Origins and perspectives of the schizophrenia research

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Schizophrenia is a complex psychiatric disorder with a heterogeneous clinical phenotype. Ancient paradigms focused on clinical experiences and hypotheses mostly without validated measurements but in the modern neuroscientific era the trend has turned oppositely; although an expanding body of evidence is available in association with the neurobiological background of schizophrenia, it seems that development of phenotypic description has been missing from the focus. However, now it is clear that a relevant and sophisticated diagnostic system is also essential for the appropriate interpretation of comprehensive molecular studies. Besides a brief review of most important data on schizophrenia research, the authors call attention to a complex diagnostic system (Composite Diagnostic Evaluation, CODE) which can be a valuable clinical partner of currently accepted models of schizophrenia, such as the neurodevelopmental hypothesis.

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DEFINITION AND SYMPTOMS OF SCHIZOPHRENIA

Schizophrenia is one of most debilitating mental illnesses with chronic psychotic symptoms. The syndrome was first described as 'dementia praecox' by Emil Kraepelin, then Eugen Bleuler changed the name of the illness from dementia to schizophrenia. Core symptoms of schizophrenia were divided into two groups traditionally by Hughlings-Jackson's and then by Strauss and Carpenter: positive symptoms (including delusions, hallucinations and though disorders) and negative symptoms (reduced interest and motivation, emotion and social interaction) resulting in disorganized behavior. These categories can be complemented with an additional group of cognitive dysfunction (impaired attention, information processing, learning and memory). Furthermore, Kurt Schneider differentiated the so-called 'first-rank symptoms' very similarly to currently used major criteria for diagnosis of schizophrenia (Urfer-Parnas et al., 2010; Rethelyi, 2011). The first symptoms usually manifest in adolescence or early adulthood but in most cases a prodromal period with nonspecific and attenuated symptoms anticipates the emergence of the first psychotic episode. The course of schizophrenias is typically characterized by psychotic exacerbations or relapses alternating with periods of partial remissions.

Recently, clinical diagnosis of schizophrenia is based on criteria of the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV) published by the American Psychiatric Association (DSM-IV-TR, 1994) or of the International Classification of Diseases, tenth edition (ICD-10) published by the World Health Organization (ICD-10, 1992). Presence of two or more of the characteristic symptoms (hallucinations, delusions, disorganized speech, catatonic behavior or negative symptoms) persisting for more than a month (criterion A) and social dysfunction due to the disturbance (criterion B) for at least 6 months (criterion C) are required for diagnosis of schizophrenia according to the DSM-IV. Exclusion criteria, as dominance of affective component (criterion D), substance use (criterion E) or other neurodegenerative syndrome (criterion F) related psychotic episode are also presented in DSM-IV. Similarly, the major criteria of diagnosis of schizophrenia in ICD-10 are persistent hallucinations and delusions, however, catatonic behavior and negative symptoms are not ranked within the core (1) symptoms. The duration criterion is different between DSM-IV and ICD-10, namely symptoms have to persist for six months in DSM-IV, while only 1 month in ICD-10 (*Table 1*). DSM-IV specifies five (paranoid, disorganized, catatonic, undifferentiated and residual) and ICD-10 six subtypes of schizophrenia (paranoid, hebephrenic, catatonic, undifferentiated, residual and simple) (*Table 1*).

Table 1 Comparison of diagnostic criteria for schizophrenia in DSM-IV and ICD-10 (DSM-IV-TR, 1994; ICD-10, 1992)

