Chapter

Aetiology and Risk Factors of Schizophrenia

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Abstract

Schizophrenia is a disorder that begins at a young age and causes severe mortality and morbidity. The aetiology and pathophysiology of schizophrenia are still not known precisely. It is a very complex syndrome, and it is thought that more than one aetiological factor plays a role in its emergence. Genetics, epigenetics, and environmental and gene-environment interaction play a role in the aetiology of the disease. In addition, post-mortem neuropathological findings, neuroimaging findings, neurochemical studies, neuropsychological study results, and neurophysiological study results shed light on the mechanisms that cause the disease to occur. This chapter will provide an overview of the diathesis-stress, neurodegeneration, and neurodevelopmental models and summarise the work done so far in many areas.

Keywords: schizophrenia, genetics, neuroimaging, neuropathology, neurophysiology, neuropsychology, neurodevelopment, neurodegeneration

1. Introduction

In its broadest terms, psychotic disorders describe mental illnesses which involve disruption in perception, thought, and behaviour. The term psychosis describes the condition in which the mind cannot distinguish between what is real and what is unreal. Although it covers many psychopathological conditions in which the aetiology, symptoms, and course of the disease are very different, the prototype of this group of disorders is schizophrenia.

The aetiology and pathophysiology of schizophrenia are not known precisely. It is a 'syndrome' with complex symptoms, and it is thought that more than one aetiological factor plays a role in its emergence. According to the generally accepted assumption, brain development is disrupted due to genetic or environmental factors in the early life stages. This disruption creates a predisposition to the disease for the person, and symptoms of schizophrenia develop in later periods of life when the person encounters a stressful environmental effect [1]. It has been reported that subtle developmental abnormalities in the brain cause the onset of the disease before emerging clinical symptoms [2].

2. Hereditary causes

Schizophrenia is known to be a highly heritable disorder. Information on this subject is obtained from twin studies, family history, and studies with adopted persons [3–5].

2.1 Family studies

Family studies conducted in the early twentieth century showed that the rate of schizophrenia in relatives of schizophrenic patients was higher than in the general population. However, these early studies were criticised for many aspects of their study design and some other technical problems [6]. Recent studies have confirmed that the risk is higher among siblings and children than among parents and found that disease risks are not significantly different from those in older studies. As a result, family studies have revealed the high familial loading of schizophrenia, with siblings demonstrating an almost 10-fold increased risk of developing schizophrenia. This rate is greater than the increased risk reported for any other environmental factor [7]. In 2010, a Danish national register-based cohort study examined the risk of severe mental disorders. The risk of schizophrenia in the offspring of parents both affected by schizophrenia was found to be 27.3% [8].

2.2 Twin studies

Twins share many aspects of their environment. If we assume monozygotic (MZ) and dizygotic (DZ) twins share their environments to nearly an equal extent, then a higher concordance in MZ twins implies the disorder is, at least partly, genetic. A concordance of less than 100 per cent in MZ twins indicates that environmental factors are also at play [7]. Twin studies played an important role in understanding the genetic aetiology of schizophrenia. Twin studies have provided evidence that both genetic and environmental factors contribute to schizophrenia (SZ) risk. Heritability estimates of SZ in twin samples have varied methodologically. Studies between 1995 and 2000 from Europe and Japan have confirmed earlier findings. They yielded concordance rates of 41–65% in monozygotic (MZ) pairs and 0–28% in dizygotic (DZ) pairs, and heritability estimates of approximately 80–85%. Studies of discordant MZ pairs provide further insights into non-inherited factors contributing to this disorder's multifactorial aetiology [9]. Another study found that the estimated 79% heritability of SZ is congruent with previous reports. The low concordance rate of 33% in monozygotic twins demonstrates that illness vulnerability is not solely indicated by genetic factors [10]. Sullivan et al. [11] calculated heritability estimates in liability and shared and individual-specific environmental effects from the pooled twin data. They found evidence for substantial additive genetic effects. Results showed that heritability in liability to schizophrenia was 81%. Common or shared environmental influences on liability to schizophrenia were 11%. They concluded that the meta-analytic results from 12 published twin studies of schizophrenia are consistent with a view of schizophrenia as a complex trait that results from genetic and environmental aetiological influences [11].

2.3 Adoption studies

The observation that schizophrenia is more commonly observed among the relatives of individuals with schizophrenia than in the general population does not indicate the mechanism that produces such familiality occurs. Results from studies of

adoptees with schizophrenia and their biological and adoptive relatives indicate that genetic factors play a highly significant role in the risk for schizophrenia. Although adoption studies have convincingly demonstrated an important role for genetic factors in schizophrenia, the necessity and specificity of such factors, their precise identity, and their interaction with environmental influences remain unknown [12].

3. Genetic studies

Many genes have been reported to be associated with schizophrenia, and these genetic features do not comply with Mendelian inheritance [13]. The first genetic studies were conducted as linkage studies, association studies, and chromosomal anomalies. As a result of linkage studies, repeated studies were carried out on chromosomes 1, 5, 8, 10, 13, and 22, and significant relationships have been demonstrated [14–19]. In chromosome anomaly studies, deletion in the 22q11 region of the 22nd chromosome and balanced translocations between the 1q42.1 and 11q14.3 regions of chromosomes 1 and 11 have been shown to be associated with schizophrenia [20]. The early studies were not fruitful. However, new technological developments have enabled the development of research methods.

3.1 Genome-wide association studies (GWAS)

GWA studies examine common alleles throughout the genome for association with a particular trait. Single-nucleotide polymorphisms (SNPs) have demonstrated that many SNPs correlate highly with neighbouring SNPs. The earliest GWA studies were not fruitful. Later studies showed dopamine receptor D2, glutamatergic neurotransmission and synaptic plasticity (GRM3, GRIN2A, SRR, GRIA1), and calcium signalling (CACNA1C, CACNB2, and CACNA1I) genes are associated with schizophrenia. Genome-wide association studies demonstrated a relationship between MHC Class 1 proteins and schizophrenia and prenatal infections [21, 22]. Supporting this finding, Aberg et al. [23] demonstrated that the major histocompatibility complex region showed a 3.7-fold overall enrichment of replication values. The replicated SNPs in TCF4, NOTCH4, POM121L2, CNNM2, AS3MT, and NT5C2 are among the most robust findings. They found that the most significant pathways involved neuronal function (axonal guidance, neuronal systems, and L1 cell adhesion molecule interaction) and the immune system (antigen processing, cell adhesion molecules relevant to T cells, and translocation to immunological synapse) [23]. In the latest and largest GWAS of schizophrenia, adding all SNPs accounts for only 7% of trait liability, which indicates additive models do not explain the risk of schizophrenia [24, 25].

