ISSN No:-2456-2165

Diving Deeper into Schizophrenia and Bipolar

Kirandeesh Kaur
Michigan State University, USA

Abstract:- Studying Schizophrenia and Bipolar has been in the research study for many years. It is because of the loss of lifestyle and living that these disorders result in, scientists have always found it vital to develop a permanent cure to these diseases. This study analyzes the severity, genetic causes, and previous approaches to these disorders with an aim to further advance the study towards a potential cure. It weighs the pros and cons of the already established approaches to formulate a new approach to address the cause. The goal is to summarize the information pertaining to these disorders gathered from several researches and increase the amount of knowledge regarding the progress and allow future research to be conducted considering the vitality of the issue.

I. INTRODUCTION

Schizophrenia is a chronic brain disorder that causes delusions, hallucinations, disorganized speech, trouble with thinking and lack of motivation. When the disease is active, it can be seen in episodes where one cannot distinguish between real and unreal experiences. As with any illness the severity and frequency of symptoms may vary; however, in people with schizophrenia, the prevalence of severe psychiatric symptoms often decreases with age. Symptoms include positive symptoms(those abnormally present) like hallucinations, negative symptoms(those abnormally absent) like inability to express emotionally, and disorganised symptoms like disordered thinking and hinderances in logical reasoning. Bipolar disorder (formerly called manic-depressive illness or manic depression) is a mental disorder that causes unusual shifts in mood, energy, activity levels, concentration, and the ability to carry out day-to-day tasks. There are three types of bipolar disorder- Bipolar I Disorder(manic episodes lasting at least 7 days), Bipolar II Disorder(less severe than the full blown manic episodes in I) and Cyclothymic Disorder(depressive symptoms lasting for at least 2 years in adults). Schizophrenia affects 20 million people worldwide and is one of the 15 leading causes of disability worldwide, while Bipolar Disorder affects 45 million people worldwide. The patients diagnosed with these disorders have a lower life expectancy than those without.

Although there is no permanent cure for schizophrenia and bipolar, research is leading to newer and safer treatments. Experts are also identifying the causes of this disease by studying genetics, conducting behavioural research, and using high-quality imaging to monitor brain structure and function. This literature view would dwell more into the potential approaches that have been summarized as effective by previous researches to cure these disorders. This will further advance the requirement of research in those significant areas that have not been studied previously and substantiate the implementation of those with the required potential. In a society where mental health(especially these disorders) is considered a taboo, it is very crucial to conduct these studies to spread awareness about these diseases and treat them with a cure.

II. LITERATURE REVIEW

SEVERITY OF THE DISORDERS

As recorded in the Seidman and Kremen (2002) Study, in a setting where normal controls, people with schizophrenia and bipolar were studied, patients with schizophrenia were significantly more impaired than controls on seven of eight neuropsychological functions (all but verbal ability), and were significantly more impaired than bipolar patients on abstraction, perceptual-motor speed and vigilance, while bipolar patients were reported to be significantly impaired compared to controls on declarative verbal memory. The analysis of the same study indicated that patients with schizophrenia had a more sever impairment than patients with bipolar psychosis. Similar to these findings, were the results of a study conducted by Harvey and Wingo (2010) that reported on the cognitive and functional disability of the bipolar patients by classifying it less severe than schizophrenic afflicted. The study also necessitated the adoption of treatments aimed at cognitive enhancement in these disorders, especially schizophrenia. In a study by Thaker and Stevens (2013), fractional anisotropy[1] of white matter integrity was conducted and studied in schizophrenia and bipolar patients and both these groups showed lower fractional anisotropy than the comparison subjects in multiple white matter regions; and the differences were more prominent in schizophrenia. The study reported the whole-brain average for fractional anisotropy to be lower in the schizophrenia relatives than in the healthy comparison subjects. It also recorded the fractional anisotropy in the relatives of these groups which was came out to be lower than in the healthy comparison subjects in 10 regions and higher than in the schizophrenia patients in 11 regions. The study also established whole brain mean fractional anisotropy as a potential

[1] Fractional Anisotropy or FA is a measure of connectivity in the brain. It was used as a basis of this study because it was noted from previous researches that brain dysconnectivity is a universal problem in patients with these mental disorders. It can be obtained from Diffusion Tensor Imaging(DTI) dataset.

endophenotype[2] just like fractional anisotropy and classified certain regions in the brain with significant heritability of average fractional anisotropy in healthy comparison subjects (see Figure 1). It asked the researchers to discuss upon the measures required to combat the development of these illnesses by studying these areas in the brain prematurely.

