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

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ABSTRACT: This research examines the neurological similarities between schizophrenia and major depressive disorder with psychotic features to compare the manifestations of psychosis in each disorder. Both disorders often involve symptoms of psychosis, although the disorders overall are very different. We hypothesize 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 the hypothesis would be rejected. The results indicated that many 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
BACKGROUND

Symptoms, Epidemiology, and Diagnosis

Schizophrenia

Patients with schizophrenia experience positive and negative symptoms. 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. These symptoms include reduced emotional expression (i.e., constricted/flat affect) and reduced motivation (i.e., avolition) [11].

Causes for this disorder are still being researched, although studies have shown that genetic and environmental factors may contribute to its development. It is 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, we can think of environmental factors as potential risk factors rather than causes. There are three different “levels” of risks: highest-level, intermediate, and lower-level [14]. Highest-level risk factors appear to have more significance compared to intermediate and lower-level risks. Intermediate risks involve 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 exposure to harmful agents before birth, and highest-level risk factors include having an affected first-degree relative.

Additional risk factors include childhood sexual abuse and traumatic brain injury. Ongoing use of cannabis in early adolescence (prior to age 16) is shown to accelerate one’s risk of experiencing psychosis [12]. Another factor that may increase one's risk for developing this disorder is social withdrawal. To reduce the risk of developing schizophrenia, individuals should avoid social isolation and seek psychological intervention if initial signs, such as behavioral changes and fragmented psychotic symptoms, begin to occur [13]. This recommendation is especially important if there is a family history of schizophrenia, as this is correlated with higher-level risk. It is not certain whether a person must be genetically predisposed in order to develop the disorder.

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 DSM-5.

MDD-PF

MDD-PF, also called psychotic depression, is a subset of major depressive disorder in which patients sometimes experience psychosis during a depressive episode. Symptoms include fatigue, social isolation, difficulty concentrating, and insomnia or hypersomnia [15]. Symptoms may differ slightly depending on the age of the patient. The exact cause is not known, although biological changes in the brain, neurochemistry, and genetics are thought to play a role. Researchers believe that imbalances in the neurotransmitters dopamine and glutamate may be present in both MDD-PF and schizophrenia, although further testing is required 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. Poor physical health and traumatic life events are associated with MDD-PF, indicating that environmental factors may play a role.

Environmental factors are limited in cases of MDD-PF, mainly due to the lack of substantial research. 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 shown to increase risk [8]. 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 susceptible individuals.

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, physicians often test for hypothyroidism, as an underactive thyroid may cause patients to feel depressed and fatigued [16]. It is common for doctors to fail to diagnose hypothyroidism due to the presence of depressive symptoms, so it is important that a blood test is done in order to rule out this possibility. A psychiatric evaluation may be used to diagnose the disorder.

Biological Factors

As with most psychiatric disorders, biological factors affect the development and manifestation of both disorders. Schizophrenia and MDD-PF are believed to
be influenced by both genetics and environmental factors.

**Schizophrenia**

Schizophrenia may involve an imbalance in certain neurotransmitters, including 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 or function and can assist researchers in understanding the neurobiology behind each disorder. This information aids in the development of treatments and diagnostic procedures. An MRI study of monozygotic twins in which one was affected by schizophrenia and one was not showed that those with schizophrenia have larger ventricles. This trend is also true of those who are unaffected carriers [4]. Studies have also shown that those who suffer from schizophrenia have smaller hippocampal volumes. Additionally, schizophrenia is structurally characterized by reduced white and gray matter. Individuals with schizophrenia may exhibit deficiencies in parts of the brain that depend on the prefrontal cortex (PFC) [4].

Biological risk factors can start 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]. These potential risk factors warrant further research to determine whether they cause psychotic symptoms.

**MDD-PF**

MDD-PF has a heritability of approximately 40% [5]. This figure is likely due to the molecular genetics and pathophysiology of MDD. However, research is fairly limited. Based on available 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 is associated with psychosis [6]. In contrast to MDD without psychotic features, additional genes were found to be associated with MDD-PF. 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, since this can inhibit the hypothalamic-pituitary-adrenal (HPA) axis [9]. The amygdala is also affected [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.

**Treatments and Prevention**

There is no cure for either schizophrenia or MDD-PF, so various treatments are often used. These treatments include antipsychotics, antidepressants, electroconvulsive therapy, and cognitive behavioral therapy.