3.2 Copy number variants

Copy number variants (CNVs) are deletions or duplications of chromosomes. The earliest report of a rare CNV associated with an increased risk of schizophrenia was a deletion of about 2.5 Mb on chromosome 22q11.2, which causes a congenital disorder described variably as DiGeorge syndrome. Deletion in the 22q11 region of the 22nd chromosome and balanced translocations between the 1q42.1 and 11q14.3 regions of chromosomes 1 and 11 have been shown to be associated with schizophrenia. These regions are found to be associated with the Disrupted-in-Schizophrenia-1 (DISC1) protein, which is related to disturbances in neural function and multiple disease-risk

pathways [20]. Rujescu et al. [26] showed that it was the CNVs that intersected exons that increased the risk of schizophrenia. NRXN1 has been shown to be a candidate gene. NRXN1 gene codes for a cell adhesion molecule, neurexin-1. Neurexin-1 mediates interactions between pre- and postsynaptic structures. It is critical for forming, maintaining, and releasing neurotransmitters at synapses [26]. CNVs also increase the risk of developing intellectual deficits, developmental delay, autism spectrum disorders, and various congenital malformations and somatic diseases. To date schizophrenia-related CNVs found are 1q21.1 del, 1q21.1 dup, NRXN1 exonic del on chromosome 2, 3q29 del, 7q11.23 dup, 15q11.2 del, Angelman/Prader-Willi dup on chromosome 15, 15q13.3 del, 16p13.11 dup, 16p12.1 del, 16p11.2 dup, 22q11.2 del [27, 28]. The 15q11.2(BP1-BP2) deletion affects brain structure in a pattern consistent with both observed during first-episode psychosis in schizophrenia [29]. 16p11.2 duplications, 22q11.2 deletions, and 3q29 deletions are found to be related to schizophrenia. Findings suggest that multiple lines of genomic inquiry—genome-wide screens for CNVs, common variation, and exonic variation—converge on similar sets of pathways and/or genes [30]. Kirov et al. showed that 3q29, 15q11.2, 15q13.3, and 16p11.2 defects result in NMDAR postsynaptic signalling and, possibly, ARC complexes, which is an intracellular part of the synapse and plays a significant role in the pathogenesis of schizophrenia [31]. Pocklington et al. [32] showed for the first time that CNVs from individuals with schizophrenia are enriched for genes involved in GABAergic neurotransmission. Previous findings of CNV enrichment among genes involved in glutamatergic signalling are independently replicated and greatly extended [32].

3.3 Epigenetic mechanisms

It is increasingly recognised that epigenetic modifications play a role in the aetiology and pathophysiology of schizophrenia. Recent findings suggest that specific schizophrenia risk loci may influence stochastic variation in gene expression through epigenetic processes, highlighting the complex interplay between genetic and epigenetic control of neurodevelopmental trajectories. In addition, a significant part of the epigenetic changes in schizophrenia can be acquired through environmental factors, and these changes can affect brain functions [33]. Genome-scale mapping of DNA methylation, histone modifications and variants, and chromosomal loopings for promoter-enhancer interactions and other epigenetic determinants provide important clues about the dysregulated expression of synaptic and metabolic genes in schizophrenia. Epigenetic studies can also display potential links to the underlying genetic risk and environmental exposures [34]. In another study, researchers proposed that epigenetic factors and regulatory non-coding RNAs mediate the effects of environmental stressors [35]. A recent study showed that histone modifications play important roles in transcriptional regulation of the genes crucial for oligodendrocyte differentiation and myelination, specifically, histone acetylation and methylation [36].

4. Environmental factors

A relationship between the development of schizophrenia and exposure to influenza virus has been shown with data based on antibody measurements [37]. The relationship between *Toxoplasma gondii* and schizophrenia has also been demonstrated by immunoglobulin measurements. It has been shown that high maternal

IL8 levels in the second and third trimesters increase the risk of schizophrenia by twofold [38]. In another study, a relationship was found between high maternal TNF-alpha levels and the development of schizophrenia [39]. It has been shown that there is a relationship between anaemia during pregnancy, malnutrition, hyperhomocysteinemia resulting from folic acid deficiency, vitamins A and D deficiency, and increased docosahexaenoic acid levels and the child's risk of developing schizophrenia in the future [40–43]. These deficiencies or excess conditions have been shown to affect gene expressions, silencing some genes, disrupting repair mechanisms, inappropriately activating some genes, and disrupting myelination [44]. Malaspina et al. showed a relationship between advanced paternal age and schizophrenia, which was later supported by other studies [45–48]. There have been many studies showing that marijuana use is associated with schizophrenia [49]. Cannabis use, especially at the age of 18 or younger, increases the risk of developing schizophrenia [50]. Studies investigating the relationship between immigration and schizophrenia have shown that the risk of schizophrenia increases in first- and second-generation immigrants. It has been stated that the possible cause of this situation is social defeat and social exclusion and that the experience of social defeat in genetically predisposed people increases the sensitivity of the mesolimbic dopaminergic pathway, making it easier for the person to develop a psychotic disorder [51, 52]. A relationship has been found between socioeconomic level and the development of schizophrenia. Two theories have been put forward to explain this relationship: (i) social cause theory and (ii) social shift theory. According to the social cause theory, being born into a family with a low socioeconomic level increases the likelihood of exposure to environmental stresses and causes the development of schizophrenia in the predisposed individual. According to the social shift theory, the person falls to a lower socioeconomic level due to the disease. Studies on this subject have yielded contradictory results, and the person losing the social status to which he/she belongs is the result of the interaction of many factors [53–59].

5. Gene-environment interaction

The gene-environment relationship is explained as sensitivity to environmental factors determined by genes and gene expression affected by environmental conditions. This situation has been defined as the stress susceptibility model (diathesis-stress). According to this model, genetic and environmental conditions predispose the individual to the development of psychosis, with a negative and additive effect on brain development, during a critical period or more than one period of brain development [37, 60–62]. Exposure to maltreatment, especially in early life, and repetition of this exposure create a predisposition to psychosis, possibly by causing changes in dopaminergic pathways originating from the mesencephalon and projecting to higher regions [63].

