

Etiopathogenesis of schizophrenia – the state of the art for 2021

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Summary

In 2021, one-hundred and ten years passed since a Swiss psychiatrist, Eugen Bleuler, introduced a term ‘schizophrenia’, denoting one of the most severe and stigmatizing psychiatric illnesses. Presently, it is known that the etiopathogenesis of schizophrenia is multifactorial, and a neurodevelopmental theory has been the most important pathogenic concept for more than 30 years. The theory postulates an interaction between genetic predisposition and environmental factors. In recent years, mainly thanks to employing the genome-wide association studies (GWASs), many molecular-genetic processes increasing a predisposition to schizophrenia have been identified. In the article, the role of pregnancy and perinatal period for risk of developing schizophrenia was considered. In patients with schizophrenia, as early as in childhood and adolescence, the disturbances of brain development occur, reflected, among others, by an impairment of cognitive functions. Childhood trauma makes a risk factor for developing schizophrenia and a less favorable course of the illness. The arising of the first psychotic episode is boosted by socio-environmental factors (e.g., migration, urbanicity) and psychoactive substance use, both increasing dopaminergic activity of the brain. In the paper, contemporary knowledge on the pathogenesis of psychotic and deficit symptoms and disturbances of cognitive functions was presented. This was done concerning the neurotransmitters’ changes and genetic and neuroimaging studies, with emerging therapeutic implications. At the end of the article, a current position of schizophrenia in the context of dichotomic division of mental disturbances put forward by Emil Kraepelin in 1899 was discussed.

Key words: schizophrenia

Schizophrenia in psychiatry, Anno Domini 2021

In 2021, the 110th anniversary is observed of coining by a Swiss psychiatrist, Eugen Bleuler (1857-1939), the term “schizophrenia” [1]. Bleuler created this name from two Greek words: “schizein” (split) and “phren” (mind). In his understanding, it would denote an “inconsistency” of mental processes in this illness. The term “schizophrenia” replaced the name “*dementia praecox*” (in Latin – early dementia)

coined in 1899 by a German physician, Emil Kraepelin (1856-1926), for a chronic illness with the early deterioration of cognitive functions [2]. As the basic symptoms of schizophrenia, Bleuler suggested “four A’s” – i.e., **autism**, **inappropriate affect**, **ambivalence**, and **disturbances of thought association**. However, several decades later, a German psychiatrist, Kurt Schneider (1887-1967), as “the first rank symptoms of schizophrenia” proposed psychotic symptoms, memorized in English as ABCD, where A is **Auditory hallucinations**, B – **Broadcasting of thought**, C – **Controlled thought**, and D – **Delusional perception** [3]. In the 1980s, clinical concepts of distinguishing so-called positive (psychotic) and negative (deficit) symptoms occurring in the same patient were put forward [4, 5]. It constituted some reconciliation of the views of Kraepelin and Bleuler, favoring the symptoms of mental deficit (negative) and those of Schneider who recognized psychotic (positive) symptoms as the main symptoms of schizophrenia. In the last two decades a revival of interest in disturbances of cognitive processes took place, presently recognized as the core symptoms of schizophrenia which again makes a return to the “roots”, in other words, to Emil Kraepelin [6].

The name “schizophrenia” has been used in the International Classification of Diseases (ICD) and the American Diagnostic and Statistical Manual for Mental Disorders (DSM) since their beginning. In both classifications, similar although not identical kinds of the illness have been delineated [7, 8]. However, in the most recent edition of DSM-5, the subtypes of schizophrenia were not distinguished [9]. An attempt to destigmatize the name “schizophrenia” was made by Japanese psychiatrists. In 2002, in Japan, the name *Seishin Bunretsu Byo* (split mind disease) was changed into *Togo Shitcho Sho* (integration disorder) [10].