**Schizophrenia**

Treatment for schizophrenia commonly involves medications and psychosocial therapy. There is no cure so many patients continue to receive treatment throughout their lives. However, some 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 and 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. Medications 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 show slight improvements in overall symptoms compared to first-generation antipsychotics. Evidence also indicates that there may be fewer side effects associated with certain second-generation antipsychotics than first-generation antipsychotics. This trend may be dependent on the specific drug used, as some second-generation antipsychotics are associated 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 and learning coping mechanisms to deal with negative emotions.

**MDD-PF**

There is currently no cure for MDD-PF but there are measures 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. Common medications used to treat MDD-PF are selective serotonin reuptake inhibitors (SSRIs), 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 attempt to commit suicide, hospitalization may be necessary. ECT is a form of brain stimulation therapy 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 is difficult to prevent due to the prominence of genetic factors.

This pathway involves the “exocytotic release of serotonin from presynaptic vesicles into the synaptic cleft.” This mechanism allows serotonin to interact with postsynaptic receptors. Since serotonin is associated with happiness and well-being, an increase in serotonin levels typically reduces depressive symptoms [34].

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**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 the onset of the disorder is acute and treatment begins early. Other factors associated with good prognosis include demonstrating good premorbid functioning and exhibiting prominent affective features [13]. If treatment begins late or onset is more severe, the prognosis is grimmer. With proper treatment, patients with schizophrenia can live healthy, happy lives.

**MDD-PF**

Unfortunately for MDD-PF patients, the prognosis does not appear to be favorable; there is a high likelihood...
of recurrence. Because of this issue, it is important that patients undergo long-term treatment to avoid relapse. According to a two-year longitudinal study, 58% of patients recovered while 21% had a chronic episode. The same study was conducted over a period of six years, in which 17% of patients experienced recovery and over 55% had chronic episodes [10]. While prognosis is 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 dependent on when treatment begins, and for treatment to be effective, it must be ongoing.

**Psychosis**

Psychosis can occur in various psychiatric disorders. Causes vary depending on the disorder. Traumatic life events and consistent marijuana usage during early adolescence may lead to psychosis, but some theorize that individuals must be genetically predisposed to develop these symptoms [6]. Antipsychotics can effectively reduce psychotic symptoms in specific disorders, but do not treat the underlying illness. Dopamine and glutamate imbalance may be crucial factors in psychotic symptoms [9].

**Objective**

This research aims to identify similarities between schizophrenia and MDD-PF. These disorders were chosen because they are distinct enough from each other that any similarities may offer significance for potential causes. Other psychotic symptoms share more similarities with schizophrenia than MDD-PF. The vast differences between the disorders are important because any shared factors may have significant implications for the treatment of psychotic symptoms. Ideally, we can observe the potential causes for psychosis when analyzing these disorders.

Based on existing literature, a connection between the disorders that can be explained by psychotic symptoms is plausible. A study comparing psychotic depression with non-psychotic depression and schizophrenia found that patients with MDD-PF exhibited cognitive defects similarly to patients with schizophrenia. This study also examined neuropsychological factors, such as attention and psychomotor speed [35]. A separate study examined the link between positive and negative symptoms in schizophrenia and MDD-PF. Results indicated that there was a significant correlation between positive psychotic symptoms and depressive symptoms in those with schizophrenia. This study also revealed a link between depressive symptoms and negative psychotic symptoms [36].

These studies amongst others indicate that there may be a connection between the disorders that can be explained by psychosis. This research examines similarities between the disorders to determine if a treatment could potentially be developed to target psychosis. We hypothesize that the neurological similarities between schizophrenia and MDD-PF will provide researchers with strategies to develop a treatment for psychotic symptoms.

**METHODS**

This research involves a meta-analysis and systematic literature review, in which schizophrenia and MDD-PF are compared to pinpoint commonalities. Five studies were gathered for each disorder, and three studies were gathered for psychosis. These studies were analyzed to pinpoint similarities between factors for psychosis, allowing us to determine whether the hypothesis would be rejected. We took this approach 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, we can draw reliable conclusions. Several studies were examined individually, then combined to analyze the consistency of the data presented. We compared several factors from each study, including neurological similarities and pathophysiology. We aim to identify similarities significant enough to be used in the development of a treatment.

**Studies**

To test the hypothesis, we compared studies to determine whether the similarities between the disorders were significant. To be considered significant, the similarities need to offer substantial potential causes and additional features for psychosis. These features should show a reasonable amount of potential to positively influence the development of treatments.