DSM-IV	ICD-10
A. Characteristic symptoms	***General criteria for paranoid, hebephrenic, catatonic and undifferentiated schizophrenia***
Two or more of the following, each present for a significant portion of time during a 1-month period: (1) delusion (2) hallucinations (3) disorganized speech (e.g. frequent derailment or incoherence) (4) grossly disorganized or catatonic behaviour (5) negative symptoms, i.e. affective flattening, alogia or avolition Note: only one criterion A symptom is required if delusions are bizarre or hallucinations consist of voice keeping up a running commentary on the person's behaviour or thoughts, or two or more voices conversing with each other.	**G1** Either at least one of the syndromes, symptoms and signs listed under (1) below or at least two of the symptoms and signs listed under (2) should be present for most of the time during an episode of psychotic illness lasting for at least 1 month
B. Social/occupational dysfunction	***(1) At least one of the following must be present:***
For a significant portion of the time since the onset of the disturbance, one or more major areas of functioning such as work, interpersonal relations or self-care are markedly below the level achieved prior to the onset (or when the onset is in childhood or adolescence, failure to achieve expected level of interpersonal, academic or occupational achievement).	– thought echo, thought insertion or withdrawal or thought broadcasting; – delusions of control, influence or passivity, clearly referred to body or limb movements or specific thoughts, actions or sensations; delusional perceptions; – hallucinatory voices giving a running commentary on the patient's behaviour, or discussing the patient between themselves, or other types of hallucinatory voices coming from some part of the body; – persistent delusions of other kinds that are culturally inappropriate and completely impossible (e.g. being able to control the weather, or being in communication with aliens from another world).
C. Duration	***(2) Or at least two of following:***
Continuous signs of the disturbance persist for at least 6 months. This 6-month period must include at least 1 month of symptoms (or less if successfully treated) that meet Criterion A (i.e. active-phase symptoms).	– persistent hallucinations in any modality, when occurring every day for at least 1 month, when accompanied by delusions (which may be fleeting or half-formed) without clear affective content, or when accompanied by persistent overvalued ideas; – neologisms, breaks or interpolations in the train of thought, resulting in incoherence or irrelevant or irrelevant speech; – catatonic behaviour, such as excitement, posturing or waxy flexibility, negativism, mutism and stupor; – "negative" symptoms, such as marked apathy, paucity of speech and blunting or incongruity of emotional responses (it must be clear that these are not due to depression or to neuroleptic medication).
D. Schizoaffective and mood disorder exclusion	***G2 Most commonly used exclusion clauses***
no major depressive, manic or mixed episodes have occurred concurrently with the active-phase symptoms	If the patient also meets the criteria for manic episode (F30) or depressive episode (F32), the criteria listed under G1 (1) and G1 (2) above must have been met before the disturbance of mood developed. The disorder is not attributable to organic brain disease (in the sense of F00-F09) or to alcohol- or drug-related intoxication (F1x.0), dependence (F1x.2) or withdrawal (F1x3 and F1x.4).
E. Substance/general medical condition exclusion	
The disturbance is not due to the direct physiological effects of a substance or a general medical condition.	
F. Relationship to a pervasive developmental disorder	
If there is a history of autistic or another pervasive developmental disorder, the additional diagnosis of schizophrenia is made only if prominent delusions or hallucinations are also present for at least a month.	

Subtypes	*Subtypes*
295.20 Schizophrenia, Catatonic Type 295.10 Schizophrenia, Disorganized Type 295.30 Schizophrenia, Paranoid Type 295.60 Schizophrenia, Residual Type 295.90 Schizophrenia, Undifferentiated Type	F20.1 Hebephrenic schizophrenia F20.2 Catatonic schizophrenia F20.3 Undifferentiated schizophrenia F20.4 Post-schizophrenic depression F20.5 Residual schizophrenia F20.6 Simple schizophrenia F20.8 Other schizophrenia F20.9 Schizophrenia unspecified