6. Physiopathology

6.1 Neuropathology

Neuropathology studies have shown that neurons and glial cells exhibit different characteristics in schizophrenia cases compared to normal individuals. Although the

changes were seen especially in the hippocampus and prefrontal cortex (PFC), they are not specific to these regions [64]. The first of the most consistent findings is the widespread reduction in decreased neuronal size and dendritic and axonal branching [65, 66]. The network system formed by axons, dendrites, and synaptic gaps is called 'neuropil'. The decrease in neuropils may explain the reduced brain volume at the macroscopic level and is called the 'decreased neuropil hypothesis'. In individuals with schizophrenia, the number of neurons decreases over time, and structural changes occur in dendrites and axons [67]. It has been reported that dendritic spine reduction in cortical neurons disrupts and damages information-processing processes [68, 69]. Synaptic changes observed in schizophrenia are generally decreasing, and this has been seen especially in glutamatergic neurons [65]. It has been shown that there is a selective loss of pyramidal neurons in the PFC [70]. Additionally, an increase in white matter density has been detected in the PFC, and it has been stated that this is due to the inhibition of neuronal migration during development [71–73]. In histopathological examinations of the Superior Temporal gyrus (Heschl's gyrus) and medial temporal lobe, it was observed that the pyramidal neurons in the cortical third layer were reduced in number, and the organisation of these neurons was impaired [74, 75]. It has been observed that the total number of neurons decreases in the thalamus, another most studied region, and as an indicator of this, there is a decrease in the amount of grey matter, but there is no change in cell density [76–78]. A decrease in the number of neurons and neuropils was detected, especially in the pulvinar and mediodorsal nuclei [64]. Although the number of neurons decreased in the basal ganglia, no change in neuron density was detected [79]. Immunohistochemical markers have shown a decrease in membrane density in the pre-synaptic axon terminal in the medial temporal lobe, frontal cortex, visual cortex, and cingulate cortex in schizophrenia patients [80–82]. In addition, SNAP-25, synapsin, and synaptophysin, proteins belonging to the synaptic structure, are found in the hippocampus and frontal cortex and were also found to be decreased [83].

Immunohistochemical methods could identify cortical interneurons, and it was shown that these neurons decrease by more than 10% in schizophrenia patients [84, 85]. Interneurons are marked by parvalbumin and somatostatin, and they are found in decreased amounts in the hippocampus and the parahippocampal gyrus in schizophrenia patients. Parvalbumin interneurons work in association with NMDA receptors [86, 87]. In patients with schizophrenia, neurons containing gamma amino butyric acid (GABA) and glutamic acid decarboxylase (GAD) are generally reduced compared to healthy individuals. This results in disinhibited excitatory neurons, leading to defective activation. GABA neurons have important functions, especially in the PFC, and play a critical role during executive functions. The decrease in these neurons leads to the impairment of cognitive functions [88]. Microglia cells are the source of the major pro-inflammatory cytokines of IL-6 and TNF-alpha. Increased microglia cell density has been detected in the PFC, auditory cortex, ACC, and mediodorsal thalamus in schizophrenia patients and associated with suicide in schizophrenia [89].

6.2 Neurochemical changes

The Proton Magnetic Spectroscopy method can noninvasively measure people's biochemical structures and metabolic activity states. This method has been used to measure N-acetyl aspartate (NAA), choline, creatinine, glutamine/glutamate (Glx), and myoinositol-1 molecules *in vivo* in schizophrenia patients. NAA is an indicator of neuron functionality, which is well-being at the cellular level, and Cho is an indicator

of myelination [90]. Creatine (Cre) is a metabolic output whose value is relatively constant. Although the function of myo-inositol is not known, it is thought to be associated with glial cells [91]. In individuals with high genetic load for schizophrenia, NAA, Cho, and Cre were detected at low levels in the thalamus, suggesting that neuronal dysfunction in the thalamus has a role and is associated with the development of schizophrenia. It has been found that right and left mPFC NAA and left mPFC Cho levels are low in schizophrenia patients. In schizophrenia patients, NAA/Cre and NAA/Cho levels were found to be lower in the hippocampus and DLPFC compared to controls. Additionally, NAA/Cre and NAA/Cho levels were lower in the temporal cortex and thalamus in schizophrenia patients than in healthy controls [92].

6.2.1 Dopamine hypothesis

In the dopaminergic pathway, which projects from the Ventral Tegmental Area (VTA) to the limbic system, hyperactivity is defined as the oldest and most widely accepted hypothesis of the mechanism leading to psychosis. Dopamine 1R (D1R) receptors are more commonly found in the Frontal Cortex. However, this subtype, unlike D2R, shows hypoactivity and negative symptoms of schizophrenia are partially attributed to the hypoactivity of this receptor (hypofrontality) [93, 94].

6.2.2 Glutamate hypothesis

Glutamate is a neurotransmitter with both metabotropic and ionotropic receptors. The type emphasised in the pathogenesis of schizophrenia is NMDA receptors. Due to hypoactivity in NMDA receptors, since GABA neurons serving as interneurons cannot be stimulated, glutamate neurons projecting to the VTA cannot be inhibited. As a result, there is an increase in activity in the dopaminergic pathways located in the VTA and extending to the limbic system [95, 96].

6.2.3 Gamma-aminobutyric acid (GABA) hypothesis

Post-mortem studies consistently show decreased GABA levels in the PFC. An increase in the number of GABA receptors may also be observed. It has been stated that this situation may occur in response to the decrease in GABA levels. It has been suggested that GABAergic anomalies may explain working memory disorders by causing neural synchrony changes in schizophrenia patients [97, 98].

6.2.4 Serotonin hypothesis

It is a hypothesis based on the antagonism of 5HT2A receptors. The underlying mechanism of psychotic states seen especially in diseases such as Parkinson's or Alzheimer's diseases is pointed out. It has been stated that hyperactivity of 5HT2A receptors has an excitatory effect on glutamatergic neurons, and increased dopaminergic neuron activation in the VTA ultimately leads to increased DA activity in the mesolimbic pathway [99].

