Identifying the Role of Environmental and Genetic Factors in the Formation of Schizophrenia at the Latent Level

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Abstract

In this work, our major objective is to identify the importance of social learning influences using poor-rich neighbourhoods as an environmental factor, stressors, and polygenetic potentiators as White - African American ethnicities, as the formation of personality organisation at the latent level of schizophrenia. Measurements will be conducted with six sub-groups taken from latent-level schizotaxia participants aged between 11 and 20 during the ten years of period. We will use two measurement mechanisms for participants at each two years during the ten years of the experiment. These are life stress measurements concerning the GAD-7 (The Generalised Anxiety Disorder 7) stress test, and BPRS (Brief Psychiatric Rating Score) schizophrenia test that will be conducted on participants. By conducting the tests for participants over the 10-years observation span, determining the occurrence of schizophrenia is critical while we are measuring the stress levels of participants regularly. For the data analysis, we aim to identify the development of schizophrenia by using two-way ANOVA, based on income & race using six different testing groups. We expect to observe any statistically significant distinction between the six data groups. We argue that the environmental factors and stressors in the community of low level of income will trigger some specific genes such as the COMT Val/Met allele, which possibly causes schizophrenia to occur. Our results show that there is a difference between low and high-income groups (regardless of race) according to p-value < 0.04. We observe statistically highly significant differences between the White-High income group and the African American-Low income group according to p-value < 0.02. In other words, the development of schizophrenia will be significantly greater than White-High income group. Finally, our ANOVA result will show that for a p-value of 0.05, we will observe no significant difference in the average and high-income groups due to both groups having to experience relatively less life stressors.

Keywords: Schizophrenia, latent level schizotaxia, low-income, high-income, COMT, two-way Annova, African-American, White, schizotypy.

Identifying the Role of Environmental and Genetic Factors in the Formation of Schizophrenia at the Latent Level

Schizophrenia (SCZ) is a considerably dangerous mental disorder and the most devastating form of psychopathology, as it not only affects the individual's sanity by dysfunctioning but also can cause serious damage to the patient's surroundings. Schizophrenia (SCZ) causes patients to have psychosis and experience extreme levels of episodes, thus, these might cause other serious disorders to occur, and make it harder for patients to deal with. Even though it is not a prevalent disorder, according to the World Health Organization (WHO, 2022), in the world, one in 300 people (0.32%) suffer from schizophrenia (SCZ), as it is often seen during late adolescence and the twenties, and the onset tends to happen earlier mostly among men than among women. This mental illness is not just a personal burden but also an economic burden, as its costs are very high. According to WHO, the direct economic burden of schizophrenia is increasing every year, as the United States has exceeded $60 billion annually. On the other hand, the staggering direct and indirect costs of schizophrenia in the United States reached $281.6 billion as of 2020 (Lecomte et al., 2022). The source of direct costs are mostly coming from healthcare, incarceration, homelessness, and housing requirements of these patients.

It is clinically observed that individuals with a family history of mental illness are at a higher risk of developing schizophrenia-spectrum disorders (Herbest, 2021). Statistics reveal that schizophrenia (SCZ), globally, is among the top ten causes of disability-adjusted life-years and negatively affects the trajectory of young people as they prepare to start an independent life. Due to its economic and heavy social burden, early and correct diagnosis of this mental disorder and its early intervention and efficient treatment are a prime priority for each nation aiming to have a healthy society.

Literature Review

Biological Aspects

One of the earlier studies conducted on schizophrenia by Os and Kapur (2009) mainly discusses critical developments in its biological aspects, the distribution and occurrence of the disease among men and women, and its drug treatment developments and effectiveness. Additionally, they described how the symptoms of schizophrenia should be better understood than other mental disorders.

Biological factors, mostly genetic factors recently obtained from different genome-wide studies in the literature, emphasize that there is a connection between common mental disorders and genes regulating specific neuronal functions (CGPGC, 2019 & Singh et al., 2022).