**Schizophrenia**

**Study 1: Neuropathology of Schizophrenia [20]**

Some structural abnormalities observed in schizophrenia include decreased cerebral volume and widened lateral and third ventricles. Cerebral weight is also reduced.
MRI studies have indicated large reductions in brain volume in the temporal lobe and in medial temporal structures, including the hippocampus and amygdala. Structural imaging indicates that grey matter is more reduced than white matter.

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

This hypothesis explores the question of whether symptoms in schizophrenia are related to dysfunctions in dopamine. Version III is the most recent version of this hypothesis since it accounts for the most recent knowledge about dopamine’s role in schizophrenia. This hypothesis seeks to comprehensively provide a framework linking risk factors to “increased presynaptic striatal dopaminergic function” [21]. This study emphasizes the environmental factors correlated with schizophrenia independent of genetics. Because both genetic and environmental factors are shown to play a role in dopamine dysregulation, it is thought that these factors work together to influence dopaminergic functions.

**Study 3: Molecular Genetics of Schizophrenia [27]**

This study focuses on linkage studies and neurotransmitter response to observe the molecular genetics of schizophrenia. Neurotransmitters such as dopamine, serotonin, and glutamate have been shown to have roles in schizophrenia. The D3 dopamine receptor gene is highly concentrated in the limbic system so it may have a role. However, studies have been unable to confirm the dopamine theory. Patients with schizophrenia display reduced non-NDMA glutamate receptors in the temporal lobe and reductions in serotonin receptors in the PFC.

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

Patients with schizophrenia exhibit decreased cerebral blood flow in the prefrontal cortex, a phenomenon called hypofrontality. This study investigates 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 in cognitive ability compared to patients with other psychiatric disorders. 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 displays a higher amount of cognitive impairment than affective psychosis. 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 and molecular genetics. The dopamine beta-hydroxylase (DBH) gene is present at lower levels in patients with psychotic depression. This gene also appears to have a linkage with schizophrenia, as a study suggested that it may play a role in modulation of psychotic symptoms [37]. This linkage is separate from the etiology of the disorder, as researchers have been unable to find significant deviations in genotypic distribution. In a study examining the effect of DBH on MDD-PF, researchers concluded that the lower plasma DBH “was not accounted for by DBH genotype” [38]. The authors hypothesized that abnormal HPA function lowered DBH expression, which promoted the development of psychosis. The effects of the DBH gene require further study to draw any conclusions about its role in the development of psychotic symptoms. Glutamate is a neurotransmitter that may be linked to MDD-PF but whether the disorder is associated with increased or decreased glutamate concentration is uncertain. Serotonin receptors and transporter have not been associated with MDD-PF. Family studies indicate that psychotic depression is often inherited.

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

This study focuses on the pathophysiology for psychotic disorders with 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 is a reduction in the size of the amygdala. Enlarged ventricles, associated with confusion and memory loss, and reductions in the volume of the prefrontal cortex were observed. MDD-PF and schizophrenia are structurally distinguished by a reduction in size of the posterior subgenual cingulate cortex (in the medial side of the cerebral cortex) in patients with MDD-PF. Further, dysfunctions in dopamine may be present in cases of MDD-PF, although the extent to which this influences the disorder is unknown [33].

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

This study contends 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 that are not present in MDD, indicating that MDD-PF can be considered distinct from MDD. In this study, patients with MDD, patients with MDD-PF, and individuals without psychiatric disorders were each given a memory test. Memory was worse in patients with MDD-PF than in either other group. Studies also indicate that patients with MDD-PF have greater degrees of cognitive impairment. This definition includes problems with prefrontal functions and memory.

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

This study demonstrated that patients with MDD-PF had much smaller amygdalar volumes. A smaller amygdala is often associated with reduced fear and risky behavior. The amygdalar volume in patients with MDD was shown to be similar to that of 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 investigated whether psychotic symptoms in MDD-PF could result from increased dopamine activity. The cortisol and hormonal responses to dexamethasone (DST) suppressors and activators were examined. DST, a drug used to treat inflammatory symptoms, has been observed to increase dopamine levels. The authors concluded 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]

Psychotic disorders commonly impair cognitive functioning, including deficits in memory and reduced amygdalar functioning. These factors are exacerbated in response to distressing emotional information such as unemployment. When patients who suffer from psychotic disorders experience an emotional distractor, connectivity between brain regions is reduced, with increased reduction in volume in cases of schizophrenia.

