophrenia. Individuals with schizophrenia may also exhibit deficiencies in parts of the brain that depend on the prefrontal cortex (PFC) [4]. This explains why working memory and interference control are sometimes impaired in individuals who suffer from this disorder.

Biological risk factors can start as early as before birth, as minor physical anomalies (MPAs) are thought to play a role in developmental disorders. MPAs have been observed to have an increased prevalence in schizophrenic patients. Nutritional factors (i.e., low levels of vitamin

D) may also play a role in the development of psychosis [2]. However, these potential risk factors do warrant further research in order to determine whether they cause psychotic symptoms.

MDD-PF

MDD-PF has a heritability of approximately 40% [5]. This is likely due to the molecular genetics and pathophysiology of MDD. However, research on molecular genetics is fairly limited for cases of MDD-PF. Based on available clinical and pharmacogenetics studies, it is thought that MDD-PF is heavily influenced by genetics. Linkage studies indicate that there is an overlap between specific genetic risks for depression and schizophrenia. In a study of patients with MDD, it was discovered that the brain derived neurotropic factor (BDNF) val66met polymorphism has an association with psychotic features [6]. In contrast to MDD without psychotic features, additional genes were found to be associated with cases of MDD in which psychotic features were present. Some of these genes include single nucleotide polymorphisms in the dysbindin (DTNBPI) gene, the A allele of the 444G/A variant in the dopamine beta-hydroxylase (DBH) gene, and the active allele of the monoamine oxidase A (MAO-A) variable number of tandem repeats (VNTR) [6].

Postmortem and neuroimaging studies have shown that reductions in grey matter and glial density in the PFC and hippocampus are characteristic of depression. High amounts of cortisol in MDD-PF may be explained by decreased hippocampal function, because this is thought to inhibit the hypothalamic-pituitary-adrenal (HPA) axis [9]. The amygdala is also affected in cases of MDD-PF [9]. This disorder is not as well-researched as other, more common psychological disorders, so there are many potential risk factors that have not been investigated. For example, MPAs and neurological soft signs (NSSs) are associated with schizophrenia and may be associated

with psychosis, but have not been investigated in cases of MDD-PF [9]. Depressive symptoms can occur due to physical health problems, (i.e., hypothyroidism, reduced estrogen levels, and disrupted circadian rhythms).

TREATMENTS AND PREVENTION

There is no cure for either schizophrenia or MDD-PF, so various treatment methods are often used. These treatment methods include and are not limited to antipsychotics, antidepressants, electroconvulsive therapy, and cognitive behavioral therapy.

Schizophrenia

Treatments for schizophrenia often involve medications and psychosocial therapy. There is no cure so many patients continue to receive treatment over the course of their lives. However, there have been cases in which patients with schizophrenia experience spontaneous remission and no longer require treatment. Studies show that in cases of schizophrenia in which patients have made a full recovery, about 12 to 22% of these patients experience one single episode of schizophrenia [13]. Treatment is often guided by a psychiatrist along with a treatment team. Hospitalization may be necessary in extreme cases. Electroconvulsive therapy (ECT) may be considered effective for patients who do not respond to drug therapy. Some of the medications that are typically used for drug therapy can be put into two categories: first-generation and second-generation antipsychotics [7]. Research has shown that second-generation antipsychotics may be associated with increased efficacy in the treatment of major depressive disorder [32]. Patients who use second-generation antipsychotics appear to show slight improvements in overall symptoms compared to first-generation antipsychotics. In particular, medications such as olanzapine, amilsulpride, and risperidone appear to be associated with an improved quality of life. Evidence

also indicates that there may be a smaller degree of side effects associated with certain second-generation antipsychotics compared to first-generation antipsychotics. This may be dependent on the specific drug that is being used because some second-generation antipsychotics have shown associations with increased sedation or weight gain.

Psychosocial therapy includes individual or family therapy, social skills training, or vocational rehabilitation. As mentioned previously, avoiding social isolation and seeking intervention if there are any early signs of schizophrenia can aid in prevention. Other methods for prevention include developing social skills, learning coping mechanisms to deal with anxiety and depression, and learning how to view the world more optimistically.