Maury et al. (2023) also investigated the potential roles and contribution of somatic CNVs (sCNVs) in schizophrenia (SCZ) risk, while germline copy-number variants (CNVs) contribute to schizophrenia (SCZ) risk is well known. They show that the ABCB11 gene is strongly expressed in human dopaminergic (DA) neurons, specifically within the dorsal stream of the substantia nigra (SN). But, so far how DA pathways become abnormal in SCZ remains unclear in the literature. Disruption of ABCB11 could change the function of this key neuronal circuitry in a relatively cell-type-specific manner. However, the exact role of ABCB11 on DA neuron physiology is still an open question.

One of the major research on schizophrenia was conducted by Meehl's (1962, 1964, 1990) works, which detailed the nature of the latent liability for schizophrenia known as schizotypy and provided a major organizing function for research on schizophrenia. In their model, they emphasized the role of genetics, known by the name hypokrisia (as a neural functioning difficulty), in the etiology of the illness. This neural transmission dysfunction, which is referred to as a CNS (Central Nervous System) anomaly, was termed Shizotaxia by Meehl. In their schizotype's occurrence model, schizotaxia as an underlying condition affected by social learning influences leads to a personality organisation. Schizotaxia itself is not a behavior or personality state; instead, it denotes an aberration in brain functioning. The following factors may accumulate and interact adversely. One is individual learning history, which we will model as environmental influences in our work, and the second is other potential genetic factors called polygenic potentiators, as we will investigate this under the specifically selected genes (the COMT and the BDNF candidate genes) and stressors modelled in our work as social life influences. Thus, based on Meehl's model, after the social learning influences, schizotypy occurs and is further affected by stressors and polygenic potentiators. To complete the latent level of any individual, stressors (life events), and polygenetic potentiators (selected candidate genes) have to affect schizotypy and lead to the manifest level schizotypes. Since schizotypes consist of three components as schizophrenia, schizoypic disorders, and endophenotypes, in this study we will focus on the occurrence of schizophrenia.

The work of Henriksen et al., (2017) provided a general overview of the genetics of schizophrenia, including its main methods, research outcomes, and boundaries of the genetically based solution to the mental disorder. They discussed, in their work, four simple genetic transmission models, including monogenic transmission, latent trait, mixed, and polygenic models. With the advancement of computer technology, molecular genetic studies have proposed better models such as "linkage analysis" and "candidate gene approach". With the advancement of computational tools, a more reliable genetic method, such as the genome-wide association studies (GWAS) method, has been developed after the human genome project, which reveals three billion gene base pairs. Even though GWAS answers some of the experimental observations, there are still some remaining unexplained

parts. These parts are explained by two additional approaches. One is single nucleotide variants (SNVs) and common-disease rare-variants hypothesis (CNVs), and the second is a rarely distributed disruptive variant.

Since schizophrenia is a complex and multidimensional disorder with a high heritability rate, most of the studies revealed that polymorphisms in the catechol-O-methyltransferase (COMT), BDNF, and FKBP5 genes might interact with early life stress and cannabis abuse or dependence, influencing various outcomes of schizophrenia spectrum disorders.

Williams et al., (2007) have done a research study examining the role of COMT in the formation of schizophrenia disorder and the possible associations of COMT with schizophrenia and other related disorders. According to Williams' work, COMT may play a role in the etiology, neurodevelopment, and expression of schizophrenia. An amino acid polymorphism (Val/Met) in the COMT gene affects the activity level of COMT, which affects the levels of available catecholamines in the brain (higher and lower levels of multiple catecholamines can indicate a serious underlying medical issue). Williams et. al. found in their study that Val/Met has been performing a possible performance on dopamine-mediated prefrontal tasks in healthy adults and patients with schizophrenia. In our study, we will use Williams' founding of the Val/Met allele as an inclusion criterion for our participants.

