

# Same Sexual Orientation as a Potential Risk Factor for Severe Mental Illness

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## ABSTRACT

Considered as a minority, the LGBTQ (Lesbian, Gay, Bisexual, Transgender, and Queer) community including homosexual males is more prone to mental distress. Studies on prevalence stated that sexual orientation minorities are susceptible to inept mental health outcomes, and the rate of anxiety disorders, schizophrenia, and psychotic illness is twice higher in gay and bisexual men rather than in heterosexuals. Along with that, several investigations found similarity between structural features in the brain of schizophrenic patients and homosexual males. This study intends to analyze the male homosexuality as a potential risk factor for schizophrenia. According to MRI (magnetic resonance imaging) findings, brain structures similarity is found between schizophrenic patients and homosexual men specifically on the thalamic grey matter volume and cortical thickness of the brain. Both schizophrenic patients and homosexual males exhibit reduced grey matter volume in the thalamus region, meanwhile schizophrenic patients have lower grey matter volume in the left putamen and homosexual males showed higher left putamen grey matter volume compared to heterosexual individuals. The cortex of schizophrenic patients is thinner in left orbitofrontal, right parahippocampal, and superior temporal area, resembling to thinner cortex in the right lateral orbitofrontal regions and regions in the visual cortex of homosexual males. Based on the reviewed journals, male homosexuality can be a potential risk factor for schizophrenia considering their correlation in neurodevelopmental deviations. Nevertheless,

further investigations are needed regarding other factors and pathways causing such structural brain changes in both conditions.

**Keywords:** grey matter, homosexual, neurodevelopmental, schizophrenia

## INTRODUCTION

Schizophrenia is a chronic mental illness with a diverse genetic and neurobiological basis that impacts early brain neurodevelopment. It manifests as a mix of psychotic symptoms (such as hallucinations, delusions, and disorganization) as well as cognitive and motivational dysfunctions [1]. Schizophrenia spectrum disorders impact about 21 million people worldwide; it is predicted that seven people out of every 1000 will acquire schizophrenia throughout their lifetime [2]. Schizophrenia is more common in adolescence or early adulthood, and males are more likely to develop it between the ages of 15 and 35 while women between the ages of 25 and 35 [3]. The majority of nations with a high prevalence of schizophrenia are in Asia with the Southeast and East Asian having the highest number of persons suffering from schizophrenia [4]. Patients with schizophrenia exhibit aggressive behavior at a greater incidence than the overall population as they used physical force or had a hostile or spiritually damaging attitude or behavior, such as verbal or physical

aggressiveness, auto-aggression, or hostility against others [5].

A biological predisposition with multi-genetic risk factors and alterations in the neurotransmitter system, immunological influence factors, and psychosocial risk factors all contribute to the likelihood of developing schizophrenia [6]. Genetic risk factors, prenatal risk factors, and delivery difficulties may all raise the likelihood of the illness [7]. Aside from these early risk factors, traumatic events during childhood, particularly cannabis usage during adolescence, a sensitive period in brain development, may impact the disease's start, progression, and relapse risk [8]. If the time and total of the individual risk factors overlap, these can disrupt neural regeneration and contribute to schizophrenia, although the entire interplay of this multifactorial process is yet known [9]. A substantial decrease in the volume of the cerebellar vermis has been found in the schizophrenia group [10]. The intensity of hallucinations was shown to be linked with decreased grey matter volume in the left and right cerebellum, a similar finding in homosexuality [10,11].

Sexual orientation refers to a person's sexual attraction to either men or women, or both. Homosexuals, who are sexually attracted to the same sex, make up a small percentage of adults, less than 5% in most Western surveys [12]. According to a growing body of research, prenatal factors impacts on sexual gender orientation, neuroanatomical and other biological connections have been discovered [13]. Multiple studies conducted have shown differences between structures and activities of the brain in homosexuality compared to heterosexuality [14–16]. Sexual minority adolescents are also more vulnerable to child abuse [17], peer bullying [18], and other types of violence than their heterosexual counterparts, which further contribute to the manifestation of mental disorder like schizophrenia [19]. Even though homosexuality is gaining acceptance as stigma and prejudice are giving way to

equality and inclusion, it is still an on-going process full of struggles and obstacles [20].

As homosexuality and schizophrenia have been extensively researched, there are a few key points to consider in terms of causality and correlation. In this review, the authors aim to discuss homosexuality as a potential risk factor for schizophrenia.

## **MATERIALS & METHODS**

A literature review approach was utilized as the review method. The references in the literature originate from renowned search engines ScienceDirect, PubMed, and ResearchGate. Keywords including “homosexual men”, “schizophrenia”, “thalamic volume” and “grey matter” are searched. The inclusion criteria were risk factors of schizophrenia involving homosexuality. Preferred research should be at least ten years old from the year of publication, and no newer studies should contradict the information presented. 56 of the 62 publications evaluated were judged to be appropriate as references for this study. The examined information is interpreted and assembled into a single scientific literature review after it has been verified and reviewed for authenticity, integrity, and consistency.