6.2.5 Norepinephrine hypothesis

This theory is based on various evidences revealing the anatomical and physiological properties of the locus coeruleus-norepinephrine (LC-NE) system and its

involvement in brain function and cognition. Theory suggests that the phenomenology of schizophrenia, particularly cognitive symptoms, can be explained by an abnormal interaction between genetic predisposition and stress-induced LC-NE dysfunction. This dysfunction leads to an imbalance between modes of LC activity, dysfunctional regulation of brain network integration and neural acquisition, and deficits in cognitive functions [100, 101]. Catecholamine-producing midbrain and brainstem nuclei are densely connected to the PFC and dACC and contribute to cognitive control processes. It has been shown that the VTA and substantia nigra, as well as the LC, are abnormal during cognitive control in patients with schizophrenia [102].

6.2.6 Acetylcholine hypothesis

A well-known characteristic of patients with schizophrenia is that they smoke excessive amounts of cigarettes. This behaviour of patients is interpreted as a method of self-treatment to improve the positive, negative, and cognitive symptoms of schizophrenia [103]. Acetylcholine in the CNS has three sources: (i) basal forebrain nuclei, (ii) pedunculopontine tegmental nucleus and laterodorsal tegmental nucleus, and (iii) giant cholinergic interneurons in the caudate-putamen and nucleus accumbens. The cholinergic nuclei innervate the hippocampus, cortical, and subcortical regions. Acetylcholine plays a regulatory role in the dopamine, glutamate, GABA, and serotonin systems. It has also been shown to have a mutual regulatory relationship with inflammatory processes [104]. The muscarinic receptors that play a role in the aetiology of schizophrenia are thought to be M1, M4, and M5 receptors. It has been shown that M1 receptors are associated with cognitive disorders, M4 receptors with positive symptoms, and M5 receptors with prepulse inhibition. The nicotinic $\alpha4\beta2$ receptor is associated with attention and memory functions, and the nicotinic $\alpha7$ nACh receptor is associated with P50 sensory transmission deficits [105–107].

7. Neuroimaging findings

7.1 Structural neuroimaging

7.1.1 Computed tomography (CT)

CT shows more significant volume reduction than expected for age in the frontal lobes, temporal lobes, caudate head, and thalamus in patients with schizophrenia. This volume decrease is progressive throughout the disease. Ventriculomegaly and cortical atrophy are also more common in patients with schizophrenia than controls. Ventriculomegaly is associated with age, impaired cognitive function, decreased response to treatment, and negative symptoms [108, 109].

7.1.2 Magnetic resonance imaging (MRI)

MRI provides high-resolution images. Increased cerebrospinal fluid (CSF) and decreased grey and white matter volume have been detected in schizophrenia. Volume reductions in the frontal lobe, temporal lobe, hippocampus, and parahippocampus have been reported, all associated with cognitive impairment [110, 111]. Auditory hallucinations have been reported to be associated with loss of superior temporal gyrus volume, and negative symptoms have been reported to be associated with loss

of prefrontal lobe volume [112–114]. Many studies have shown that volume reduction in schizophrenia patients is in thalamocortical connections and prefrontal cortex grey matter [115]. Regions with decreased grey matter volume in voxel base morphometry are the frontal gyri, the temporal gyri, the parahippocampal gyri, the posterior and anterior insulae, dorsal anterior cingulate cortex (dACC), posterior cingulate cortex (PCC), bilateral angular and supramarginal gyri, bilateral thalamus, and caudate nuclei [116–118]. Although the large cava septum pellucidum is more common in patients with schizophrenia, it is not considered a causal factor [119]. However, this can be considered evidence of abnormal neurodevelopmental processes that contribute to the development of schizophrenia [120]. Histologically, this decrease in grey matter is accompanied by a decrease in dendritic and synaptic density, which leads to communication disturbances along neural circuits [69].

7.2 Functional neuroimaging

7.2.1 Single-photon emission computed tomography and positron emission tomography

Single-photon emission computed tomography (SPECT) and positron emission tomography (PET) are radionuclide neuroimaging techniques.

PET is based on the idea that people with schizophrenia have a different pattern of cerebral glucose use than normal individuals. Many researchers have noticed hypofrontality in fluorodeoxyglucose positron emission tomography (FDG PET) studies performed in schizophrenia. Decreased metabolism was observed in the frontal and temporal cortex of the patients but not in the parietal and occipital lobes [121]. However, not all studies have been able to replicate the same result [122].

SPECT detects gamma rays emitted from radionuclides. Fluorine-18 is a radionuclide that labels glucose molecules to form F18 deoxyglucose (FDG). There are two types of radionuclide studies in patients with schizophrenia: blood flow-glucose metabolism studies and neuroreceptor research. Blood flow and glucose metabolism studies are carried out in two stages: rest and active. During activation with the Wisconsin card sequencing test, patients with schizophrenia have a less significant increase in blood flow to the dorsolateral prefrontal cortices [123]. Abnormalities in blood flow to the temporolimbic pathways are associated with disorders inhibiting subcortical dopamine release and positive disease symptoms. Auditory hallucinations have been proven to be associated with increased blood flow to the medial, temporal, and limbic areas [124]. Radionuclide studies in patients with schizophrenia have shown an increase in dopamine at synapses. Each anti-psychotic drug has different receptor affinities, which PET and SPECT can demonstrate [125–128].

7.2.2 Functional magnetic resonance imaging (fMRI)

The fMRI is based on measuring locally increased cerebral blood flow of functional brain regions during a specific task called blood oxygen level-dependent (BOLD) imaging. fMRI studies in patients with schizophrenia include investigating executive and cognitive functions such as attention, memory, psychomotor function, and basic stimulus processing. In a recent meta-analysis, structural and functional studies investigated the areas of processing speed, attention, working memory, verbal learning and memory, visual learning and memory, executive function/reasoning, problem-solving, verbal fluency and verbal comprehension, emotional perception, social perception and knowledge, theory of mind, and attribution bias. The authors

noted that when cognitive tasks were presented, there was a decrease in the activation of the dorsomedial prefrontal cortex, the complementary motor area, and the right lower frontal gyrus [129]. Typically, frontal hypoperfusion, anterior cingulate cortex (ACC) hypoperfusion, and medial frontal gyrus hypoperfusion are the areas and findings that have been studied the most in patients with schizophrenia [130–132]. In contrast, increased blood flow was found in the thalamus [133], putamen and inferior temporal gyrus, and unaltered blood flow in the nucleus caudatus [134]. However, some studies have shown results opposite to these findings [135]. Multiple brain networks have been discovered using resting-state fMRI, including the default mode network, central executive network, salience network, language, sensorimotor, auditory, and visual networks [136–140]. Default mode network (DMN) abnormalities, DMN abnormal activity, DMN with the severity of positive symptoms, and central executive and salience network dysconnectivity have been detected in schizophrenia [141–143]. Connections of the thalamocortical network have also been implicated in schizophrenia and psychosis, with reduced connectivity between the mediodorsal thalamus and the insula and orbitofrontal regions [144].