Racial Aspects

It is statistically shown that African Americans are 2.4 times more likely to be diagnosed with a schizophrenia-spectrum diagnosis compared with White individuals, who are more likely to receive an effective diagnosis. Schwartz et al., (2019) addressed this affective diagnosis issue by using both traditional symptom rating scales, clinical diagnoses, and objective behaviorally based measures of psychopathology to explore differences between African Americans and White individuals diagnosed with a schizophrenia-spectrum disorder. We believe that, even if the research conducted by Schwartz et al. clearly proves that there is a clinical misdiagnosis for Afro-Americans with the misinterpretation of disorganization and the Communication Disturbances Index (CDI), there is still a concrete difference available of higher rates of schizophrenia among the Afro Americans. The main reason for this is that there is a genetic root feeding the potential occurrence of schizophrenia under certain circumstances, such as environmental stressors. In our study, we aim to establish the environmental stressors as a part of social learning influences in already existing environments as rich x poor communities for the formation of schizotypy.

In the work of Trierweiler et. al (2000), the diagnosis of schizophrenia in 292 inpatients from an area that was primarily made up of African Americans, wew investigated. Using a free-response questionnaire, clinicians gave thorough explanations of the diagnoses they made. The results showed

that although African American and non-African American patients were assigned different rates of psychotic symptoms such as hallucinations, these assignments did not correspond with variations in the rates of diagnosis. On the other hand, Trierweiler et. al indicates that, symptoms that were equally reported for both races were associated with more African American patients obtaining a diagnosis of schizophrenia. Significant variations in the attribution of negative symptoms were found, which resulted in greater prevalence of schizophrenia among African Americans, but diagnoses for thinking disorders were similar in both racial groups. The results of logistic regression analysis revealed possible racial biases in the diagnostic procedures of doctors, as they used distinct diagnostic models for patients based on race.

Environmental Aspects

Besides genetic risk factors, it has been demonstrated in the literature that a number of environmental exposures including urban lifestyle, stressful life events and early life stress, prenatal infections and obstetric complications interfering with brain development, and substance abuse or dependence, may underlie the development of schizophrenia (Marangoni C, Hernandez M, Faedda GL, 2016, Dean K, Murray RM, 2005). Misiak et al., (2017) discussed in their work an updated, systematic, and comprehensive review of studies investigating interactions between genetic variation in candidate genes and environmental factors in patients with schizophrenia spectrum phenotypes.

Recently, researchers have highlighted the fact that while genetic factors may increase the risk of experiencing SCZ, environmental stressors such as autoimmune insult, traumatic life events, or substance abuse often act as actuators (CGPGC, 2019 & Singh et.al. 2022).

Termorshuizen et al., (2020) studied the incidence of psychotic disorders in certain migrants and minority ethnic groups in Europe. Since the incidence pattern for these groups is unknown within this continent, they compared the incidence rates for minorities and the incidence rate ratios (IRRs, minorities v. the local reference population), across sites in France, Italy, Spain, the UK, and the Netherlands. They analyzed the European Network of National Schizophrenia Networks Studying Gene-Environment Interactions (EU-GEI) data on incident cases of non-organic psychosis from 13 sites. They found that incidence rates vary by region of origin, region of destination, and their combination. More specifically, they found a 7-fold variation in the incidence rates of psychosis among minorities, and a consistent gradient of rates (reference population < members of any minority < individuals from non-Western countries, < individuals from sub-Saharan Africa) emerged across sites. These findings reveal that they are strongly influenced by the social context and affect the etiology of the disorder. This research suggests that being a racial minority contributes to a higher rate of SCZ, most likely because of higher stressors.

As we mentioned above, there is an urgent need for mental disorders, including SCZ, to be correctly diagnosed with adequate consideration of both genetic and environmental factors, to receive appropriate care and early intervention, which can improve the prognosis.

The hypothesis of the Research

In this work, our major objective is to identify the importance of social learning influences such as poor-rich neighborhoods as an environmental factor, stressors, and polygenetic potentiators such as White - African American ethnicities, as the formation of personality organization at the latent level. As given in Figure 1 by Faber et. al. (2023), we are aiming to investigate how the schizotypy