Therefore, at the beginning of the third decade of the 21st century, in the illness called “schizophrenia”, three groups of clinical symptoms can be distinguished, namely psychotic and deficit symptoms as well as disorders of cognitive functions. Since the 1960s, the pathogenetic studies have concerned mainly psychotic symptoms primarily because of the introduction of their effective treatment in the early 1950s [11]. The research on deficit symptoms and cognitive dysfunctions was significantly intensified in the 1990s. Presently, it is widely accepted that the etiopathogenesis of schizophrenia is multifactorial, and a neurodevelopmental theory has remained the most important pathogenetic concept for more than 30 years. Its quintessence assumes that in patients with schizophrenia, a genetic predisposition to the illness occurs and an impairment of brain development determined by various factors of the prenatal, perinatal, and early period of life until adolescence takes place. This results in the brain being more vulnerable to stress factors acting in adolescence and early adulthood, such as environmental factors and psychoactive substance use. In consequence, this leads to a clinical appearance of the illness, usually in the form of the first psychotic episode. Such a hypothesis was independently formulated in 1987 by a British psychiatrist, Robin Murray, and an American psychiatrist, Daniel Weinberger [12, 13]. On the 30th anniversary of this idea, both researchers published articles on this subject in the “Schizophrenia Bulletin” in which they confirmed its scientific foundation. In his publication, Daniel Weinberger discusses in detail the most recent genetic and epigenetic data about this concept [14]. On the other hand, Robin Murray focuses mostly on environmental factors precipitating

the first psychotic episode of schizophrenia. According to him, the neurodevelopment hypothesis of schizophrenia can be nowadays defined as the developmental risk factor model of psychosis [15].

In this paper, the current status of the verification of the elements of the neurodevelopmental theory of schizophrenia will be discussed. The contemporary data on the pathogenesis of psychotic and deficit symptoms, as well as cognitive dysfunctions in schizophrenia will also be presented, mainly in the context of changes in neurotransmitter systems and the resulting therapeutic implications. At the end of the article, a current position of schizophrenia against the backdrop of dichotomic division of mental disturbances into “*dementia praecox*” and “*manisch-depressives Irresein*” put forward by Emil Kraepelin in 1899 will be discussed [2].

Genetic factors of schizophrenia

An essential component of the “genetic” part of the neurodevelopmental theory is showing that many genes connected with a predisposition to schizophrenia can influence the early period of brain development, brain maturation, and the differentiation of nerve cells. In the field of molecular genetics, the neurodevelopmental concept of schizophrenia found its first confirmation in 2002, when in the research of the Icelandic population, an association with a predisposition to schizophrenia was demonstrated for the neuregulin 1 (*NRG1*) gene, located on chromosome 8p12 and connected with the processes of brain development [16]. A year earlier, a paper was published where, based on the analysis of chromosome 1 translocation in a Scottish family with multiple cases of schizophrenia, a gene Disrupted in Schizophrenia 1 (*DISC1*), located on 1q42 was identified as predisposing to schizophrenia [17]. Further studies showed that the protein coded by the gene plays an important role in the development and maturation of the brain as well as in the differentiation and proliferation of neurons [18].

For more than a decade, the genome-wide association studies (GWASs) allowing to identify several millions of polymorphisms of the whole genome’s genes have made the forefront of genetic research. In the GWAS study performed in 2008, an association with schizophrenia was demonstrated for the zinc finger protein 804 (*ZNF804*) gene located on chromosome 2q32 [19], whereas a paper from 2009 indicated a connection between a predisposition to schizophrenia and the region of the Major Histocompatibility Complex (MHC) located on chromosome 6p21 [20]. Both these findings were replicated in subsequent GWAS studies.

The most important molecular-genetic research of schizophrenia using the GWAS approach was published in the journal Nature in 2014. The study included 37 thousand schizophrenia patients and 133 thousand healthy persons, and demonstrated the association with schizophrenia for the polymorphisms of 108 genes. Among them are found the dopaminergic receptor D2 (*DRD2*) gene, the genes of the glutamatergic system and tissue plasticity (*GRM3*, *GRIN2A*, *GRI1*, *SRR*) and the genes of calcium channel subunits (*CACNA1C*, *CACNA1I*, *CACNB2*) [21]. In the context of the polygenic pathogenesis of schizophrenia, each of these genes can contribute to less than 1% of the effect on the occurrence of the illness.