7.2.3 Diffusion tensor imaging (DTI)

The DTI is used in general neuroimaging to visualise the relationship of white matter, projection, or commissural fibres. Diffusion tensor imaging also allows white matter paths to be imaged in colour three-dimensional images, called tractography. Diffusion tensor imaging studies have shown that patients with schizophrenia have reduced fractional anisotropy in the cingulum and corpus callosum. The results of such studies can be biased, as these findings may also be influenced by various characteristics of the subject's age, gender, and hand dominance [145, 146]. The uncinate fascicle is particularly interesting, as it connects the amygdala to regions of executive function (medial and orbitofrontal cortices). Decreased fractional anisotropy and decreased structural integrity were detected in this circuit [147]. In terms of specificity, four of the neuropsychiatric disorders studied, obsessive-compulsive disorder, major depressive disorder, bipolar disorder, and schizophrenia, had abnormal DTI measurements of varying degrees in the corpus callosum and superior longitudinal fascicle [148].

7.2.4 Magnetic resonance spectroscopy (MRS)

With MRS, concentrations of different chemical species can be analysed *in vivo*. N-acetyl aspartate (NAA), creatinine (Cre), choline (Cho), myoinositol (mI), and glutamate-glutamine (Glx) are frequently analysed markers in MRS studies. NAA is a marker of neuronal integrity, and its low concentration indicates neuronal or axonal damage. Cho is part of the cell membrane and reflects cell membrane turnover rates. The increase in Cho levels reflects cellular hyperplasia. Cre is a marker of energy metabolism functioning, and Cre levels decrease in hypermetabolic states. Glutamine and glutamate are components of the neurotransmitter system, and their concentrations can be measured as two separate peaks. Lactate, acetate, aspartate, and lipid molecules are indicators of pathological conditions at the cellular level. Changes at the molecular level in the internal environment are evident even before morphological changes are observed [149, 150].

In schizophrenia, lower levels of glutamate in the ACC and higher levels in the centrum semiovale were noted. Others have found decreases in GABA, NAA, mI,

and total Cho in the ACC in first-episode psychosis patients [151]. In general, the most consistent finding in most studies is that NAA is reduced in schizophrenia and first-episode psychosis. This finding suggests the possibility of neuronal damage/dysfunction early in the disease. There is a negative correlation between NAA levels in the dorsolateral prefrontal cortex and negative symptoms in schizophrenia [152]. A higher glutamate/creatine ratio in the medial frontal cortex was (i) positively associated with overall symptom severity, (ii) positively associated with schizophrenia symptomatology severity, and (iii) negatively associated with overall functioning [153].

7.2.5 Magnetoencephalography (MEG)

The MEG is an electrophysiological measuring device that measures the magnetic fields emitted by postsynaptic neuronal activity in the brain. MEG measures brain function with millisecond temporal resolution. When combined with the patient's brain anatomical structure on MRI, MEG can show the 3D location of brain activity (spontaneous or evoked) in real time with millisecond temporal resolution [154]. In the resting state, the most robust finding of MEG is an increase in slow-wave activity in the delta (1–4 Hz) and theta (4–8 Hz) bands localised in the frontotemporal and parietal regions in patients with schizophrenia. Zeev-Wolf et al. found that patients with high positive symptoms commonly had low alpha power, and more beta power was seen in the left hemisphere of patients with high negative symptoms [155]. Due to MEG's ability to precisely measure neural oscillation processes and its good spatial localisation using advanced resource reconstruction algorithms, MEG is a valuable technique for assessing whole brain functional activity.

7.2.6 Functional near-infrared spectroscopy (fNIRS)

The fNIRS is a non-invasive imaging method for measuring cortical activity *in vivo*. The measurement of fNIRS is based on the different absorption properties of infrared light by oxy (Oxy-Hb) and deoxy (Hb) haemoglobin [156]. Compared to fMRI, the fNIRS environment is much more natural and resembles real-world environments. It is comparatively less sensitive to head movements. It is easy to use and noiseless. These advantages allow the monitoring of cortical activity during complex tasks. fNIRS has a high temporal resolution, provides a representative experimental environment, and can contribute highly to social cognitive neuroscience, especially neuroimaging [157, 158].

8. Neurophysiological study findings

When schizophrenic patients follow an object with their eyes, a pendulum-like movement is observed. It is also seen more frequently in the first-degree relatives of patients than in the normal population. In twin studies, eye movement disorders were found to be a highly heritable biological marker [159, 160]. The recovery of eye movement disorder similar to the P50 gating disorder by using nicotinic stimulation suggests that in both cases, it results from a common mechanism that depends on the failure of hippocampal inhibitory interneurons to be stimulated by nicotinic cholinergic receptors [161].

8.1 EEG findings

The P300 response measures the neural activity underlying the processes of immediate memory and attention orientation. While its amplitude is related to the attentional resources directed to the task, its latency reflects the speed at which the stimulus is classified [162]. Although amplitude reduction is a relatively constant finding, a prolongation of P300 latency has been reported in schizophrenia [163]. Additionally, it has been reported that as the disease progresses, the latency is prolonged in parallel with the progressive volume decrease in the frontal, temporal, and hippocampal regions [164–166]. It has been shown that there is a hierarchical sequence between schizophrenia patients, healthy relatives of schizophrenia patients, and healthy controls according to the amplitude of the P300 wave, and these findings together have been interpreted as P300 anomalies may be a hereditary marker in schizophrenia [167].

9. Neuropsychological study findings

It was determined that schizophrenia patients performed lower than healthy individuals in tests evaluating attention, learning and memory, executive functions, working memory, language functions, and social cognitive functions. Low cognitive skills performance is an essential reason for a person's decreased functionality [168–170].