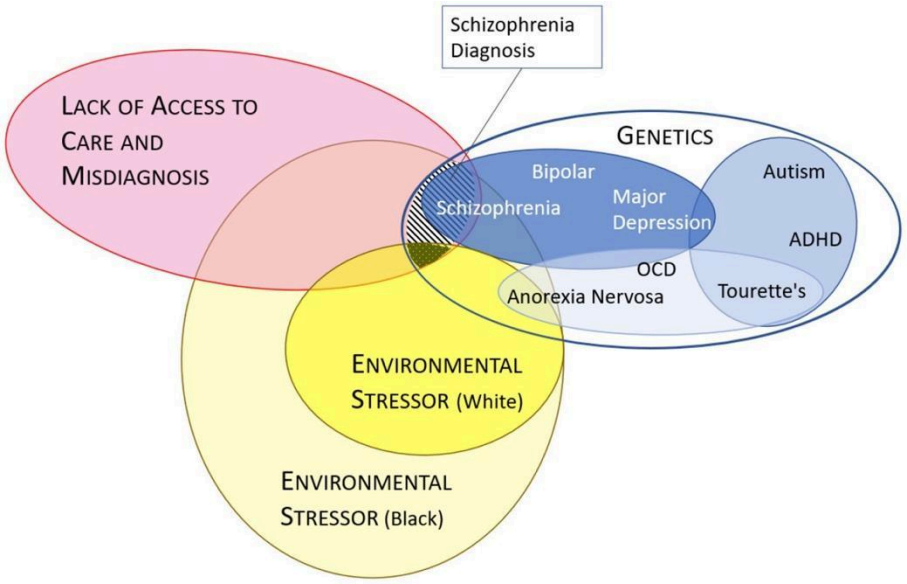

Figure 1. Major factors affecting the diagnosis of Schizophrenia (Faber et al., 2023).

occurs at the manifest level of Meel's model under the influence of environmental stressors (expected to be bigger for African Americans) and genetic factors, and especially which social stressors play a major role and at which time frame of the individual's early stage of his/her life.

All in all, to summarise what has been said above, we aim to prove three hypotheses

1. Participants in the low-income group will have a higher rate of developing schizophrenia.
2. The participants that develop schizophrenia disorder at the end of the ten-year observation period will be from the majority of the African-American x low-income group which will get a greater score of BPRS and GAD-7
3. There will be a minor difference in the average-income group and high-income group in developing SCZ.

Methods

Participants

The overall participant number selected to propose this study is 900 individuals. Each sub-group was selected to have 150 participants. All of the participants will be recruited from New York City to balance the environmental contributors. White participants will be recruited from white neighborhoods, and African American participants will be selected from African American neighborhoods.

They will be separated into two sections as White and African American, and will be separated into their ingroups in their already existing sectioning as average x poor x rich; White-average, African American-average, White-poor, African American-poor, White-rich, and African American-rich. An extra group was formed as “average” for both races to neutralise the living standards/income effect for participants and observe whether selected candidate genes have activation or effect in the case of neutral/average life stressors.

The socioeconomic status of selected individuals will be determined by their incomes. Participants will be asked to report their yearly income for an accurate grouping of candidates. The grouping of participants will be done based on a report on the distribution of household net worth by race in New York City that was done in 2021. Participants that have an income below $50,000 will be considered poor, $50,000 to $150,000 average and those above $150,000 will be considered rich.

We major the fundamental effects of environmental stressors by assuming that low-income individuals live in a poor community and have a low status. On the contrary, we assume that participants from high-income households most likely live with higher living standards as well as high social status. We also assume that the average group represents mid-level income and living standards.

Inclusion criteria

Participants will be included in the inclusion criteria if they;

1) are at the stage of latent schizotaxia, an increase in the delta and theta frequencies
2) are between the ages of 11 and 20 at the start of the test
3) have at least one parent or one first-degree relative with schizophrenia
4) have the COMT candidate gene Val/Met allele polymorphism.

Exclusion criteria

Participants are excluded from the study if they;

1) are not at the stage of latent schizotaxia (not an increase in the delta and theta frequencies.)

Materials

Since schizophrenia has a high heritability rate, and polymorphisms in some specific potential candidate genes, such as COMT and BDNF, these genes might interact with early life stress, including the usage of cannabis, or dependence, influencing various outcomes of schizophrenia disorder.

All of the tests and interviews that are going to be mentioned below, both adolescent (underage) and adult (overage), are going to be conducted on 6 of the groups; White-averege, African American-average, White-rich, African American-rich, White-poor, African American-poor.