## **RESULTS AND DISCUSSION**

### **The Pathogenesis of Schizophrenia**

Positive and negative symptoms, mood symptoms, disorganization symptoms, and cognitive deficits are all clinical characteristics of schizophrenia [21]. Positive and negative symptoms have been identified as features of schizophrenia that are unexpressed in normal peers, which include an additional different basic distortion of ideas and perception and loss of normal function and behavior [22]. Positive symptoms are extremely exaggerated beliefs, perceptions, or acts that demonstrate the person's inability to distinguish between what is and isn't reality, such as hallucinations and delusions [23]. On contrast, negative symptoms are defined

as a reduction or lack of typical behaviors and functions connected to motivation and interest, as well as verbal/emotional expression [24]. Furthermore, schizophrenia is characterized by cognitive impairment in attention, working memory, verbal learning and memory and executive skills [25].

Schizophrenia is a complex condition with multiple pathways dysregulated in its pathophysiology, with compelling evidence supporting roles for dopaminergic, glutamatergic, GABAergic, and cholinergic neurotransmitter systems and their interrelations in the pathophysiology of the disorder [26]. There are additional claims that schizophrenia is a neurodevelopmental condition based on anomalies in the brain structure, the absence of gliosis and the fact that patients' motor and cognitive deficits predate the illness onset [26]. One leading pathophysiology hypothesis of schizophrenia involves neurodevelopmental component [27]. Adolescence is a dynamic stage defined by substantial functional and neuroanatomical physiological changes, which is when many schizophrenia symptoms start or worsen [28]. The stages are marked by: 1) development of excitatory, inhibitory, and monoaminergic neurotransmitter systems, 2) stability of synapses to improve neuronal function efficiency, and 3) the start of integration between late and early developing brain regions [29]. As a result, genetic predisposition and environmental disruptions that cause alterations or imbalances in the timing of various developmental stages may contribute to the risk of schizophrenia [30].

The defective brain development trajectory appears to be set during gestation, long before clinical signs of the condition show in early adulthood [31]. Neuroanatomical alterations revealed by Positron Emission Tomography (PET) and Functional Magnetic Resonance Imaging (fMRI) studies show a decrease in grey matter volume, which is seen not just in the temporal lobe but also in the parietal lobes

[32,33]. Differences in the frontal lobes and hippocampus are also seen, which may contribute to the disease's cognitive and memory deficits [34]. In the schizophrenic brain, specific temporolimbic and prefrontal subregions appear to be disproportionately defective [35]. Most investigations have found that these anomalies are restricted to grey matter but not to a specific kind of cortex, i.e., both the allocortex, which includes the hippocampus, and the isocortex, including the superior temporal gyrus (STG), are impacted [36–38]. In schizophrenia, a lower thalamic volume may indicate a higher vulnerability to the illness, while grey matter volume reduction in the cerebrum, particularly in the frontal lobes, and lateral and third ventricular enlargement appear to be linked to prognosis [39]. Gyrification is also known to occur prenatally, implying that abnormalities in cortical folding are indicative of early developmental problems [40]. This support to the theory that schizophrenia is caused by poor neurodevelopment.

### **Male Homosexuality Brain Structure**

Sexual orientation is an attraction that can occur in one individual towards others with the opposite gender, the same gender, or both. This attraction can be sexual, physical or emotional. Heterosexuality is the term used to describe individuals which are sexually attracted to the opposite gender. On the other hand, homosexuality is used if the individuals are attracted to the same gender [41]. There are four parts of the human brain that are responsible for regulating sexual orientation. The first one is the hypothalamus, more specifically in the anterior and preoptic area. The second one is the dorsomedial and anterior part of the thalamus. The third and the fourth ones are the perirhinal parahippocampus and the septal area [42].

Homosexual males do not only differ with their heterosexual counterparts in the terms of sexual orientation. Some studies have found that there are some differences in the

brain morphological structure between homosexual and heterosexual males [15,43–45] but not so many if compared in females [16]. The thalamus of homosexual males which is also responsible for sexual orientation, appears to have less overall volume [43] and less grey matter volume than the heterosexual male [44]. There are also distinctive cortex thicknesses in the brain of homosexual males which are thinner in the right visual cortex, the right lateral orbitofrontal part of the brain, right part triangularis, inferior temporalis [45], and in the cuneus cortex [43]. Homosexual males are also found to have thicker precuneus and medial prefrontal cortex [15]. These differences are believed to be caused by hormonal imbalance in fetal development. Diminished androgenization or in this case referring to testosterone hormone can have impact on brain development, thus causing changes in the cortex thickness [15]. Despite of having these dissimilarity, the brain volume of both sexual orientations are still the same [45].