EPIDEMIOLOGY OF SCHIZOPHRENIA

A systematic review of epidemiological data indicates that the median *lifetime prevalence* of schizophrenia is 4.0 per 1000 persons with 80% confidence interval estimates ranging from 1.8–11.6 per 1000 persons. The same review found the median *incidence* rate of schizophrenia as 15.2 per 100'000 persons per year with 80% confidence interval estimates ranging from 7.7 to 43.0 per 100'000 persons per year. Although previously it was the long-held view that schizophrenia affects 1 out of every 100 individuals, new data indicate that this proportion was overstated. According to recent results the *lifetime morbid risk* (the likelihood that a particular individual will develop schizophrenia in their lifetime) is 7.2 per 1000 persons, so it is somewhat lower than previously thought. Several other dogmas about the epidemiology of schizophrenia have been refuted in the last decade. For instance, the common wisdom that schizophrenia affects all individuals equally, regardless of race, gender or nationality was questioned by McGrath et al. in 2004. Authors demonstrated in their systematic review - including data from 32 countries - that rates for the incidence of schizophrenia fell within a range of 7.7 to 43.0 per 100'000 per year. This result suggests that the *incidence* of schizophrenia shows prominent variations between different locations. Similarly, results of a systematic review suggest that there is a significant variation in the *prevalence* of schizophrenia between different sites. In addition, two systematic reviews, using different summary methods, have shown that males are more likely to develop schizophrenia than females and that this difference is not the consequence of methodological factors related to age range or diagnostic criteria (both studies found that the male/female risk ratio to develop schizophrenia was 1.4:1). Without going into details we would like to mention that several factors (e.g. urbanicity, migration status, latitude, economic status of the country, etc.) influence the epidemiological features of schizophrenia in a given population. Some results indicated that the incidence of schizophrenia is changing over time but other findings did not support this notion. The frequency of several subtypes of schizophrenia – classified by the principally used diagnostic systems DSM and ICD – are different (McGrath et al., 2008; McGrath and Susser, 2009; Saha et al., 2006).

Life expectancy of patients with schizophrenia is 12-20 years less than members of the general population. Median standardized mortality ratio (SMR) for all-cause mortality is approximately 2.6 among patients with schizophrenia. Furthermore, the mortality gap between patient and average populations has increased in the last decades probably because patients with schizophrenia are not benefiting from advances in medical care to the same extent as the average population. Elevated mortality in the patient group is mainly attributable to excess suicide rate (see discussed below) and – to a lesser extent – death by neoplasms and cardiovascular diseases. Some frequent somatic diseases and symptoms (e.g. metabolic syndrome, diabetes mellitus, dyslipidaemia, epilepsy, parkinsonian signs (even in drug-naive patients) and perhaps hypertension) are more prevalent among patients with schizophrenia than among control subjects. Some results suggest that increased non-suicide death in schizophrenia is the aftermath of modifiable risk factors (e.g. smoking, low level of physical activity, low access to healthcare etc.). An intriguing – but poorly proofed – possibility is that antipsychotic therapy (especially with second-generation agents with their well-known adverse metabolic side effects) may contribute to the elevated mortality risk of patients with schizophrenia. There is higher than average suicide mortality and rate of suicide attempts associated with schizophrenia. Previously, the lifetime risk of suicide death was routinely reported as 10% in patients with schizophrenia, but a recent meta-analysis with different methodological approaches has found it as 4,9%. Suicide attempts are more frequent, the rate of it varies between 20% and 40%. Suicide is especially

prevalent during the first two years after diagnosis/illness onset (50% of suicide cases are occurred in this period). Not only some somatic, but also several psychiatric diseases (e.g. substance use disorder; obsessive-compulsive disorder; posttraumatic stress disorder; panic disorder etc.) are more frequent among patients with schizophrenia compared to members of general population. It is well known that there are gender differences in some epidemiological and clinical characteristics of schizophrenia. For instance, female patients have a later onset of illness, less frequent substance abuse, more positive and affective and less negative symptoms compared to males. Results are more ambiguous in regard to differences in functional (psychosocial) and symptomatic outcome between sexes. Another interesting epidemiological aspect of schizophrenia is the robustly confirmed fact about the reduced fertility of patients (indicated by the number of offspring) compared with the average population. It was a long-held theory that the genetic variants predisposing to schizophrenia are maintained in the population by the high fecundity of unaffected relatives of patients. However, results of a recent meta-analysis failed to confirm this theory (Hodgson et al., 2010; McGrath et al., 2008; Kasckow et al., 2011; Wildgust and Beary, 2011; Carlborg et al., 2011; Bundy et al., 2011).