In many GWAS studies, microscopic chromosomal aberrations resulting in the variations of genome fragments, i.e., copy number variations (CNVs) in schizophrenia patients were found. They were demonstrated in many genome areas, most frequently in the regions of chromosomes 1q21, 15q11, and 22q11 [22, 23]. These aberrations play a disrupting role in brain development during the fetal period and early childhood. Besides schizophrenia, they occur, even to a greater extent, in such neurodevelopmental disorders as autism and intellectual disability. Therefore, given the presence of CNVs, schizophrenia can be genetically related to the neurodevelopmental disorders mentioned above. Studies on the deletion of the above mentioned region 22q11.2, where many genes are located, e.g., the catechol-O-methyltransferase (*COMT*) gene, showed that this abnormality increases the risk of schizophrenia 25-fold [24].

Contemporary research also shows that a predisposition to schizophrenia shares common genetic elements with other psychiatric illnesses, mainly with bipolar affective disorder. In 2009, Swedish researchers analyzing more than 2 million families showed a genetic overlap between schizophrenia and bipolar affective illness: the first-degree relatives of individuals with either schizophrenia or bipolar disorder had an increased risk for both these illnesses [25]. In the GWAS study, common genes for schizophrenia, bipolar disorder, and several other psychiatric disorders were demonstrated [26]. Nevertheless, a large group of genes characteristic for schizophrenia has been identified, whose combination represents the polygenic risk score for schizophrenia (PRSS). This score has been widely used in research, aiming to demonstrate its relationship with clinical parameters or response to pharmacological treatment [27].

In schizophrenia, epigenetic changes are also present, such as abnormal DNA methylation and histone modification which can modulate gene expression without influencing the genome structure. These changes constitute a mediating mechanism for environmental factors in the early period of life and may play a role in leading to the first psychotic episode [28]. Among new research methods, whole exome-sequencing analysis may be of interest. The exome is a collection of all the exons, i.e., the pieces of a gene coding the amino acid sequence in a protein molecule. Using this method, a loss of function of the *SETD1A* gene was demonstrated. This gene is located on chromosome 16p11 and is coding methylation of the amino acid lysine. Its loss of function was found not only in schizophrenia but also in such neurodevelopmental disorders as intellectual disability and epilepsy [29].

As related to genetics, clinical research can be recognized in which an increased risk of schizophrenia with higher paternal age was demonstrated. It can be explained by a growing number of *de novo* mutations in male germ cells with age [30].

Pregnancy and the perinatal period and risk of schizophrenia

An important element of the neurodevelopmental hypothesis of schizophrenia is an assumption that the factors acting during pregnancy and the perinatal period can exert an effect on the development of the illness. Cannon et al. [31], on the basis of a meta-analysis of 20th-century publications, listed three groups of factors increasing the risk of schizophrenia: (1) complications of pregnancy (bleeding, diabetes, Rh

incompatibility, preeclampsia); (2) abnormal fetal development (congenital malformation, low birth weight, reduced head circumference); and (3) complications of delivery (asphyxia, uterine atony, emergency Cesarean section). Polish researchers comparing 50 patients with a first psychotic episode and 50 matched healthy persons found an association between obstetric complications and lower Apgar score and subsequent risk of developing psychosis [32].

The most significant pathogenic factors of pregnancy and the perinatal period increasing the predisposition to schizophrenia include fetal malnutrition, preterm birth, asphyxia, and infections. Concerning infections during pregnancy, in many studies the role of influenza infection, mainly in the first trimester, has been demonstrated. The second microbe with the most evidence regarding this issue is a protozoan, *Toxoplasma gondii*. The data on the significance of Herpes simplex virus type 2 (HSV-2) is still controversial. The mechanism of brain damage as a vector of susceptibility to schizophrenia is connected with abnormal activation of the immune system. In the mothers of schizophrenic patients, significantly elevated levels of pro-inflammatory cytokines were observed during pregnancy and the perinatal periods. It was also found that the immunological activation was propped up by a genetic predisposition, among others the *NRG1* and *DISC1* genes [33].