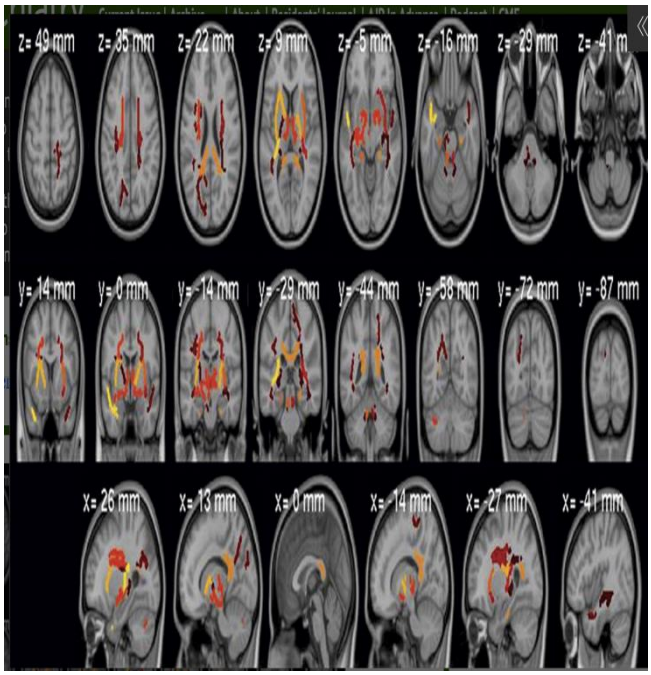

Figure 1. Regions With Significant Heritability of Average Fractional Anisotropy in Healthy Comparison Subjects

CAUSES OF THE DISORDERS

Bipolar and Schizophrenia are mainly classified as heritable and the major factor that is contributing as a hinderance to the cure of these is the complexity of psychosis in these disorders. The extensive research in these disorders has led to several potential endophenotypes but not in the case of Bipolar I. There are several theories that claim that genetic liability in these disorders has evolved as a secondary consequence of selection for human cognitive traits through evolution. Crespi and Summers (2006) evaluated this hypothesis and discovered significant evidence for positive selection-28 of the 76 genes demonstrated to mediate liability to schizophrenia, including *DISC1*, *DTNBP1*and *NRG1*, which exhibited especially strong and well-replicated functional and genetic links to this disorder. Strong evidence of non-neutral, accelerated evolution was found for *DISC1*, particularly for exon 2, the only coding region within the schizophrenia-associated haplotype. As notified by Craddock, Donovan and Owen(2005), the gene NRG1 was associated with high likelihood to cause both Schizophrenia and Bipolar as it was studied in a diverse setting involving people from Indonesia and UK. There is quite an impressive support from numerous studies that provide significant evidence implicating dysbindin- a gene that is highly prevalent in schizophrenic patients. The studies also nullify the impact of the same gene in bipolar patients except those more likely to have mood disorders. A recent Irish Study of High Density Schizophrenic families reported that Dysbindin risk haplotype is more likely to be inherited by schizophrenic patients with more prominent negative symptoms, raising the possibility that it might also refer to a sub-group of bipolar probands considering the overlap in clinical diagnosis of the two. Though the evidence studied in case of Schizophrenic setting of same diversity is highly conflicting, at least five independent datasets contribute evidence that variation at the *DAOA*[3]/*G30* locus on chromosome 13q influences susceptibility to bipolar disorder, including three US family samples, a German case-control sample, and a large UK case-control sample. This has also been established as the best-supported locus for bipolar disorder. The finding also implied the importance of variations in the probands with respect to proportion of schizophrenic cases that have endured mood disorders since they carry the risk of inheriting the variation, in the replicability of genetic association studies. The Edinburgh group identified another gene Disrupted In Schizophrenia I or *DISC1* with no linkage to schizophrenia in their sample but primarily to bipolar. The gene *COMT* has been intensively studied because of its key role in dopamine catabolism. Most studies have focused upon a valine to methionine change at codon 158 of the brain-predominant membrane-bound form of *COMT* (*MB-COMT*) and codon 108 of the soluble form (*S-COMT)* which confers higher activity and thermal stability to both forms of *COMT* and has been fairly consistently associated with reduced performance in tests of frontal lobe function- majorly leading to psychosis. However, there have been contrary results that state that it might not be the gene *COMT* but genetic variation in this region or locus(probability of some other gene) influencing susceptibility across the psychotic spectrum. BDNF or Brain Derived Neurotropic Factor is a gene that has been traced to have linkages with bipolar disorder or schizophrenic probands with high vulnerability to mood disorders. Apart from magnificently contributing towards these disorders, these findings leave important implications for major psychosis because they suggest an overlap in the biological basis of these disorders which have been previously established as distinct entities by clinical diagnosis.