10. Psychological approach to psychotic disorders

The leading cognitive model of psychotic disorders is the Theory of Mind (ToM). ToM is based on understanding the differences between one's own and others' mental states. Premack and Woodruff first proposed the theory (1978), and then the works of Baron-Cohen and Frith came to the fore [171–173]. Garety et al. described probabilistic inference, that is, Jumping to Conclusion Bias (JTC) [174]. Accordingly, a person with psychotic thought content makes a judgement without collecting sufficient data. The probabilistic inference proposed by Garety et al. was used at a high rate in later studies. They have shown consistency and have been designed to include different probabilities and conditions [175–177]. Higgins [178], on the other hand, created a model based on the inconsistency in self-value (the self that actually exists, the self that one wants, and the one that society wants). These inconsistencies determine the person's perception of himself/herself, and he stated that depressed people emerge with a difference between the person they are and the person they want to be [178]. Bentall et al. stated that psychotic patients make attributional biases and develop delusions [179]. To evaluate patients' attribution, they invented the Internal, Personal, and Situational Attributions Questionnaire (IPSAQ) to evaluate attributional biases and errors [180]. Kinderman et al. discussed a possible relationship between ToM deficits and attributional biases and errors [181].

11. Diathesis-stress model of schizophrenia

The diathesis-stress model explains schizophrenia as the result of the interaction between genetic predisposition (diathesis) and environmental stressors.

This model suggests that a person may have a genetic predisposition to schizophrenia, but the combination of this predisposition and stressful life experiences triggers the onset of the disorder. Many neuropsychiatric disorders and schizophrenia are thought to develop concerning hypothalamic-pituitary-adrenal (HPA) axis dysfunction, neurodevelopmental characteristics, epigenetic regulation, neurotransmitter systems, inflammatory processes, and brain structure and function. The events or 'stressors' can be psychological (e.g. social rejection) or biological (e.g. physical injury or illness) [182]. The activation of the stress system causes a series of integrated physiological responses. This response consists of the HPA axis and the secretion of adrenal stress hormones, which trigger a fight or flight response, prompting the organism to use coping strategies. Therefore, it has been hypothesised that adverse events early in life may shape the maturation of the neuroendocrine systems and corticolimbic circuits, leading to increased stress responses in adulthood.

Several theories have been proposed to explain how stressors can become 'built-in' in brain physiology. One of the best known is the 'cumulative stress' hypothesis. Stress affects the developmental program of an organism, leading to specific functional and structural changes in the brain (e.g. hippocampal damage, ventricular expansion, altered cell architecture, migration of neurons) and disruptions in neurochemical parameters (dopamine (DA), glutamate, γ-amino butyric acid (GABA), serotonin) [183]. In response to stress, CRH is synthesised, which causes ACTH to be released from the pituitary glands, and then, glucocorticoids (GCs) are released from the adrenal glands. This system is controlled by the feedback system in the brain. CRH directly affects the brain, including the locus coeruleus, the periventricular nucleus of the hypothalamus, the bed nucleus stria terminalis (BNST), and the central nucleus of the amygdala. The interaction of CRH with the noradrenergic system in these regions can lead to significant changes in homeostasis, that is feedforward activation, which can lead to psychopathology. Neurotoxicity in the hippocampus and PFC causes disruptions in the negative feedback system that reduce HPA axis activation [184].

Epigenetic mechanisms, which affect the management of DNA function without changing the DNA structure due to environmental factors, stand out as an essential issue. It plays a role in reshaping brain circuits during the developmental process. The most affected regions are the temporal and prefrontal cortical-thalamic-ventral striatal pathways [183]. A primary irregularity in the executive functions of the prefrontal cortex can lead to abnormal regulation of stress-induced circuitry in regions downstream of the prefrontal cortex, such as the amygdala, ventral striatum, and hippocampus [184]. The synaptic pruning hypothesis is one of the leading models for the development of symptoms in schizophrenia. Synaptic pathology can occur in sensitive adolescents due to an abnormal process of neuromodulation, which can be amplified by environmental factors such as genetic predisposition or early life stress exposure. In schizophrenia, dendritic pathology consistently has been found with stress-induced changes in both the hippocampal formation and the prefrontal cortex [183]. Howes [185] emphasised the importance of microglia and inflammatory processes in brain development. Microglia have a central role in the inflammatory response and are involved in synaptic pruning and neuronal restructuring. Microglial activation occurs in response to psychosocial stress. Perinatal activation of microglia may sensitise them to stressors later in life. Genetic research has shown that variations in the complement system are associated with schizophrenia and that this system also regulates microglial synaptic pruning [185].

To summarise the possible risk factors:

Prenatal stress: prenatal stress leads to cognitive impairments, neuromotor abnormalities, and hyperreactivity to stress. Maternal biopsychosocial stress, death of the father during pregnancy, unwanted pregnancy, and exposure to war and natural disasters cause a prolonged increase in HPA axis activity and changes in GC receptor density. Several maternal complications are associated with adverse foetal development, including low birth weight, cognitive deficits, depression, schizophrenia, anxiety, attention-deficit/hyperactivity disorder, antisocial behaviours, depression, diabetes, infection/inflammation, and obesity. The enzyme 11β-hydroxysteroid dehydrogenase type 2 (HSD2) acts as a shield, ensuring rapid inactivation of GCs in the mother. Controlled fluctuations in the expression levels and functionality of HSD2 are necessary to ensure that GCs reach the foetus in the right amount and at the right time for the maturation of the organs. Many factors, including hypoxia, catecholamines, and proinflammatory cytokines, can downregulate placental HSD2 activity, increasing GC transport to the foetus [183, 184].

Postnatal stress: early stressors can cause long-term changes in neuroendocrine responses to brain morphology and emotional and behavioural regulation. Neuroendocrine activity can reprogram the nucleus accumbens to increase dopamine release due to stress. Studies on genetically high-risk populations show that stress in childhood increases the risk of schizophrenia. In addition, childhood abuse predicts the development of psychotic disorders [184]. Tetrahydrocannabinol and amphetamines have been observed to increase cortisol levels in both schizophrenia patients and control cases. Opiates, on the other hand, have been found to suppress cortisol secretion [186].