Deterioration of cognitive functions and brain development in the early life period

The Kraepelinian concept of “*dementia praecox*” assumes an impairment of cognitive functions at the early stage of the illness. However, the evidence exists nowadays indicating that a disturbance of brain development resulting in an impairment of cognitive functions can precede the appearance of the first episode of schizophrenia by many years [34]. The studies performed in the last two decades show an intellectual deficit during adolescence in persons who later develop schizophrenia [35].

In patients with schizophrenia, the disturbances of brain development are already present in childhood, and during adolescence lead to abnormalities in synaptic “pruning” in the prefrontal and temporal cortex. “Pruning” means the elimination of unnecessary synaptic connections. In patients with schizophrenia, this phenomenon is excessive and results in a reduction of the number of postsynaptic elements in these brain structures [36]. It is one of the most important causes connected with a progressive cognitive deficit before the first psychotic episode.

Many genes associated with a predisposition to schizophrenia are located on the HLA complex on chromosome 6p21. Among them, there is the complement component 4 (*C4*) gene. In patients with schizophrenia, a preponderance of the gene’s allele connected with increasing activity of this component was found. Since in mice this gene plays a role in the elimination of synapses during the early postnatal period, a hypothesis was proposed that in patients with schizophrenia it can be connected with excessive synaptic pruning during adolescence [37].

The evidence for brain function abnormalities obtained from studies of the first-episode schizophrenic patients indicates that they are not due to a progression of

the illness or pharmacological treatment. Already during this time, in patients with schizophrenia, the disturbances of interneuronal connections (connectome) of the brain occur. Such disruptions of white matter connections, especially in the prefrontal and temporal cortex, were found by Dutch investigators, both in patients, where they correlated with cognitive impairment and in their first-degree relatives [38, 39]. In such patients, a disrupted synchronization of neural oscillations is also demonstrated, corresponding with cognitive deficits [40].

Childhood trauma in the pathogenesis of schizophrenia

The experience of early childhood trauma can influence the future risk of occurrence and course of schizophrenia. A pioneering study on this subject was published in 1999 when Israeli researchers showed that parental loss, mostly before 9 years of age, increases the risk of schizophrenia by 3.8-fold [41]. In the 21st century, there has been dynamic research progress on this topic. The possible neurobiological mechanisms have been indicated by which the negative early childhood experiences increase the probability of schizophrenia and its less favorable course. Childhood trauma constitutes a severe stress event, resulting in activation of the hypothalamic-pituitary-adrenal axis and a sensitization of the dopaminergic system, precipitating the first psychotic episode of schizophrenia [42]. Besides the stress axis disturbances, as a consequence of negative childhood experiences, disturbances of brain development and cognitive dysfunctions occur. In their inception, a genetic predisposition and epigenetic factors play a significant role [43].

The factors precipitating the first psychotic episode of schizophrenia

In recent decades, two important groups of factors were identified which precipitate the occurrence of the first psychotic episode of schizophrenia. The common final effect of their action likely causes an increase of the brain dopaminergic system activity [44]. The first category includes socio-environmental factors such as, among others, migration and urbanicity. A recent meta-analysis of the impact of the migration process performed by Bourque et al. [45] showed that the risk for psychotic disorders, mainly schizophrenia, in the first-generation immigrants was 2.3-fold higher than in the country of origin, and in the second generation – 2.1-fold higher. Irish researchers based on the literature review and prospective studies in Ireland stated that living in big cities, compared with rural areas, increased the risk of schizophrenia 2-fold in males and 1.34-fold in females [46]. The second group of factors is of biological or, strictly speaking, pharmacological character and involves the use of psychoactive substances. The effect of the use of such psychostimulants as amphetamine or cocaine on schizophrenia risk has been repeatedly confirmed [47]. However, in recent years, a possibility of inducing the first episode of schizophrenia by chronic cannabinoid use has been pointed out [48].

Recently, Guloksuz et al. [49] investigated the interaction of genetic and environmental factors employing the polygenic risk score for schizophrenia (PRSS). They

showed an additive interaction between the PRSS and childhood trauma and chronic cannabinoid use.

