



**The Effect of Genetics Polymorphism,
Drug Use and Structural Abnormalities
in Brain Tissue on the Onset of Psychosis**
Genetik Polimorfizm, Madde Kullanımı ve Beyin Dokusundaki
Yapısal Anormalliklerin Psikoz Başlangıcına Etkisi

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ABSTRACT

Countless investigations concerning the development of psychosis seek to label specific risk factors as causal. Through analyses of these reports, it is evident that there is no single element that can be labeled as an absolute prerequisite to the onset of psychosis. There are, however, a variety of predispositions an individual could possess that would cause an inability to properly process neurotransmitters. The resulting chemical imbalance would then manifest in the form of mental illness. It is therefore the intent of this review article to acknowledge, discuss and evaluate the collaborative impact of various environmental stressors, and demonstrate that their detriment on healthy brain functioning increases the likelihood of psychosis. We conclude that when presented with a trigger, a traumatic event incurred by an individual, the impaired brain would not be able to effectively manage neurotransmitters.

Key words: Psychosis, predispositions, polymorphism, cannabis, abnormality.

ÖZET

Psikoz gelişiminde risk faktörlerini araştıran çok sayıda çalışma bu risk faktörleri ile kesin bir bir bağlantı saptayamamıştır. Bu çalışmaların ayrıntılı değerlendirmesi psikozun başlamasına kesin olarak yol açtığını gösteren herhangi bir neden ortaya koyamamıştır. Bununla birlikte, bir bireyin nörotransmitterleri uygun biçimde düzenlemesinde sorunlara yol açacak çeşitli yatkınlıkları bulunmaktadır. Ardından beliren kimyasal dengesizlikler kendisini ruhsal bozukluk şeklinde



gösterebilir. Bu gözden geçirme makalesinin amacı çeşitli çevresel stres faktörlerinin ortak etkilerini kabul ederek tartışıp değerlendirmek, ve sağlıklı beyin işlevleri üzerindeki zararlı etkilerinin psikoz gelişimine olan katkısını göstermektir.

Anahtar kelimeler: Psikoz, yatkınlık, polimorfizm, esrar

Introduction

Psychosis, a form of mental disorder, is commonly described as involving “a loss of contact with reality”. It is widely known to affect human populations around the world and recognized as a leading cause of morbidity^{1,2}. Individuals affected with psychosis are normally characterized by exhibiting delusions and hallucinations^{3,4}. In efforts to identify the mechanism by which the onset of psychosis occurs, many have proposed a variety of factors which were thought to contribute to its development. Among the most frequently discussed are drug use, structural abnormalities in brain tissue, and genetics. A collaborative analysis of previous research indicates that no single factor can be labeled as an absolute determinant of development of psychosis. While drug use has been proven to increase the risk of developing mental illness, the majority of users are able to withstand succumbing to disorder^{5,6}. Structural abnormalities in the frontal and temporal lobes have been repeatedly found in patients displaying psychotic symptoms⁷⁻¹⁰. However, many do not display any neurological deficits. Although there have been a few genetic factors that have shown to be frequently associated with mental afflictions, recent findings have not been consistent. No study has presented concrete evidence that possession of a certain combination of alleles leads to psychosis¹¹. Concordance for mental illness among monozygotic twins is less than 50%, suggesting the interplay of environmental influences¹². It is therefore the purpose of this review article to acknowledge, discuss and evaluate the collaborative impact of various environmental stressors, and demonstrate that their detriment on healthy brain functioning increases the likelihood of psychosis.

The possession of each of the aforementioned characteristics increases the risk of psychosis, but does not guarantee it. This gives rise to the notion that there is an additional factor that leads to the onset of psychosis. It seems plausible that if an individual possesses a combination of these attributes, they are more likely to develop psychosis if they are subject to a trigger of some sort; a traumatic event, for example. If an individual possesses certain

predispositions, it would make it more difficult for them to process the emotions of the event in a way that would allow them to move past it in a healthy fashion. For example, if they have an inability to properly process neurotransmitters in their prefrontal cortex due to a genetic variation or structural deformity. Perhaps they began using drugs at an early age affecting the functioning of their neural processes. Any of these would make it increasingly difficult for the individual to cope with a monumental, negative experience, and would such increase the chances of them developing psychosis.