[2] Assessing endophenotypes has an advantage since they identify aberrant genetic effects even when such effects are not discernable at the clinical level.5 In contrast to the complex clinical phenomenon that define psychotic disorders such as schizophrenia and bipolar, endophenotypes represent neuronal deficits nearer to the genetic effects.

[3] *DAO* is expressed in the human brain, where it oxidizes D-serine, a potent activator of NMDA glutamate receptor. Co-incubation of *G72* and *DAO in vitro* revealed a *functional* interaction with *G72* enhancing the activity of *DAO*. Consequently, *G72* has had been named D-amino-acid oxidase activator (*DAOA*).

ISSN No:-2456-2165

Apart from the several genetic causes that have been debated upon by scientists, schizophrenia might also develop as a result of influence of several social and environmental factors. As a study by Patel and Cherian in 2014 reports, several environmental and social stressors like childhood trauma, minority ethnicity, residence in an urban area, social isolation, discrimination or economic adversity, may predispose individuals toward delusional or paranoid thinking and hence contribute to these illnesses. A study conducted by World Health Organisation in 10 countries found that the disorders occurred with comparable frequencies across the various geographically defined populations establishing a possible linkage between geography of location and their development and demographics a factor for further scientific considerations. Abnormality at dopamine receptors especially D2 has also been recognised as a potential contributor to the development of psychosis by several research studies.

PREVIOUS APPROACHES

A study conducted in Japan in 2020 analysed the post mortem white matter of a schizophrenic brain and compared it with a sample control, keeping the other influential factors of age, sex, region in consideration. The research concluded lesser white matter in schizophrenic probands due to lack of a critical lipid, sphingolipid, that helps in the preparation of myelin. The presence of myelin is extremely essential for the transfer of nerve impulses, the damage of which may result in several neurological issues. Apart from this post mortem study that identified the loss of sphingolipid, a study conducted by Medical Research Council London Institute of Medical Sciences in 2020 studied the cognitive aspect of the disorder and using dysfunctional synapses as a basis, recorded PET brain scans using tracers in 18 schizophrenic and 18 normal controls. The injected tracer bound specifically to a protein found in synapses called SV2A (synaptic vesicle glycoprotein 2A), which had been shown in animal and post-mortem studies to be a good marker of the density of synaptic nerve endings in the brain. They found that levels of the synaptic protein SV2A were lower in the front parts of the brain - regions of the brain involved in planning and cognitive ability - in people with schizophrenia(see Figure 2). This research shifted the focus of science towards targeting the protein SV2A while evaluating the synaptic losses in the disorder.