MDD-PF

Similarly to schizophrenia, there is no permanent cure for MDD-PF, but there are measures that can be taken to manage the symptoms. These include medications, psychotherapy, hospitalization, and brain stimulation therapies. Antidepressants in combination with antipsychotic medications may help treat the disorder, although these medications may not be effective until months after a patient begins taking them. A common medication that is used to treat MDD-PF is selective serotonin reuptake inhibitors (SSRIs), which are antidepressants that increase serotonin levels and are often used in combination with antipsychotics [17]. Psychotherapy involves learning cognitive and behavioral skills to alleviate symptoms with a mental health professional. If MDD-PF is severe, typically if patients begin harming themselves or attempting to commit suicide, hospitalization may be necessary. ECT, which is also sometimes used to treat schizophrenia, is a form of brain stimulation therapy that may be utilized to treat MDD-PF. Prevention of the initial onset of MDD may be possible. If a person is at risk for

depression, undergoing cognitive or behavioral therapies may be beneficial. However, prevention of depression has not been studied extensively and it is a difficult disorder to prevent due to the genetic factors being so prominent.

Newer forms of treatment may be developed following the discovery of new information regarding each disorder, including previously unknown causes and molecular markers. Molecular markers are crucial, because they may aid in identifying an alteration in genetic expression that causes susceptibility to the disorder.

PROGNOSIS

For both schizophrenia and MDD-PF, prognosis is largely dependent upon the individual. Prognosis can be affected by a number of factors, including the severity of symptoms, how early intervention begins, and genetic predisposition.

Schizophrenia

The prognosis for schizophrenia is better when onset of the disorder is acute and treatment begins early. Other factors that are associated with good prognosis include demonstrating good premorbid functioning, being married, and exhibiting prominent affective features [13]. If treatment begins late and/or onset is more severe, the prognosis is grimmer. However, with proper treatment, those who have schizophrenia are able to live healthy, happy lives.

MDD-PF

Unfortunately for those who suffer from MDD-PF, the prognosis does not appear to be favorable. MDD-PF is thought to be a debilitating disorder with a high likelihood of recurrence. Because of this, it is important that patients undergo long-term treatment in order to avoid relapse. According to a study in which patients were examined over the course of two years, 58% of

patients recovered from MDD-PF while 21% had a chronic episode. The same study was conducted over the period of six years, in which 17% of patients experienced recovery and over 55% had chronic episodes [10]. While prognosis can be dependent on the individual, statistical data indicates that a higher percentage of patients tend to experience relapse over a longer period of time. Prognosis is largely dependent on when treatment begins, and in order for treatment to be effective, it must be ongoing. Individuals who suffer from the disorder are likely to experience relapse.

PSYCHOSIS

Psychosis, rather than being its own psychological disorder, is a symptom that can occur within various neurological and psychiatric disorders. Causes are varied depending on the psychological disorder in which it manifests. In the cases of schizophrenia and MDD-PF, psychosis appears to be mainly genetic. Traumatic life events and consistent marijuana usage during early adolescence may lead to the development of psychosis, but some theories have speculated that individuals must be genetically predisposed in order to develop these symptoms [6]. Antipsychotics can effectively reduce psychotic symptoms in specific disorders, but they do not treat the underlying illness. Typical antipsychotics, also called first-generation antipsychotics, are usually less expensive than second-generation drugs, and they have been around for a longer period of time. It is not known which of these types of treatment is more effective, although some evidence suggests that second-generation antipsychotics may be associated with more improved symptoms.

Dopamine and glutamate imbalance may be crucial factors in psychotic symptoms. It is thought that the psychopathology for psychosis is influenced by imbalance in dopaminergic

activity. Glutamate abnormalities have also been shown to play a role in psychosis [9]. Because both of these neurotransmitters are involved in schizophrenia, MDD-PF, and psychosis, they may play a major role in the development of psychosis. Examining the biological factors for these imbalances may aid in recognizing common features for the two disorders.