Before starting the experiment, an EEG (electroencephalogram) test will be done on participants to detect if they have latent schizophrenia or not. An EEG is a test that looks for anomalies in an individual's brain's neurons electrical activity, or brain waves (Johns Hopkins Medicine, 2024). In the study of Teixeira et. al. (2023), the following frequency ranges are used to demonstrate neural movements back and forth in a regular rhythm: delta (1-3 Hz), theta (4-7 Hz), alpha (8–12 Hz), beta (13–30 Hz), and gamma (31–80 Hz). The authors concluded from the EEG data they have gathered that individuals with psychotic diseases have a significantly different activity, with an increase in the delta and theta frequencies.

Our study will be based on Teixeira's work regarding the increase in the delta and theta frequencies will be the defining factor in our study to determine participants' latent schizotaxia. Moreover, the participants will be recruited from hospitals or psychiatrists since they consist of data for EEG.

Procedure

Our main objective in this study is to look at the COMT Val/Met allele in participants with existing latent schizotaxia and observe if the genes would activate in 10 years with certain stressors in their lives or not. The participants will be observed for 10 years and asked questions every two years to keep track of their mental health when faced with life stressors. It is known that these candidate genes mentioned above interact with life stressors, including substance abuse. We expect that the levels of stressors will be causing a trigger with the existence of these genes earlier.

At the beginning of the study (within the first month), we will conduct two testing sections, Testing 1 and Testing 2, to identify the existing distribution of psychotic disorders among the participants.

Testing 1: This testing identifies the stress levels of the participants' experiences every two years (odd years of the experiment) during the 10-year observation period. This testing includes a single test, GAD-7 (The Generalized Anxiety Disorder 7) which is a self-reported questionnaire for screening and severity measurement of generalized anxiety disorder. Testing 1 is applied to both adult and underage participants, and can be seen in Table 1.

Table 1. Stress test questionnaire (based on GAD-7) for all participants

Question No	**Questions measuring life stressors**
1	Feeling nervous, anxious, or on edge
2	Not being able to stop or control worrying
3	Worrying too much about different things
4	Trouble relaxing
5	Being so restless that it is had to sit still
6	Becoming easily annoyed or irritable
7	Feeling afraid, as if something awful might happen

The scoring for GAD-7 is calculated by assigning numbers for each question, ranging from 0 to 3 (0, 1, 2, 3). Based on the participants' answers, they will be assigned a point, with the maximum point being 21 and the minimum being 0.

The consideration of stress levels for this test is as follows:

0–4: minimal anxiety

5–9: mild anxiety

10–14: moderate anxiety

15–21: severe anxiety

Based on GAD-7 grading, if 10–14: moderate anxiety and above points are received, then the participant is going to be considered stressed. For the participant to be considered not anxious and not under any considerable stressful life event, they must receive points of 5-9: mild anxiety and below.

Dhira et. al. , (2021) conducted a study on university students from Bangladesh to test the validity and reliability of GAD-7 testing. Data from 677 university students was gathered using a convenience sample-based repeated cross-sectional survey approach. The exploratory and confirmatory factor analyses (EFA and CFA) were used to evaluate the factor structure of the GAD-7. The Patient Health Questionnaire Anxiety-Depression Scale (PHQ-ADS) and PHQ-9 were used to determine the GAD-7's convergent validity. The study's findings validated the support for excellent internal consistency as well as good convergent validity.

Testing 2: This is a schizophrenia testing section that will be conducted on the participants every two years (even years), including the first year (first month) of the study and at the end of the 10-year observation period. This schizophrenic testing section will be conducted on, likewise with Testing 1, both underage and adult participants.

The Brief Psychiatric Rating Scale (BPRS) test that can be seen in Table 2 will be used to determine whether an individual in our study has developed schizophrenia or not. It is a rating scale that a clinician or researcher may use to measure psychiatric symptoms such as depression, anxiety, hallucinations, psychosis, and unusual behavior. The scale used in the test is one of the oldest, most widely used scales to measure psychotic symptoms.