Cannabis and Psychosis

Although substances such as LSD (“acid”) and psilocybin (“magic mushrooms”) have been associated with the development of psychosis¹³, the most intricately studied is cannabis^{12,33}. It is widely known that cannabis use can induce brief episodes of psychotic symptoms, such as paranoia or hallucinations⁶. In some individuals, cannabis has been labeled as a contributory cause of the development of psychosis. However, only a fraction of cannabis users actually develop severe, long-term psychosis¹⁴. The ability of the majority of those who use marijuana to withstand development of psychosis sparked a plethora of investigations into the reasoning behind the fact that some users succumb to psychosis, and others do not. Additionally, questions were raised as to whether cannabis actually played a causal role in psychosis or if drug use was therapeutic- a consequence of the psychosis itself.

A monumental cohort study in 1987 followed 45,000 Swedish males for 15 years. The results showed that heavy marijuana use at the age of 18 was associated with a six-fold increased chance of developing psychosis¹⁵. However, this study was unable to prove whether cannabis use was the cause of psychosis, or if the fact that the patient was psychotic led them to self-medicate with marijuana (cause vs. consequence). In aims to put this argument to rest, a longitudinal study concluding in 2002¹⁴ assessed a set of adolescent cannabis users and controlled for preexisting psychosis. Their results consisted of three findings. Firstly, that cannabis use is associated with an increased risk of psychosis after controlling for preexisting conditions. Secondly, that early cannabis use constitutes a greater risk for developing psychosis than later use. Thirdly, this risk is associated with cannabis alone, excluding other substances. Following the release of these results, several meta-analyses have been published on the issue of whether cannabis use is a cause or consequence of psychosis. Results consistently label cannabis use as a causal attribute. Several follow-up studies on the link

between cannabis and the development of psychosis report a dose-response effect⁵. It is more likely that an individual will develop psychosis if they begin heavy, frequent use at a young age⁶. A positive correlation between the potency and frequency of cannabis use has also been shown to increase the risk of psychotic illness¹⁶.

The mechanism by which cannabis use influences the development of psychosis relies heavily on the effect the endocannabinoid system has on dopamine. Dopamine is a powerful regulator of various aspects of cognitive brain function¹⁷. It plays a crucial role in directing behaviors such as control of emotion, motor, and reward systems¹⁸. Delta-9-tetrahydrocannabinol (THC), the main psychoactive ingredient in cannabis, stimulates CB1 receptors in the brain via endocannabinoid transmitters¹². This ultimately results in the increase of dopamine release downstream in regions of the forebrain¹⁹. Thus, for proper cognitive function, the buildup of dopamine must be depleted via specific systems in the brain. Correct functioning of these mechanisms is crucial for effective neurotransmitter regulation. In the prefrontal cortex, Catechol-O-Methyltransferase codes for the metabolizer responsible²⁰⁻²⁴. As we will see, alterations in this mechanism have significant implications on dopamine reuptake.

Further evidence of cannabis impairing proper neural functioning is demonstrated by the effect maternal THC consumption has on the development of the fetus. Perinatal THC exposure alters fundamental developmental processes, particularly impairing establishment of connectivity between brain regions that play a role in mood, motivation, and cognition¹⁸. Cannabis alters the activity of tyrosine hydroxylase, the rate-limiting enzyme in dopamine synthesis²¹⁻²⁵. It is thus evident that exposure to cannabis during fetal development is not benign. The available mechanisms in the body do not have the ability to sufficiently compensate for these developmental shortcomings. This impact on the dopamine system leaves the developing fetus vulnerable to dysfunction later in life, increasing sensitivity to events and environmental stressors that could influence the onset of psychosis¹⁸.