SIGNIFICANCE

As stated previously, psychosis can have damaging effects in those who are affected. If left untreated, more severe health problems such as neurological damage may occur. Psychotic symptoms involve delusions, hallucinations, and paranoia, all of which have associations with being “out of touch” with reality. These can be scary for patients to experience and can often interfere with normal functioning. For this reason, it is important that psychotic symptoms are treatable. Because psychosis often requires ongoing treatment, it would benefit those who suffer from psychotic symptoms if a permanent cure were to be developed. By examining two slightly distinct disorders and comparing their manifestations of psychotic symptoms, the potential causes for psychosis can be identified. From here, treatments that target these specific causes would be able to be developed.

METHODOLOGY & AIMS

This research involves a meta-analysis and systematic review approach, in which schizophrenia and MDD-PF and compared in order to pinpoint commonalities. Five related studies were gathered for each disorder, and three studies were gathered for psychosis as a symptom. Additional studies involving both disorders were also examined. These studies were analyzed to pinpoint any similarities between factors for psychosis, and this analysis allowed for the determination of whether or not the hypothesis would be rejected. Because this research emphasizes the causes for psychosis, the studies mainly focus on specific causes. This approach was taken because, by combining data from multiple studies and by isolating data from previous studies, any existing biases in previous research can be minimized. Using this method, reliable conclusions can be drawn. Several studies involving MDD-PF, schizophrenia, and psychosis were examined individually and then combined in order to analyze the consistency of the data presented. As stated in the hypothesis, the aim is to identify similarities that are significant enough to potentially be used in the development of a treatment for psychosis. Some of the factors that were compared include neurological similarities, cognitive effects, and pathophysiology for each disorder. Additionally, structural changes, neurotransmitter imbalance (i.e., dopamine and glutamate), and diagnostic methods were contrasted. Epidemiology and treatment mechanisms were also compared. The DSM-5 was frequently referenced throughout the research process, in addition to numerous peer-reviewed journal articles.

STUDIES

In order to test the hypothesis for this research, recent studies were compared in order to determine whether the similarities between the two disorders were significant. In order to be considered significant, the similarities between the disorders need to offer substantial potential causes and additional features for psychosis. These potential causes and other features do not need to be various. They should simply show a reasonable amount of potential to positively influence the development of treatments. Studies that focused on the neurobiological factors for each disorder were examined. Specifically, the structural changes, molecular genetics, and functional impairments were examined for each disorder.

SCHIZOPHRENIA

Study 1: Neuropathology of Schizophrenia [20]

Some of the structural abnormalities that have been observed in schizophrenia include a decrease in cerebral volume and widening of the lateral and third ventricles. Cerebral weight is observed to be decreased as well. MRI studies have indicated especially large reductions in brain volume in the temporal lobe and in medial temporal structures, including the hippocampus and amygdala. Structural imaging also indicates that grey matter is more reduced compared to white matter. There is speculation that patients with schizophrenia have a reduction in the size of the thalamus. It has also been reported that patients experience structural abnormalities in the cerebellum, although further research must be done to confirm either of these theories.

Study 2: Dopamine Hypothesis of Schizophrenia: Version III – The Final Common Pathway [21]

This hypothesis seeks to explore the question of whether symptoms in schizophrenia are related to dysfunctions in the regulation of dopamine. There is emphasis on the possibility that

dopamine may play a dominant role in psychosis. Version III is the most recent version of this hypothesis since it accounts for the most recent knowledge about dopamine's role in schizophrenia. It is expected to be revised in the future as research continues to be conducted on factors associated with schizophrenia. This study emphasizes the fact that there are environmental factors correlated with schizophrenia that cannot be explained by genetics. For example, it has been observed that increased dopaminergic activity can result from factors such as social isolation. Because both genetic and environmental factors are shown to play a role in dopamine dysregulation in schizophrenia, it is thought that these factors work together to influence dopaminergic functions. This in turn may have an effect on symptoms in schizophrenia.