Study 2: Dopamine and Psychosis [24]

Studies have shown that psychosis may be triggered by dopamine dysfunction. This study focused 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. Further, additional factors occurring alongside dopamine dysfunction may affect the development of psychosis. The links between schizophrenia, psychosis, and dopamine were extensively researched in this study, and results indicate that excessive dopamine activity may lead to the cognitive impairments seen in schizophrenia. These impairments include issues with working memory, abstract reasoning, and other cognitive functions that rely on the prefrontal cortex. Based on the results of this study, dopamine may play a central role in the psychotic symptoms seen in schizophrenia and other psychotic disorders.

In a study examining the effects on dopamine-targeting therapies on schizophrenia, researchers concluded that antipsychotic treatments that block dopamine receptors show efficacy in treating positive symptoms [39]. A separate study found that dopamine treatments have been successful in treating schizophrenia, although current treatments mainly target the dopamine D2 receptor [40]. Multiple studies demonstrate the effective treatment of schizophrenia with therapies that target dopamine. The effects of dopamine-targeting therapies on MDD-PF have not been thoroughly studied, but these therapies show promise in the treatment of psychotic symptoms in schizophrenia.
Study 3: Progressive Brain Structural Changes Mapped as Psychosis Develops in ‘At Risk’ Individuals [28]

This study emphasizes findings indicating that individuals 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 greater structural changes in brain structure in the prefrontal cortex than other regions of the brain, even before symptoms of a psychotic disorder develop. This finding 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 observation emphasizes that patients with MDD-PF are less likely to display certain psychotic features compared to schizophrenia, since MDD-PF has an additional feature (depression) not present in either schizophrenia or psychosis. This distinction enables effective comparison of certain features in order to determine whether they are significant.

We compared several factors, including structural changes and molecular backgrounds. Multiple studies concluded that there are changes in brain volume in both disorders. Specifically, it has been shown that amygdalar and hippocampal volumes are reduced in patients with schizophrenia. Patients with MDD-PF have large reductions in amygdalar volume, but no significant changes in hippocampal volume. Whether this decrease in amygdalar volume is significant depends on whether psychosis is affected by structural changes in the amygdala. Based on existing research, a reduced amygdalar volume appears to be related to psychosis, so this factor could be considered significant. Other structural changes observed in both disorders include enlarged ventricles and reduced prefrontal cortex volume. Because these factors are consistent in both disorders, they may be considered significant for the hypothesis. However, to be considered significant, there must be additional supporting data, as these structural brain changes may be associated with another common variable.

The molecular backgrounds for each disorder include neurotransmitter and hormone involvement. One study concluded that dopamine dysregulation is not related to psychotic symptoms in MDD-PF. This conclusion contradicts the dopamine hypothesis of schizophrenia, which contends that dopamine dysregulation has a role. However, another study concluded that reduced concentrations of dopamine may be associated with MDD-PF. This study does not offer reliable evidence that MDD-PF is associated with decreased dopamine secretion, as another study concluded that the linkage may be insignificant or even nonexistent. This study indicated that dopamine dysregulation was unrelated to hyperactivity in the HPA axis, which was hypothesized to stimulate psychotic symptoms in depression. The hormonal responses of DST suppressors were found to be similar to those of non-suppressors to apomorphine (APO), a dopamine agonist.

Since dopamine dysfunction in MDD-PF patients may be unrelated to psychosis, we cannot conclude that dopamine directly causes psychosis. Because research regarding dopamine's role in MDD-PF is limited, dopamine may have a larger role that has not yet been studied. This implication is supported by the dopamine hypothesis of schizophrenia, which highlights current evidence consistent with dopamine dysfunction playing a central role in psychosis. Since this is only speculation, the dopamine hypothesis is not significant enough to support our hypothesis. Other neurotransmitters such as serotonin and glutamate appear to have larger effects on one disorder compared to the other, or have inconsistent associations with each other. These factors are not sufficient supporting factors for the hypothesis. However, they do provide clues regarding methods needed to develop treatments for psychosis.