The pathogenesis of psychotic and deficit symptoms and cognitive dysfunctions

The majority of information on the pathogenesis of the groups of symptoms of schizophrenia has been connected with changes of neurotransmitter systems. Frequently, it has been supported with genetic and neuroimaging data. In some studies, certain common mechanisms of deficit symptoms and cognitive dysfunctions have been indicated. The data connected with neurotransmitters bear the pharmacotherapeutic implications.

The most important for the theory of pathogenesis and the practice of schizophrenia treatment has been the dopaminergic system of the brain. The discovery of the role of this system in the mechanism of action of antipsychotic drugs in the 1960s [50] resulted in the development of the “dopaminergic” pathogenetic concept of psychotic symptoms. Nowadays, it is thought that in the generation of psychotic symptoms (also known as “positive”) a crucial role is played by the hyperactivity of dopaminergic subcortical structures, mainly those of the striatum [51]. In a neuroimaging study, in patients with an exacerbation of schizophrenia, increased amphetamine-induced release of dopamine in the striatum was demonstrated, which correlated with the severity of positive symptoms [52]. A probable mechanism of dopaminergic dysfunction in schizophrenia is increased presynaptic dopamine synthesis which results in its excessive release [53]. The neuropsychological concept regarding the role of dopamine in the generation of psychotic symptoms assumes the importance of this neurotransmitter for the assessment of the salience of the stimuli. Dopaminergic hyperactivity causes that all stimuli, independently of their meaning, are assessed as salient which leads to information overload of the brain. Psychotic symptoms such as delusions and hallucinations are produced as a result of an adaptative reaction of the brain to such a situation [54].

So far, all antipsychotic drugs used in the treatment of schizophrenia act on the dopaminergic system. Mostly, they exert an antidopaminergic effect by blocking the D2/D3 receptors. This applies to both classical and atypical antipsychotic drugs [55]. As previously mentioned, the dopaminergic receptor *DRD2* gene was identified in the GWAS as connected with a predisposition to schizophrenia [21]. In the treatment of schizophrenia, the partial agonists of D2/D3 receptors have also been employed such as aripiprazole, brexpiprazole, and cariprazine [56], and recently, lumateperone was added here [57]. In the therapeutic mechanism of the atypical antipsychotic drugs and partial agonists of dopaminergic receptors, a significant role is played by their concomitant action on serotonergic receptors.

The dopaminergic system also plays an important role in the pathogenesis of deficit (negative) symptoms and impairment of cognitive functions in schizophrenia. Dopaminergic hypoactivity, especially of dopaminergic type 1 receptors in the prefrontal cortex, has proved significant here [58]. In the pathogenesis of negative symptoms, besides diminished prefrontal function of DRD1, reduced dopaminergic activity in the

caudate nucleus has also been postulated [59]. In a neuroimaging study, a deficit of dopamine release in the dorsolateral prefrontal cortex was observed, and its severity correlated with impairment of working memory [60]. For a therapeutic effect for negative symptoms, the stimulation of the cortical dopaminergic system can be obtained by dopamine autoreceptor blockade (amisulpride), agonistic action on dopamine D2/D3 receptors (aripiprazole, brexiprazole, cariprazine), and by inhibiting serotonergic 5-HT₂ receptors (a majority of the atypical antipsychotic drugs).

A possible pathogenic role of serotonin in schizophrenia was considered as early as in the 1950s when it was discovered that a psychomimetic substance – lysergic acid diethylamide (LSD) – influences the serotonergic system. [61]. More than 60 years of further studies revealed that the most important in this respect are serotonin 5-HT_{2A} receptors, playing a significant role both in the brain development as well as in a predisposition to schizophrenia [62]. In genetic studies, the association of the polymorphism of the *5-HT_{2A}* gene with neurophysiological disturbances in schizophrenia [63] as well as the abnormal methylation of this gene in the illness [64] were found. The blocking of 5-HT_{2A} receptors in the prefrontal cortex can increase the activity of the dopaminergic system in this brain structure. It may be important for the action of the atypical antipsychotic drugs and their possible effect on deficit symptoms and cognitive dysfunctions in schizophrenia [65]. Recently, attention has also been paid to the serotonergic receptors 5-HT₆ and 5-HT₇, and a possibility of application of the therapeutic action on these receptors [66].