Study 3: Molecular Genetics of Schizophrenia [27]

This study focuses on linkage studies, neurotransmitter responses, and other factors in order to observe the molecular genetics of schizophrenia. Neurotransmitters such as dopamine, serotonin, and glutamate have been shown to have a role in schizophrenia. Amino acids such as glycine and cysteine also have manifestations in the disorder. The D3 dopamine receptor gene is present in high concentrations in the limbic system so it may have a large role in schizophrenia. However, studies have not been able to confirm the dopamine theory. Glutamate appears to show evidence of an association with schizophrenia. Patients with schizophrenia display reduced non-NDMA glutamate receptors in the temporal lobe compared to individuals who do not have schizophrenia. Studies have also demonstrated that patients with schizophrenia have reductions in serotonin receptors in the PFC. The serotonin transporter gene is also shown to be involved with psychosis. It is possible that other neurotransmitters such as GABA are associated with schizophrenia, but existing evidence is too weak to allow for any conclusions to be made.

Study 4: Prefrontal Functioning during Context Processing in Schizophrenia and Major Depression [29]

It has been observed that patients with schizophrenia exhibit decreased cerebral blood flow in the prefrontal cortex, called hypofrontality. This study seeks to find out whether hypofrontality occurs only in schizophrenia or if it manifests in other psychotic disorders. Results indicated that patients with schizophrenia exhibit larger reductions in cognition than patients with non-psychotic depression. It is uncertain whether dysfunctions related to context processing in the prefrontal cortex are specific to cases of schizophrenia, or if these dysfunctions appear in other psychiatric disorders.

Study 5: Cognitive Impairments in Psychotic Disorders [18]

This study asserts that patients with schizophrenia experience a higher degree of impairment to cognitive abilities compared to patients with MDD-PF and other psychiatric disorders such as bipolar disorder. These disorders do still involve an impairment to cognitive function, but the impairment is less severe than as observed in schizophrenia. In the case of schizophrenia, working and episodic memory are affected, partly due to the fact that the prefrontal cortex is impaired and has difficulty communicating with other regions of the brain. Schizophrenia appears to display a higher amount of cognitive impairment than affective psychosis, although the overall degree of cognitive impairment seen in schizophrenia and psychosis is very similar. Results indicate that all psychotic disorders involve cognitive damage at some level.

MDD-PF

Study 1: Clinical and Molecular Genetics [23]

This study explores the inheritance of psychotic depression with reference to family studies, other psychotic disorders, and molecular genetics including pharmacogenetics studies. Dopamine has been observed to play a role in the development of MDD-PF. The dopamine beta-hydroxylase gene is reported to show lower plasma levels in patients with psychotic depression when compared to patients with nonpsychotic depression. Glutamate may be linked to MDD-PF but it is not certain whether increased or decreased glutamate concentration is associated with the onset of the disorder. Serotonin receptors and transporter have been shown to not have an association with MDD-PF. Genetic and family studies do indicate that psychotic depression is often inherited and may be heavily influenced by genetics. This highlights part of the reason why it is so important that genetic research continues to be conducted on this disorder.

Study 2: Structural and Functional Neuroimaging Studies in Major Depressive Disorder with Psychotic Features [25]

This study focuses on the pathophysiology for psychotic disorders such as MDD-PF and schizophrenia, with a particular emphasis on MDD-PF. Structural changes in patients with MDD-PF are observed in proportion to changes in MDD without psychotic features. One structural change seen only in MDD-PF patients involves a reduction in the size of the amygdala. Enlarged ventricles and reductions in the volume of the prefrontal cortex were also observed. A distinction in structural features between MDD-PF and schizophrenia includes a reduction in size of the posterior subgenual cingulate cortex (in the medial side of the cerebral cortex) in patients with MDD-PF. There is evidence that dysfunctions in dopamine may be present in cases of MDD-PF, although the extent to which this influences the disorder is unknown.

Study 3: Cortisol Activity and Cognitive Changes in Psychotic Major Depression [26]

This study built on the fact that MDD-PF is a distinct disorder rather than simply a subset of MDD. While this disorder is technically a subset of MDD, there are features present that are not present in MDD, indicating that MDD-PF can be considered to be distinct from MDD without psychotic features. In this study, patients with MDD, patients with MDD-PF, and individuals without psychiatric disorders were each given a memory test. Memory was shown to be worse in patients with MDD-PF than in either of the other groups. Studies also indicate that patients with MDD-PF have greater degrees of cognitive impairments that those with MDD without psychotic features. This includes problems with prefrontal functions and memory.