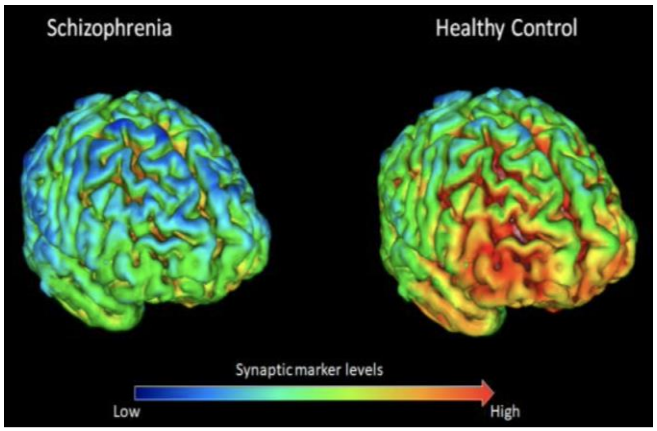

Figure 2. The figure depicts the PET brain scan of a schizophrenic proband and a normal control (without schizophrenia). The previous studies had employed methods of postmortem brain analysis, animal, and cell models in the lab to elucidate the cause of the disorder. The figure shows that healthy volunteers have on average higher synapse marker protein than participants with schizophrenia.

In a newly published study by Neuroscience Research Australia (NeuRA) in 2020, researchers discovered some abnormal activity happening in the immune cells that influenced the dopamine activity of the brain. It is the overactivity of the immune cells of the brain which caused the destruction of the dopamine producing region of the brain, hallucinations, and delusions in people with schizophrenia. In the same study, it was found that macrophages or immune cells of the brain were higher in number in suspects and probands which could explain the occurrence of major positive symptoms of the disease. The research encouraged treatments modulating neuroinflammation in the brain, especially in the dopamine region to curb the major symptoms developed because of overactivity and prevent immune cells from damaging the area.

Stem cells were extracted from the skin of bipolar patients for a study in 2015 and they were coaxed to grow into neurons. It was discovered that these neurons had higher excitability than normal neurons, but they calmed down on exposure to lithium. In a study conducted by Evans in 2015, it was identified following the dietary plan of bipolar patients and normal controls that there is comparatively less consumption of plasma linoleic acid (LA) by bipolar patients. Though there were other types of reduced plasma levels like PHQ9, LFQ and SF12-MH that were identified alongside highly reduced levels of LA, the significance of their contribution to the disorder was extremely minimal. In another study conducted in 2017, a significant single nucleotide polymorphism-based genetic correlation was discovered between Attention Deficit Hyperactivity Disorder (ADHD) and Bipolar Disorder that suggested possibility of treatment overlap between the two below the age of 21. Researchers who performed Magnetic Resonance Imaging (MRI) on the brains of people with bipolar disorder in 2015 found abnormal signals in certain parts of the brain that suggested abnormal cellular function in those cells that helped coordinate voluntary movement. The study also recorded the role of mitochondria in those elevated signals with evidence that correlated the functionality of mitochondria-patterns of energy production and use- with psychosis. In majority of the research that has been conducted for bipolar disorder, abnormality in the vertical hippocampus area- which is responsible for mood and anxiety- has been recorded and constant emphasis for cure has been generated over this region, especially in case of bipolar disorder with prominent mood dysfunction.