### **The Clinical Sign of Homosexual Men**

Recent studies have found some evidence stating that sexual orientation is linked to some biological conditions such as a certain protein that can be found in the mother of homosexual men [46]. Therefore, there are some biological or clinical changes that are different between homosexual men and heterosexual men besides from the brain morphology. Single nucleotide polymorphism (SNP) in SLITRK-5, SLITRK-6, and Thyrotropin Receptor (TSHR) genes are some of the clinical factors that are associated with homosexuality in men [47,48]. There are also some associations between homosexuality in men and Grave's disease, which homosexual men are more likely to suffer from Grave's disease [49] and linked with the mutation in TSHR and deviation in the inactivation of X chromosome [48].

### **The Association between Schizophrenia and Male Homosexuality**

Based on recent fieldworks, it has been known that factors contributing to the occurrence of schizophrenia are genetic and environmental factors. A population level study stated that a single environmental factor had higher potential as a risk factor for schizophrenia than any allele examined in genome-wide association studies [50]. Environmental stressors such as experience of discrimination, social isolation, childhood traumas, and substance abuse may lead to deviations in neurodevelopment especially when an individual is exposed to further environmental stresses in their adolescence which can stimulate the hypothalamic-pituitary-adrenal hyperactivity and as a result, raised the body cortisol levels damaging the developmentally compromised hippocampus [51]. In addition to the harmed hippocampus whose grey matter is a significant biomarker for various neurological and psychiatric disorders, consistent finding in MRI studies of schizophrenia showed reduced grey matter volume (GMV) in the thalamus region, which is similar to the brain morphology of homosexuality [15,52].

As a minority, the majority of LGBTQ community including homosexual individuals frequently come across psychosocial stressors from their surroundings, causing them to have high mental health distress [53]. A research by Bolton and Sareen proclaimed that sexual orientation minorities are vulnerable to poor mental health outcomes, and the rate of anxiety disorders, schizophrenia, and psychotic illness is twice higher in gay and bisexual men compared to those in heterosexuals [54]. Moreover, some studies discovered a significant effect of sexual orientation to the thalamus and precentral gyrus, showing lower thalamic GMV in homosexual males rather than in heterosexual males and higher GMV in the putamen of homosexual compared to heterosexual individuals [44]. Meanwhile the MRI in patients diagnosed with

schizophrenia demonstrates decreased GMV in thalamus and left putamen compared to healthy individuals, whose disruption resulted in psychotic symptoms of the patient. Corresponding to such case, another study identified that decreased GMV in the hypothalamus and left putamen affects the alteration of fronto-limbic activity linked with striatal novelty processing leading to delusions in schizophrenic patients [55].

Another important hallmark for studying brain-behavior relationships in various clinical conditions related to cognitive functions is cortical thickness [45]. At standard, schizophrenic patients had thinner left orbitofrontal, right parahippocampal, and superior temporal cortical thickness and thicker superior parietal and occipital lobe cortical thickness than healthy individuals [56]. As the disease progresses, excessive cortical thinning was found in extensive areas on cortical mantle mainly in bilateral of temporal cortex and left frontal area which lead to poor outcomes of the illness [56]. Whereas resembling images also found in the cortices of homosexual males in which they have thinner cortex than that of heterosexual males in the right lateral orbitofrontal regions and regions in the visual cortex [45]. This variation may be caused by sexual orientation as heterosexual males and homosexual males did not differ in brain volumes and yet the sexual orientation related differences shown in this study is similar to those in sex related differences, suggesting that brain morphology of homosexual males differ from heterosexual males in areas believed to have high density of androgen receptors [45].

## CONCLUSION

Male homosexuality as one of the conditions associated with structural changes of the brain has a few similarities in neuroimaging findings to those in schizophrenic patients, both suggested to be caused by multiple factors including deviations in neurodevelopmental processes. The MRI studies of schizophrenic patients

showed reduced grey matter volume in the thalamus and left putamen which is believed to be associated with psychotic symptoms in schizophrenia, similar to the brain imaging of homosexual males which showed lower thalamic grey matter volume and higher left putamen grey matter volume than in heterosexual males. Another feature showing resemblance in both conditions is the cortical thickness of the cortex, which in schizophrenic patients is found to be thinner in the left orbitofrontal, right parahippocampal, and superior temporal area and proceed to undergo excessive thinning as the disease progresses. Such condition is comparable to thinner cortex in the right lateral orbitofrontal regions and regions in the visual cortex of homosexual males compared to the cortical thickness in heterosexual males. In accordance with the correlation in the structural changes of the brain between these two conditions, morphological features of the brain in homosexual males can be a risk factor for developing schizophrenia.

## Declaration by Authors

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