Study 4: Hippocampal and Amygdalar Volumes in Psychotic and Nonpsychotic Unipolar Depression [30]

According to this study in which the hippocampal and amygdalar volumes in patients with major depressive disorder (MDD) without psychotic features and MDD-PF were compared, it was demonstrated that patients with MDD-PF had much smaller amygdalar volumes. The amygdalar volume in patients with MDD was shown to be similar to healthy subjects. There was no significant difference in hippocampal volumes between the groups.

Study 5: Dopaminergic Function and the Cortisol Response to Dexamethasone in Psychotic Depression [31]

This study tested the hypothesis that psychotic symptoms in MDD-PF could result from increased dopamine activity. After the cortisol and hormonal responses to DST suppressors and activators were examined, the conclusion was that psychotic symptoms in MDD-PF do not appear to be related to dopamine regulation.

PSYCHOSIS

Study 1: Disconnection between Amygdala and Medial Prefrontal Cortex in Psychotic Disorders [22]

A common characteristic that appears in psychotic disorders is an impairment in cognitive functioning, including deficits in memory and reduced amygdalar functioning. These factors are enhanced in response to distracting emotional information such as unemployment. When patients who suffer from psychotic disorders experience an emotional distractor, a reduction in connectivity between brain regions has been observed, with a particular increase in reduction of brain structures in cases of schizophrenia.

Study 2: Dopamine and Psychosis [24]

Studies have shown that psychosis may be triggered by a dysfunction in dopamine synthesis, as stated in the dopamine hypothesis of schizophrenia. This study focuses on the links between psychosis and dopamine activity. Some studies suggest that psychosis is affected by factors other than dopamine activity such as prefrontal functioning. There are implications that these additional factors occur alongside dopamine dysfunction. Schizophrenia's link with psychosis and dopamine was extensively researched in this study, and results indicate that excessive dopamine activity may lead to the cognitive impairments seen in schizophrenia. These impairments include those that occur in working memory, abstract reasoning, and other cognitive functions that rely on the prefrontal cortex. Based on the results that were gathered in this study, it is plausible that dopamine plays a central role in the psychotic symptoms seen in schizophrenia and other psychotic disorders.

Study 3: Progressive Brain Structural Changes Mapped as Psychosis Develops in 'At Risk' Individuals [28]

This study emphasizes findings that indicate that individuals who are at risk for developing psychotic disorders display progressive structural changes in the brain prior to developing the disorder. Results indicate that those who experience psychosis demonstrate much greater changes in brain structure in the prefrontal cortex than any other region of the brain, even before symptoms of a psychotic disorder developed. This implies that reductions in the volume of the prefrontal cortex may be associated with the development of psychosis.

RESULTS

It is important to note that patients with MDD-PF exhibit a reduction in size of the posterior subgenual cingulate cortex, while patients with schizophrenia do not. Because this feature is not seen in either schizophrenia or psychosis, it is likely the result of depressive features rather than psychotic features. This emphasizes the fact that patients with MDD-PF are less likely to display certain psychotic features compared to schizophrenia, since MDD-PF has an additional feature (depression) that is not displayed in either schizophrenia or psychosis. This distinction enables effective comparison of certain features in order to determine whether or not they are significant, since the disorders are different enough that any similarities they have may be significant for the hypothesis.

The factors that were compared when examining the studies include structural changes, molecular backgrounds, and other biological factors. Multiple studies have concluded that there are changes in brain volume in schizophrenia as well as in MDD-PF. Specifically, it has been shown that amygdalar volume as well as hippocampal volume are reduced in patients with schizophrenia. Patients with MDD-PF have been shown to have large reductions in amygdalar volume, but no significant changes in hippocampal structure compared to those who are not affected with MDD without psychotic features. Whether or not this decrease in amygdalar volume is significant is largely dependent on whether psychosis as a symptom is affected by structural changes in the amygdala. Based on existing research, a reduced amygdalar volume does appear to be related to psychosis, so this factor could plausibly be considered significant. Other structural changes that are observed in both disorders include enlarged ventricles and reduction in volume of the prefrontal cortex. Because these factors are consistent in both disorders and in psychosis as a

symptom, they may be significant for the hypothesis. However, in order to be considered significant, there must be additional supporting data since these structural brain changes may be associated with another common denominator.