12. Neurodegeneration model of schizophrenia

The neurodegeneration model of schizophrenia suggests that the disorder involves progressive neurostructural changes, particularly in grey matter content and ventricular size. This model considers schizophrenia as a disorder that has neurodevelopmental antecedents but is characterised by the course of neurodegeneration. Brain gliosis is indicative of neuronal degeneration. Glial cells respond to specific neuron injuries and are seen in brains with neurodegenerative disorders. Post-mortem examinations show that patients with schizophrenia do not have gliosis, which contradicts the hypothesis that schizophrenia is a neurodegenerative disorder [187]. On the other hand, some studies have shown histopathological findings and evidence that schizophrenia is a limited neurodegenerative disease. Reports of neuropathological abnormalities in the brains of post-mortem schizophrenia patients have shown that they are present in almost all areas of the brain [188]. In post-mortem studies completed by Schnieder et al., it has been stated that differences in astrocytosis and microgliosis have been observed in the brains of schizophrenia patients, although not conclusively [189]. Oligodendrocytes, on the other hand, presented remarkable new findings. This type of gliosis is thought to be observed in schizophrenia and can be interpreted as an altered response to a pathological process in the brain [190]. Some researchers suggested that the altered mechanism observed in the myelination process in schizophrenia may be the trigger for white matter loss in the prefrontal cortex. These researchers also noted that inhibitory synapse formation decreases during the disease, and excitatory synapses are excessively shortened [191, 192]. Since shortening is a form of axonal degeneration, retraction or excessive excretion supports the neurodegeneration hypothesis [193]. Neuroplasticity has been proposed as another mechanism to

explain progressive degeneration in schizophrenia [194]. Other variables that support the neurodegeneration hypothesis are based on the presence of chemical alterations. Dopamine, glutamate, and GABA are associated with neurodegenerative processes [195–197]. In addition, it has been stated that apoptotic hyperfunction may support degenerative processes in schizophrenia [198]. High levels of Bax/Bcl-2 are indicative of susceptibility to apoptosis, and patients with chronic schizophrenia exhibit a 50% higher Bax/Bcl-2 ratio than the non-psychiatric population [199]. Despite the findings mentioned here, more studies are needed in this area.

13. Neurodevelopmental model of schizophrenia

The neurodevelopmental model of schizophrenia suggests that the disorder develops over time because of abnormal neurodevelopmental processes that begin early in life, potentially during prenatal development. According to this hypothesis, disorders in neuronal developmental processes, such as migration and arborisation in the prenatal period, lead to abnormal brain maturation [200]. Over time, the individual interacts with environmental factors and the disease is triggered. In this process, the person is influenced by external and internal factors [201, 202]. According to this theory, biological variants of the disorder are present long before the development of pathological symptoms in the individual. However, by interacting with many external factors, clinical impairment will not occur until obvious symptoms appear [203–207]. Genetics, neurodevelopmental processes, and schizophrenia are inextricably linked. All molecules that influence neural development are controlled by specific genes involved in brain development and pre- and postnatal maturation. Numerous links have been discovered between schizophrenia and genes-encoding proteins such as neuroregulin 1 (NRG1), dysbindin, DISC-1, regulatory of G protein signalling 4 (RGS4), COMT, and proline dehydrogenase [208–211]. Deficiency in reelin expression has been observed in patients with schizophrenia after death. Reelin is a protein that directs the migrations of certain groups of neurons and is released extensively in this process [212, 213]. In addition, a decrease in polysialic acid (PSA) expression on neural cell adhesion molecules (NCAM) has been observed in patients with schizophrenia. This molecule is involved in axonal growth, synaptogenesis of interneurons, and the formation of inhibitory circuits [214, 215]. It has also been stated that proteins such as brain-derived growth factor (BDNF), glial cell-derived neurotrophic factor (GDNF), and epidermal growth factor (EGF) are also involved in this process [216–218]. The presence of several minor physical abnormalities in patients with schizophrenia supports the hypothesis of abnormal neurodevelopment. These abnormalities occur during the first trimester of pregnancy and early in the second trimester. Researchers have found that the smaller circumference of the head at birth, delayed brain development, droopy ears, palate arch anomalies, epicanthus, cleft palate, telecanthus, craniofacial minor physical abnormalities and a large gap between the first two toes have a relationship with schizophrenia [219–221]. Given that hereditary factors alone cannot explain the aetiology of schizophrenia, research has been conducted on the role of environmental factors. Infections, delivery time, obstetric complications, substance use, childhood and adolescent traumas, social exclusion and social defeat, children of mothers who had influenza in the second trimester of pregnancy and mothers who had rubella infection during pregnancy, the place of birth, and the size of cities can predispose to psychosis in sensitive individuals [222–228]. Meta-analytic studies on cognition before and in the early stages of

the disease have revealed that attention, memory, and executive functions worsen in patients with schizophrenia than controls [229, 230]. One of the most consistent findings in schizophrenia is dysfunction in motor skills. It has been stated that it can be considered a predictive finding in children and adolescents who develop schizophrenia in the future [231, 232]. Notwithstanding, the available data are far from reaching a definitive conclusion.

14. Conclusions

Schizophrenia was identified at the end of the nineteenth century and the beginning of the twentieth century. Immediately afterwards, scientists began to conduct studies to understand the nature of schizophrenia. At the beginning of the twentieth century, studies were carried out to understand whether schizophrenia was a familial disorder. However, these studies were found inadequate in many respects, and their validity was questioned. New studies have been conducted since the second half of the twentieth century.

Results from family, twin, and adoption studies have made significant contributions to our understanding of schizophrenia. As a result of these studies, it was shown that the risk of schizophrenia increases as the degree of kinship gets closer and decreases as the degree of kinship gets farther away. Data obtained from twin studies indicate that schizophrenia is not only a genetically inherited disorder, but environmental factors also play a role in the development of the disease. Adoption studies have found that the risk of the disease is higher in adoptees whose biological parents have a history of schizophrenia.

In later periods, genetic studies were carried out along with technological developments. The results of genome-wide association studies, copy number variant studies, sequencing studies, and epigenetic studies have significantly contributed to our understanding of the molecular genetic aetiology of schizophrenia. However, none of these studies could reveal a specific genetic abnormality or disturbance for schizophrenia. The results were generally interpreted as suggesting that many genetic abnormalities contribute to the development of schizophrenia through additive influence and dynamic interaction.