Cognitive impairments are associated with both disorders, although patients with schizophrenia display higher degrees of damage. Psychotic symptoms are associated with cognitive impairments similar to the impairments displayed in schizophrenia. Since these psychotic impairments 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 less 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 set the disorder apart from both schizophrenia and psychosis.
### Table 1. Structural Brain Changes Associated with Schizophrenia and MDD-PF

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

### Table 2. Molecular Structures Associated with Schizophrenia and MDD-PF

<table>
<thead>
<tr>
<th>Molecular Structure</th>
<th>MDD-PF</th>
<th>Schizophrenia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cortisol</td>
<td>Increased concentrations</td>
<td>Increased concentrations</td>
</tr>
<tr>
<td>Serotonin transporter</td>
<td>No association</td>
<td>Reduced</td>
</tr>
<tr>
<td>Serotonin receptor 1A/2A/2C</td>
<td>No association</td>
<td>Reduced</td>
</tr>
<tr>
<td>Dopamine beta-hydroxylase</td>
<td>Decreased concentrations</td>
<td>Decreased concentrations</td>
</tr>
<tr>
<td>D1 receptor</td>
<td>Possible reduction</td>
<td>May be associated with reductions in the prefrontal cortex</td>
</tr>
<tr>
<td>D2 receptor</td>
<td>Possible reduction</td>
<td>Increased concentrations</td>
</tr>
<tr>
<td>D3 receptor</td>
<td>Possible reduction</td>
<td>Increased concentrations; weak association</td>
</tr>
<tr>
<td>5-hydroxytryptamine; 5HT</td>
<td>No association</td>
<td>Findings are inconsistent but indicate a possible association with negative symptoms and ventricular enlargement</td>
</tr>
<tr>
<td>Glutamate and Glutamine combined</td>
<td>Possible association</td>
<td>Increased concentrations especially as patients age; associated with positive symptoms</td>
</tr>
<tr>
<td>Dopamine transporter</td>
<td>Possible reduction</td>
<td>No association</td>
</tr>
<tr>
<td>Non-NDMA glutamate receptor</td>
<td>Possible association</td>
<td>Reduced</td>
</tr>
</tbody>
</table>

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Schizophrenia is considered almost synonymous with psychosis so it is expected that schizophrenia and psychosis would display more similar features. Because this possibility is hypothetical, cognitive impairment will not be considered a significant supporting factor.

In terms of symptoms and epidemiology, any similarities would be considered insignificant, as these factors would not reasonably provide information needed that would aid in the development of treatments. The best treatments would target certain structural abnormalities in the brain, so it would not be practical to expect a treatment to be derived based on epidemiology and similar factors. Current treatments can offer insight into symptom management, but the development of cures is heavily dependent on genetic research.

**DISCUSSION**

Both schizophrenia and MDD-PF appear to be affected by 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 than environmental factors. Association studies indicate that several vulnerability genes may contribute to an increased risk of psychotic symptoms in depression, including brain derived neurotrophic factor (BDNF), dopamine beta-hydroxylase (DBH), and dopamine receptor 2 (DRD2). Additional gene variations, such as serotonin transporter (5-HTT) and dysbindin (DTNBP1) are associated with antidepressant treatment response in MDD-PF [6].

Hormones such as cortisol and neurotransmitters such as glutamate and glutamine also appear to have roles in the development of MDD-PF. Studies indicate that there is promise in targeting specific molecular markers for the treatment of psychotic symptoms in depression. Psychosis is shown to be affected by genetics and environment. Because of these effects, it is important to address the genetic and environmental risk factors for each disorder. Genetic similarities are more likely to offer support for our hypothesis, since medicinal treatments can directly target biological abnormalities. Environmental factors are better treated with psychological therapies and cannot be directly targeted.

Due to limitations in current research, examination of the similarities between these disorders is difficult. For example, structural abnormalities could hypothetically be a cause for psychosis assuming that there is no other common factor. It is not known whether these abnormalities are associated with a completely different aspect of each disorder. These factors provide clues for the structures that must be targeted, but further research must be conducted.

**CONCLUSION**

Based on the data and the lack of substantial research, the hypothesis for this research must be rejected. The amount of existing research regarding the disorders, especially MDD-PF, is limited. Because of this limitation, many 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 be more strongly supported after substantial research is conducted. For the time being, there is not enough available information to draw any reliable conclusions regarding possible treatments.

Based on the information we gathered, there appears to be promise in targeting specific genes and neurotransmitters for the treatment of psychosis. With further research on psychosis, we can discover previously unknown factors associated with these disorders, such as new molecular markers. The advent of these new molecular markers along with a better understanding of the effects of anatomical features on psychotic symptoms could eventually lead to newer, more successful therapies in the future.
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