Structural Abnormalities and Psychosis

There have been a multitude of reports of brain malformations in patients displaying psychotic symptoms, supporting the notion that altered neurodevelopment is a risk factor for psychosis. A study in 2009 by Didier et al¹⁸ sought to analyze the change in gray matter during the onset of psychosis, citing that longitudinal magnetic resonance imaging studies had

shown progressive gray matter reduction in the earliest stages of psychosis. They analyzed gray matter before the onset of illness in individuals who were at high risk of psychosis based on afflicted family members. A progressive gray matter reduction of the superior temporal gyrus was noted during the transition to psychosis. This suggests underlying neurobiological features of emerging psychotic disorders⁷. Later studies have also noted structural abnormalities of the prefrontal and temporal lobes⁸. These findings are of extreme importance because it gives evidence to the fact that structural abnormalities are linked to psychosis. The cardinal feature of psychosis in all patients is a chronic distortion of reality⁹. Since hierarchical temporal processing manages interpretation of reality, a deficit in temporal neural development is a noted underlying basis of reality distortion and psychoses¹⁰. Malformation in the prefrontal cortex, where significant dopamine regulation occurs, is also of note.

A recent study of importance in April of 2013 by Zhang et al²⁶ ties structural abnormalities and drug use to a polymorphism in a gene that has been repeatedly tied to psychosis through its control of dopamine in the prefrontal cortex. The polymorphism discussed is a single nucleotide substitution in the Catechol-O-Methyltransferase gene. The COMT gene codes for the metabolizer that is most responsible for clearance of dopamine and other catecholamines in the brain^{20-24,34}. As previously discussed, dopamine signaling in the prefrontal cortex is critical for modulating higher order cognitive functions, impacting many domains of human behavior, thought, and emotion²⁵. Because of dopamine's vital activity in relation to mood disorders, the COMT gene has been studied extensively to determine its relationship to a variety of clinical phenotypes, including psychosis. It has been demonstrated that genetic variation in the COMT genotype influences the regulation of dopamine in the individual, therefore affecting neural function, demonstrating a possible genetic predisposition to psychosis²².

Genetics and Psychosis

There have been a handful of functional polymorphisms identified in the COMT gene²¹. The most avidly studied is a single nucleotide substitution in which an Adenine replaces a Guanine nucleotide, resulting in a change in amino acid production from the wild type Valine to mutant Methionine^{22, 27}. In the soluble form of COMT, the substitution is at position 108. However, when membrane-bound, the substitution is located at position 158²⁰. Dopamine signaling affects cognitive performance through a U-shaped relationship; too much or too

little dopamine can have deleterious effects²⁵. The Valine and Methionine alleles have different effects on COMT efficiency. Depending on the combination of COMT alleles present in the genotype, there will be a different level of dopamine depletion. The relationship between the number of Valine alleles and prefrontal inefficiency is linear²¹. The closer the genotype is to Valine homozygosity, the nearer to normal COMT function it has shown to be²⁷. The more temperature-stable Valine allele leads to higher COMT protein levels and enzymatic activity compared with the Methionine form. Methionine is thus referred to as the 'low functioning COMT allele'²⁰. It does not act as efficiently in the depletion of dopamine as the Valine allele, and allows dopamine to accumulate. Prefrontal cortex function is distorted in response to the dopamine buildup, altering activation during working memory and neuropsychological performance²¹.

Given the evidence that a Methionine homozygote codes for a lower functioning mechanism of dopamine depletion, it would make sense that mental disorder would be associated with this genotype. It results in a dopamine accumulation that cannot be dealt with properly. There are several reports in support of this. The low COMT activity Methionine allele is dominant in rapid-cycling bipolar manic-depressive disorder, a mental illness that presents psychosis as a signature symptom²⁰. In a study comparing patients presenting psychotic mania, those carrying the Valine allele performed better than Methionine carriers on tests measuring executive function, memory, verbal fluency, and intelligence^{28,29}. This provides phenotypic evidence that the Valine allele is higher functioning.