Table 1: Structural Brain Changes Associated with Schizophrenia and MDD-PF

Brain Structure	MDD-PF	Schizophrenia
Cerebrum	Reduced blood flow	Reduced blood flow
Prefrontal cortex	Reduction in volume	Reduction in volume
Amygdala	Reduction in volume	Reduction in volume
Hippocampus	No significant change	Reduction in volume
Posterior subgenual cingulate cortex	Reduction in volume	No significant change
Ventricles	Enlarged	Enlarged
Thalamus	No significant change	Possible association
Cerebellum	No significant change	Possible association
White matter	Disrupted	Reduced
Gray matter	Disrupted	Reduced to a higher degree compared to white matter

The molecular backgrounds for each disorder include associated neurotransmitters and hormones. One study concluded that dopamine dysregulation is not related to psychotic symptoms in MDD-PF. This is in contrast to the dopamine hypothesis of schizophrenia, in which it is thought that dopamine dysregulation may have a role in the development of schizophrenia. However, there

is another study that concluded that dopamine dysregulation may be associated with MDD-PF, but this study specifically highlighted reduced concentrations of dopamine having an association. Schizophrenia, on the other hand, is associated with increased dopamine secretion. This study does not offer reliable evidence that MDD-PF is indeed associated with decreased dopamine secretion because another study concluded that the linkage may be insignificant or even nonexistent. Since dysfunctions in dopamine activity in MDD-PF patients may not be related to psychosis, it cannot be concluded that dopamine is a direct cause for psychosis, regardless of dopamine's association with psychosis in other psychotic disorders. Because the research regarding dopamine's role in MDD-PF is relatively limited, it is possible that dopamine has a larger role that has not been studied yet. This may especially be the case since the dopamine hypothesis of schizophrenia highlights the fact that current evidence is consistent with the possibility of dopamine dysfunction playing a central role in psychosis. Since this is only a speculation, the dopamine hypothesis is not significant enough to support the hypothesis for this research. Other neurotransmitters such as serotonin and glutamate were shown to have greater effects in one disorder compared to the other, or had associations that were not consistent with each other. Therefore, this factor can be disregarded as a supporting factor for the hypothesis.

Table 2: Molecular Structures Associated with Schizophrenia and MDD-PF

Molecular Structure	MDD-PF	Schizophrenia
Cortisol	Increased concentrations	Increased concentrations
Serotonin transporter	No association	Reduced
Serotonin receptor 1A	No association	Reduced
Serotonin receptor 2A	No association	Reduced

Table 2: Molecular Structures Associated with Schizophrenia and MDD-PF

Serotonin receptor 2C	No association	Reduced
Dopamine beta-hydroxylase	Decreased concentrations	Decreased concentrations
D1 receptor	Possible reduction	May be associated with reductions in the prefrontal cortex
D2 receptor	Possible reduction	Increased concentrations
D3 receptor	Possible reduction	Increased concentrations; weak association
5-hydroxytrytamine; 5HT	No association	Findings are inconsistent but indicate a possible association with negative symptoms and ventricular enlargement
Glutamate and Glutamine combined	Possible association	Increased concentrations especially as patients age; associated with positive symptoms
Dopamine transporter	Possible reduction	No association
Non-NDMA glutamate receptors	Possible association	Reduced

Cognitive impairments are associated with both schizophrenia and MDD-PF, although patients with schizophrenia display higher degrees of damage. On its own, psychotic symptoms are associated with cognitive impairments that have very similar profiles to the impairments displayed in schizophrenia. Since these impairments in psychosis are more similar to schizophrenia than to MDD-PF, it is difficult to say whether this factor could be considered significant for the hypothesis. It is possible that those with MDD-PF display diminished amounts of cognitive impairment because psychotic features are a "smaller portion" of the disorder compared to schizophrenia. Patients with MDD-PF often experience psychotic symptoms in addition to depression, which sets it apart from both schizophrenia and psychosis. Schizophrenia, on the other hand, is almost considered to be synonymous with psychosis, so it is expected that schizophrenia and psychosis would display a greater amount of similar features. However, because this possibility is hypothetical, cognitive impairment will not be considered as a significant supporting factor.