During this process, many researchers tried to identify environmental factors that contribute to the development of schizophrenia and conducted studies in this field. Repeated studies have consistently shown that factors such as infections during the intrauterine period, immune system activation, nutritional disorders, advanced paternal age, cannabis use at an early age, and immigration are risk factors for the development of schizophrenia. Immune system dysfunctions show a remarkable feature at this point. Genetic studies show that the MHC Class 1 gene region plays a role in the development of schizophrenia. Likewise, the demonstration that immune dysfunctions in the mother during pregnancy increase the risk of developing schizophrenia for the child in the future. This situation constitutes an excellent example of gene-environment interaction.

In post-mortem neuropathological examinations, thinning of the cortical grey matter was detected in patients with schizophrenia. The first of the most consistent findings is the widespread reduction in neuronal size with accompanying reduced dendritic and axonal branching. Another important finding is that a decrease in the number of neurons was detected, especially in regions such as the prefrontal cortex, temporal cortex, hippocampus, and insula. Synaptic changes observed in

schizophrenia are generally decreasing, and this is especially seen in glutamatergic neurons. Additionally, an increase in white matter density was detected in the PFC, and it was stated that this was due to the inhibition of neuronal migration during development. Data regarding the anterior cingulate cortex and orbitofrontal cortex are inconsistent. It has been reported that although there is a decrease in total number of neurons in the thalamus and basal ganglia, the neuron density does not change. Another neuropathological finding is the relatively consistent occurrence of ventricular dilatation. In neuropathological studies, pyramidal cell loss was detected in prefrontal and temporal cortices. Additionally, a decrease in GABAergic interneurons was detected in the prefrontal cortex. A decrease in Purkinje cells was also detected in the cerebellum.

Dysfunction of several neurotransmitter systems has been proposed to explain schizophrenia neurochemically. The dopamine hypothesis was first put forward. It has been suggested that psychotic symptoms result from hyperactivity of dopamine D2 receptors or excess dopamine in synapses in mesolimbic dopaminergic pathways. It has been suggested that negative symptoms in schizophrenia are related to the hypoactivity of dopamine D1 receptors in the prefrontal cortex. Although this theory was supported, it was insufficient to explain the pathophysiology of schizophrenia. The glutamate hypothesis, which was put forward later, suggested that GABAergic pathways control dopaminergic pathways originating from the ventral tegmental area. This GABAergic pathway is controlled by glutamate, and in glutamate deficiency, the GABAergic system cannot be stimulated and cannot control the dopaminergic system. In theories based on GABAergic system disorder, it has been suggested that loss of cortical GABAergic neurons disrupts information processing and top-down control processes. Theories based on the serotonin system have been put forward with the understanding that psychotic symptoms seen in Parkinson's disease and Alzheimer's disease are related to serotonin 5HT2A receptor activity. It has been stated that the hyperactivity of 5HT2A receptors has an excitatory effect on glutamatergic neurons, and the increase in dopaminergic neuron activation in the VTA of glutamatergic neurons ultimately leads to an increase in dopaminergic activity in the mesolimbic pathway. In addition, the fact that the activity of second-generation antipsychotics affects both the dopamine and serotonin systems supports this idea. Theories about acetylcholine have generally been associated with nicotinic alpha7 receptor activity located in the hippocampus, and it has been stated that some symptoms of schizophrenia are the result of this receptor dysfunction. In addition to alpha receptors, muscarinic acetylcholine receptors, especially M1, M4, and M5 receptors, also have a role emerging of psychosis. Additionally, some researchers put forward that norepinephrine has a significant role in the development of psychosis and the deterioration of cognitive functions based on HPA axis dysfunction.

Imaging methods have also been used extensively in the aetiology of schizophrenia. In structural neuroimaging studies, dilatation in the brain ventricles and cortical thinning have emerged as the most consistent findings with computed tomography. In MRI studies, thinning was detected in the prefrontal and orbitofrontal cortex. Results regarding the anterior cingulate cortex are inconsistent. Some studies reported that the amount of grey matter increased in the caudate nucleus, while others reported a decrease. It has been observed that there is a decrease in the amount of grey matter in the thalamus. Additionally, thinning was detected in the cerebellar cortex. Diffusion tensor examinations revealed increased white matter density, but organisational disorder exists. These results are interpreted as a supportive finding for neuronal migration defects. In conclusion, this finding supports the idea that schizophrenia is a

neurodevelopmental disorder. fMRI studies are the most studied method when functional neuroimaging studies are examined. Accordingly, the most common findings in fMRI studies were a decrease in prefrontal cortex activity, a decrease in temporal cortex activity, and an increase in activity in the mesolimbic regions during psychotic exacerbation. Anterior cingulate cortex, insula and cerebellum activity patterns gave variable results. Functional near-infrared spectroscopy studies are relatively new and have advantages and disadvantages compared to fMRI studies. In fNIRS studies, abnormal activity patterns have been consistently observed in the prefrontal, temporoparietal, and temporal cortex. These findings support neuropsychological theories such as cognitive impairments and theory of mind deficits seen in schizophrenia. Methods such as positron emission tomography and single-photon emission tomography have low practical applicability. These methods are primarily used in determining molecular structures and drug development studies.

EEG is the leading study method in neurophysiological studies. The literature reports P300 gating dysfunction as an endophenotype. Another finding is related to the P50 response. Neuropsychological studies have found impairments in attention, working memory, semantic memory, executive functions, language functions, learning, motor function speed, and changing setup. However, none of these tasks were specific to schizophrenia, and each function was affected to varying degrees.

In the psychological approach to schizophrenia, an attempt has been made to explain especially the delusional thought development processes. In this regard, the theory of mind deficits, self-discrepancy theory, attributional bias, and judgmental bias (jumping to conclusion bias) have emerged. Theory of mind has mainly taken up room in autism studies. Self-discrepancy studies have not yielded consistent results. Attributional bias and reasoning bias theories are still being studied, and they stand out as the two theories that provide the most comprehensive explanations for the development of delusional thoughts.

Authorship

Adnan Kuşman completed the literature search, designed the study, and wrote the protocol and the manuscript. The author has seen and agreed with the manuscript's content and guarantees the references' accuracy.

Conflict of interest

The author declares no conflict of interest.

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