III. CONCLUSIONS

There have been several attempts to trace the cause of these disorders- genetic and otherwise (environmental and other stresses) but all have concluded to enhancing the complexity of diagnosis of these disorders due to the prevalent genetic overlap between them. The complexity can be explained by the selection of subsequent genes during evolution as also established by previous research along with consideration of demographics-an influential factor in the diagnosis of the disorders. The previous research has also focused upon using MRI, PET brain scans to obtain areas of the brain most affected by the disorders- vertical hippocampus, dopamine producing region, less white matter or myelin (in case of schizophrenia) and identifying vital cellular components like plasma linoleic acid, and healthy mitochondria (in case of bipolar). One potential approach can be using the concept of regenerative medicine-therapeutic stem cells or neural stem cells (NSCs) to facilitate neural repair and secretion of required growth factors in human brain. The cells can be generated in vitro using concepts of biotechnology like gene therapy- with the accurate genetic constitution as opposed to those found in the probands- and culture medium containing the critical lipids(sphingolipids) and plasma linoleic acid (LA)- variable from disorder to disorder. Since abnormality in dopamine receptors or dopamine producing region has also been reported, there can be a possible injection of allosteric modulators for these receptors that change their shape to enhance the production of dopamine by broadening the spectrum of stimuli. Though the research has been successful at obtaining the areas most affected by the disorders and tracing their genetic cause to some extent, we still not have obtained a permanent cure for these disorders or attempts been made to evaluate further upon the critical findings of the previous studies.

REFERENCES

[1]. Annie.Hauser. “After Searching 12 Years for Bipolar Disorder’s Cause, a Team Concludes It Has Many.” *University of Michigan*, 27 Jan. 2020, labblog.uofmhealth.org/body-work/after-searching-12-years-for-bipolar-disorders-cause-a-team-concludes-it-has-many.

[2]. Buckley, Peter F. “Update on the Etiology and Treatment of Schizophrenia and Bipolar Disorder.” *CNS Spectrums*, vol. 13, no. S1, 2008, pp. 1–12. *Crossref*, doi:10.1017/s1092852900028212.

[3]. Cardno, Alastair G., et al. “A Twin Study of Genetic Relationships Between Psychotic Symptoms.” *American Journal of Psychiatry*, vol. 159, no. 4, 2002, pp. 539–45. *Crossref*, doi:10.1176/appi.ajp.159.4.539.

[4]. Craddock, N. “Genes for Schizophrenia and Bipolar Disorder? Implications for Psychiatric Nosology.” *Schizophrenia Bulletin*, vol. 32, no. 1, 2005, pp. 9–16. *Crossref*, doi:10.1093/schbul/sbj033.

[5]. Esaki, Kayoko, et al. “Evidence for Altered Metabolism of Sphingosine-1-Phosphate in the Corpus Callosum of Patients with Schizophrenia.” *Schizophrenia Bulletin*, vol. 46, no. 5, 2020, pp. 1172–81. *Crossref*, doi:10.1093/schbul/sbaa052.

[6]. Evans, Simon J., et al. “Plasma Linoleic Acid Partially Mediates the Association of Bipolar Disorder on Self-Reported Mental Health Scales.” *Journal of Psychiatric Research*, vol. 68, 2015, pp. 61–67. *Crossref*, doi:10.1016/j.jpsychires.2015.06.001.

[7]. Harvey, Philip D., et al. “Cognition and Disability in Bipolar Disorder: Lessons from Schizophrenia Research.” *Bipolar Disorders*, vol. 12, no. 4, 2010, pp. 364–75. *Crossref*, doi:10.1111/j.1399-5618.2010.00831.x.

[8]. “New Study Finds Evidence for Reduced Brain Connections in Schizophrenia.” *EurekAlert!*, 14 Jan. 2020, www.eurekalert.org/pub_releases/2020-01/urai-nsf011320.php

[9]. *NIMH » Bipolar Disorder*. www.nimh.nih.gov/health/topics/bipolar-disorder.

[10]. “Researchers Open the Door to New Schizophrenia Treatment.” *NeuRA*, 30 Sept. 2020, www.neura.edu.au/news/researchers-open-the-door-to-new-schizophrenia-treatment.

[11]. Seidman, Larry J., et al. “A Comparative Profile Analysis of Neuropsychological Functioning in Patients with Schizophrenia and Bipolar Psychoses.” *Schizophrenia Research*, vol. 53, no. 1–2, 2002, pp. 31–44. *Crossref*, doi:10.1016/s0920-9964(01)00162-1.

[12]. *Web Starter Kit*. www.psychiatry.org/patients-families/schizophrenia/what-is-schizophrenia. Accessed 8 July 2021.