As already mentioned, in the mechanism of action of atypical antipsychotics and partial agonists of dopaminergic receptors, there is a combination of their effect on the dopaminergic (D2/D3 receptors) and serotonergic systems (5-HT_{2A} and 5-HT_{1A} receptors). However, as to the antipsychotic action of the “pure” serotonergic drugs, the most data have been accumulated for pimavanserin, a reverse agonist of the serotonergic 5-HT_{2A} receptor. The therapeutic action of pimavanserin has been demonstrated in Parkinson’s disease psychosis, and some attempts of using it in schizophrenia have also been undertaken [67].

In the mid-1990s, a glutamatergic hypothesis of schizophrenia was formulated, postulating a decrease in the activity of the glutamatergic N-methyl-D-aspartate (NMDA) receptor in this illness [68]. In further years, ketamine, a substance acting antagonistically on the NMDA receptor, served for creating a model of schizophrenia presenting psychotic, deficit, and cognitive symptoms [69], and the role of the glutamatergic system in a predisposition to schizophrenia has been confirmed in numerous molecular-genetic studies [70]. The glutamatergic system is important for the development of the brain. In this process, a dysfunction of NMDA receptors on GABA-ergic neurons takes place in the early period of life [71], and the epigenetic changes of the glutamatergic system genes can be contributing factors [72]. As a therapeutic implication of the glutamatergic system changes in schizophrenia, attempts of using so-called inhibitors of the glycine site, a part of the NMDA receptor, for augmentation of antipsychotic drugs in the treatment of negative symptoms were made [73]. On the other hand, despite an initial promise, the antipsychotic action of the metabotropic glutamatergic receptor type 2/3 has eventually not been confirmed [74].

As to the pathogenesis of cognitive dysfunctions in schizophrenia, a paper should be noted, suggesting the foundation of the generalized cognitive deficit in this illness as a dysfunction of the cortico-cerebellar-striatal-thalamic loop and task-positive and task-negative cortical networks [75]. It is also worthwhile to mention the results of a recent genetic study indicating a correlation between cognitive dysfunction and the magnitude of the CNV changes [76].

Schizophrenia and the dichotomic division of mental disorders by Emil Kraepelin

In 2019, the 120th anniversary of the fundamental concept of the division of mental disorders by Emil Kraepelin into “*dementia praecox*” and “*manisch-depressives Irresein*” was observed [2]. As mentioned, the name “*dementia praecox*” was replaced by Eugen Bleuler by the term schizophrenia, and the closest equivalent for “*manisch-depressives Irresein*” is presently bipolar affective disorder. In a clinical sense, Kraepelin’s dichotomic idea was undermined as early as in 1933, when Jacob Kasanin introduced the term schizoaffective psychosis [77]. After more than 50 years from this event, Timothy Crow placed this psychosis in the middle of the proposed continuum of psychiatric disorders [78]. On the neurobiological ground, a significant questioning of Kraepelin’s division took place in the 1990s when it was found that there is a remarkable overlap of genes predisposing to schizophrenia and bipolar disorder and that atypical antipsychotic drugs are therapeutically effective in both these illnesses. However, in the context of the neurodevelopmental theory of schizophrenia, some neurobiological distinctiveness from bipolar disorder can be observed in many areas. It has been demonstrated that schizophrenia patients are affected by more factors impeding brain development and are particularly susceptible to them. In the genome of schizophrenia subjects, there are more CNV changes, and infectious factors occurring during pregnancy, perinatal traumas, certain socio-environmental factors as well as psychoactive substance abuse are of greater significance in this illness. A modified neurodevelopmental concept of schizophrenia considers these factors as a so-called “second hit” superimposing on a genetic predisposition. As a result, patients with schizophrenia during the first psychotic episode present more intensified neuroanatomical changes and cognitive function disturbances, compared to patients with bipolar disorder [79].

In conclusion, in the context of a discussion about the current topicality of Kraepelin’s concept, it seems that his dichotomy still retains certain merit.

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