In terms of epidemiology, symptoms, and prognosis, any similarities would be considered insignificant because these factors would not reasonably provide information needed that would aid in the development of permanent treatments. Treatments would be best developed to target certain neurotransmitters or structural deficiencies in the brain. It would not be practical to expect a treatment to potentially be derived based on information related to epidemiology and similar factors. Current treatments can offer insight into ways that symptoms can be managed but the development of cures is mainly dependent on genetic research.

CONCLUSION

Based on the information that was gathered, the hypothesis for this research must be rejected. Unfortunately, the amount of existing research regarding the disorders, especially MDD-PF, is very limited. Because of this, many of the similarities between MDD-PF and schizophrenia are speculative rather than definite. With so many gray areas in current research, it is difficult to pinpoint exactly what needs to be targeted in the treatment of psychosis. The hypothesis may possibly be more strongly supported in the future after substantial research is conducted on each disorder. For the time being, there is not enough available information for any reliable conclusions to be drawn regarding possible treatments.

DISCUSSION

Both schizophrenia and MDD-PF appear to be affected by both genetic and environmental factors, although the extent to which each disorder is affected is unknown. MDD-PF has demonstrated a high degree of heritability so it is possible that the disorder is more strongly affected by genetics compared to environmental factors. Psychosis is also shown to be affected by genetics and environment. Because of this, it was important to address both the genetic and environmental risk factors for each disorder when conducting this research. The genetic similarities are more likely to offer support for the hypothesis, considering the fact that medicinal treatments can directly target biological factors such as structural abnormalities and neurotransmitter imbalance. Environmental factors are better treated with psychological therapies and cannot be directly targeted.

Some of the similarities that have been pinpointed include structural abnormalities and neurotransmission. Patients with MDD-PF and patients with schizophrenia demonstrate reduced prefrontal volumes, smaller amygdalar structures, and dilated ventricles. Dopamine may have associations with each disorder although further research must be conducted in order to confirm this. Serotonin and glutamate are shown to have associations with schizophrenia and either reduced or no associations with MDD-PF. With regards to cognitive impairments and the effects of dopamine, the differences between the disorders outweigh the similarities. While both disorders display deficits in cognitive functioning and dysregulation of dopamine, the disorders are not affected to the same extent and certain factors manifest themselves in different ways.

Due to the limitations in current research, there are a lot of uncertainties and hypotheticals when examining the similarities between MDD-PF and schizophrenia. For example, the structural

abnormalities could hypothetically be a cause for psychosis assuming that there is no other common denominator. Since it is not known whether these abnormalities are associated with a completely different aspect of each disorder, it is best to reject this as a potential cause. Although the hypothesis was rejected, this does not mean that it will never be supported by data or that it will always be rejected. Considering that the largest problem when gathering data was that there is a lack of considerable research, the hypothesis may be better supported in the future, assuming that substantial research will be done on both disorders, as well as on psychosis on its own.

LIMITATIONS

There is currently a lack of considerable research regarding psychosis and MDD-PF. Schizophrenia has been researched more thoroughly, but there is still a lot that is not known about the disorder. Because this research was based primarily on existing research, it was at times difficult to find exact data regarding the biological background for schizophrenia and MDD-PF. Many of the potential genetic causes for the disorders were not definite causes; rather, they were considered potential risk factors or associated factors. Additionally, some environmental factors, potential causes, and diagnoses for each disorder, as well as for psychosis, were under-researched. Because of this, many of the comparisons made throughout this research were hypothetical and unconfirmed.

One other limiting factor in this research is the fact that a lot of studies relate psychosis directly to schizophrenia. This made it difficult to find studies that focused primarily on psychosis. For example, many studies referenced the dopamine hypothesis of schizophrenia and some studies had a slight implication that dopamine dysregulation was related to psychotic symptoms. However, this may only be the case for some psychotic disorders, since one study indicated that it was unlikely that the psychotic symptoms in MDD-PF are associated with dopamine dysregulation. This lack of research on psychosis on its own made it difficult to compare symptoms of psychosis in MDD-PF and schizophrenia, since psychosis and schizophrenia were often studied so closely in relation to each other.

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