Complications of Designating a Single Cause for Onset of Psychosis

The isolated study of allele variation on COMT function demonstrates that dopamine regulation is influenced by genotype. If all patients presenting psychotic symptoms possessed the mutant phenotype, it would provide a strong argument that psychosis is purely genetic. However, many psychotic patients do not possess a mutant genotype, and many sane individuals do²⁸. In fact, a study comparing this polymorphism in bipolar patients displaying psychotic features reported that in patients with psychotic episodes the proportion of Val/Val homozygotes was twice that of Met/Met homozygotes²². The genotype therefore cannot be used as an absolute determinant. Further contradictory evidence comes from a study in January of 2013³⁰ in which it was reported that neonates homozygous for the COMT Valine allele exhibited reduced grey matter in the temporal cortex and hippocampus. Given that the

Methionine allele is the mutant version and associated with defective activity, one would assume that the structural malformations would be of higher association with a Methionine homozygote.

An additional contradictory report comes from a study concluded in October of 2013 by Vinkers et al³¹. The focus of their study- child maltreatment, cannabis use, COMT Val158Met and psychosis- is precisely the center of attention of our review article. They proposed that the lower functioning polymorphism in COMT would be associated with psychosis when the other risks were involved. Their results showed that cannabis and childhood maltreatment were linked to increased levels of psychotic experiences, citing a consistency with previous evidence that these environmental factors affect the functionality of the dopamine system. However, they go on to make an argument for the vulnerable genotype as the Val/Val homozygote. This is contradictory because it is not the polymorphism, the Methionine allele is. Upon scrutiny of this study, it is clear that there are flaws throughout their methodology that may have led to skewed outcomes. They acknowledge that their findings were unexpected, and mention a few possibilities as to why they may have obtained these results. They noted the complexity of the relationship between dopaminergic activity and the enzymatic actions of COMT, and their inability to directly translate them. They mentioned that there could be other neurotransmitters at play. Additionally, they did not monitor the molecular changes due to the interaction between the various environmental influences. A monumental flaw was that only a small percentage (14% in one sample and 33% in the other) had ever used cannabis. The power to detect gene-environment interactions rapidly declines with lessened exposure rates³². Additionally, their indexing of cannabis use was inconsistent across the two sample groups. The authors also noted that the reports of maltreatment were taken after the fact- given the nature of the participants; it is possible that some of the reported instances could be a product of their affliction, and not have actually occurred.

There are a few additional overlooked details in the study that could have impacted the results. Although childhood maltreatment was reported as significant in all samples after exclusion of other factors, the results still may not have been accurate. It is worth noting that the authors defined maltreatment as abuse (sexual/emotional/physical) or neglect (emotional/physical) during childhood, equating this to occurrence of trauma incurred by the individual. This assumption is flawed. There are a wide variety of traumatic occurrences that the individual could be subject to which would significantly impact them other than

childhood abuse or neglect. The authors failed to address this, and made matter-of-fact correlations of 'trauma' to other factors without acknowledging that the individual filling out the survey could have succumb to some other tragedy. The post-traumatic stress effects of war or significant loss, for example, could devastatingly impact the human psyche, but would have gone unnoticed using the authors' criteria of trauma. These inconsistencies demonstrate the need for further examination of collaborative risk factors combining allelic variations and environmental influence.

Conclusions

The aforementioned studies provide evidence that any one factor cannot be held accountable for the development of psychosis. It is evident that these characteristics- drug use, structural deformities, less functional allelic variations- each contribute to the inability of the brain to properly process neurotransmitters. When a brain such as this is presented with a sudden influx of neurotransmitters, as would happen when experiencing a traumatic event, it would be unable to properly manage the surge of chemicals. The neurotransmitters would accumulate and the impaired brain would not be able to compensate for the imbalance, leaving the individual susceptible to the development of psychosis. A patient could be able to manage life continually coping with the predispositions their brain is afflicted with, but when faced with monumental trauma, may not be able to continue to cope. The improperly functioning brain would be overwhelmed, and it is at this point that they would succumb to psychosis.

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