The severity of the participants' schizophrenia is scaled from the points they are graded for each term. Each term is scaled between 0-7 where 0 corresponds to “not assessed” and 7 to an “extremely severe” case. BPRS considers scale 3 as mild, 4 as moderate, and 5 as moderately severe.

Table 2. Brief Psychiatric Rating Score (BPRS) for all participants.

No	**Areas**	**Scoring**
1	Somatic Concern	0-7
2	Anxiety	0-7
3	Emotional Withdrawal	0-7
4	Conceptual Disorganization	0-7
5	Guilt Feelings	0-7
6	Tension	0-7
7	Mannerisms and Posturing	0-7
8	Grandiosity	0-7

9	Depressive Mood	0-7
10	Hostility	0-7
11	Suspiciousness	0-7
12	Hallucinatory Behavior	0-7
13	Motor Retardation	0-7
14	Uncooperativeness	0-7
15	Unusual Thought Content	0-7
16	Blunted Affect	0-7
17	Excitement	0-7
18	Disorientation	0-7

The maximum number of points an individual can receive from this testing is 126, and 0 as the minimum point. If an individual receives points 5, moderately severe, and above from all 18 terms, then the participant is going to be considered schizophrenic, as it results in minimum points of 90 and above. Any point below the point of 90 is going to be considered non-schizophrenic.

In the study of Hofmann et. al., (2022), the validity and reliability of BPRS were investigated. BPRS testing was compared with mini-ICF-APP (assessment of functioning and disability throughout the diagnostic spectrum) and the results were correlated. The author wrote that both tests were able to pinpoint common symptoms that were present at every point of the diagnostic range, impacting both the severity and a subset of symptoms unique to each diagnosis. Therefore, the study demonstrates that the BPRS test could be used in clinical work as it has high validity and reliability.

The final diagnosis with both testings will be conducted at the end of the 10-year observation and diagnosis period for the last time to determine whether they have developed schizophrenia disorder or not.

Data analysis

In this study for the data analysis section, we aim to identify the development of schizophrenia by using two-way ANOVA, based on income & race using six different groups. We expect to observe any statistically significant distinction between the six data groups. For the usage of two-way ANOVA, we have four assumptions. The criteria for using two-way ANOVA is as follows:

1. We assume that the observations from our six groups are normally distributed
2. We assume that the number of observations (tests) is the same for each group
3. We assume that the variances for each group are equal
4. We will conduct our observations (tests) in each group independently

Our three hypotheses are going to be proved by our two-way ANOVA.

Hypothesis #1: Participants in the low-income group will have a higher rate of developing schizophrenia.

Due to the 10-year test for stress levels of participants, we will observe a difference between low and high-income groups (regardless of race) according to p-value < 0.04. The potential reason for this difference is that low-income groups will be exposed to a higher occurrence of frequency of life stressors compared to high-income groups.

Hypothesis #2: The participants that develop schizophrenia disorder at the end of the ten-year observation period will be from the majority of the African-American x low-income group.

We are going to observe statistically highly significant differences between the White-High income group and the African American-Low income group according to p-value < 0.02. In other words, the development of schizophrenia will be significantly greater than White-High income group. A potential reason that might be the cause for the difference is that racial minority contributes to a higher rate of SCZ, most likely because of higher stressors and the longer duration of the stressors.

Hypothesis #3: There will be a minor difference in the average-income group and high-income group in developing SCZ

Our ANOVA result will show that for a p-value of 0.05, we will observe no significant difference in the average and high-income groups. The possible reason for this minor difference could be caused by both groups having to experience little life stressors.

On the whole, our two-way ANOVA will support race & income being correlated with each other. In our belief, a low level of income will trigger some specific genes such as the COMT Val/Met allele, which possibly causes schizophrenia to occur. On the other hand, African American participants who have a low income will face a higher percentage of developing schizophrenia than any other subgroup. We expect the reason for this to be that besides their extreme life stressor as having a low income, being a racial minority contributes to being a significant stressor. Moreover, African

Americans might face severe discrimination in the area they live, which we assume, might cause extreme stress. Thus, with a technically equal living environment and allele polymorphism, our study proposed to test race contribution to the occurrence of SCZ.

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