ETIOLOGY OF SCHIZOPHRENIA

According to our current knowledge schizophrenia is a complex disease caused by multiple etiological factors. Heritability of schizophrenia has long been known; Kraepelin has already mentioned that about 70% of his patients with dementia praecox had a family history of psychosis. Since that age several evidence based studies confirmed this observation. Pattern of familial heritability of schizophrenia suggests that incidence of schizophrenia is increased among closer relatives. In case of monozygotic twins with 100% identical genome, one has 48% chance to have schizophrenia if other is ill. In case of 50% shared genome (dizygotic twins), 17% is this chance. Incidence of schizophrenia decreases proportionally among second and third degree relatives with less and less shared genomic substance (Tsuang et al., 2001). Adoption studies provided evidence that these findings are due to genetic background and not to environmental factors, however, to date we still not know exactly which genomic regions are responsible for the disorder. Analyses of relatively frequent single nucleotide polymorphisms (SNP) provided possibilities of performing 'linkage' and 'candidate gene association' studies. Linkage analyses revealed associations between loci on 21 of the 23 chromosomes, but also regions on 1q, 2q, 8q, 22q and schizophrenia (Lewis et al., 2003). On the other hand, candidate genes, as neuregulin-1 (NRG-1), catechol-O-methyl-transferase (COMT), brain derived neurotrophic factor (BDNF), disrupted in schizophrenia-1 (DISC1), NMDA receptor subunit (NR1) have also showed associations with the disorder, but most of results are inconsistent or only partly replicable (Lu et al., 2011; Tsuang et al., 2001). Gene expression studies provided evidences that genes encoding for neuroimmune transcriptums are appeared to have significant role in pathomechanism of the disorder (Garbett et al., 2008). Besides SNPs, rare genetic variants such as copy number variants (CNV) can be alternatives to find the link between schizophrenia and DNA according to certain scientists (Buizer-Voskamp et al., 2011) More recently, as a possible answer to lack of convincing results given by genetic studies, new theories suggest role of epigenetics in development of schizophrenia. Epigenetic mechanisms typically involve heritable biological factors independently of DNS sequence, like DNA methylation, histone acetylation and non-coding RNAs, microRNAs ect. (Bale et al., 2011; Must et al., 2011; Vereczkei and Mirnics, 2011).

Environmental factors are also involved in the etiology of schizophrenia. In utero exposure to infections, hypoxia, malnutrition and other prenatal noxa increase the risk for schizophrenia (Buka et al., 2001). These early life experiences may determine disease risk through influencing programming of epigenetic marks (Bale et al., 2011). Postnatal risk factors, such as stressful life events, dysfunctional family structure (included expressed emotions), low social status, regular cannabis consumption etc. can be regarded as a trigger for the development of (Schenkel and Silverstein, 2004; Makkos et al., 2011; Keri and Kelemen, 2008).

MORPHOLOGICAL, FUNCTIONAL AND NEUROBIOLOGICAL EVIDENCE IN SCHIZOPHRENIA

Morphological lesions of brain were already described in the beginning of the 20th century based on pneumoencephalography. These investigations suggested an enlargement of the cerebral ventricles which was confirmed later with CT and MRI scans. Although this structural alteration was consistently confirmed in schizophrenia, unfortunately, it was not proved specific for schizophrenia. Further studies with analysis

of specific brain regions reported reduced volume of structures that play crucial role in schizophrenia, such as the limbic structure (especially in patients with pronounced negative symptoms); superior temporal gyrus (in those who have massive auditory hallucinations) and prefrontal cortex which was shown not only decreased volume but its hypoperfusion and low glucose metabolism were also detected by fMRI and PET investigations. Moreover, postmortem brain morphological studies of patients with schizophrenia suggested reduced cortical thickness, loss of pyramidal cells, malformed cell structure and decreased number of GABA interneurons (Shin et al., 2011).

Dysregulation of the *dopaminergic* system in schizophrenia is well-accepted in the literature but theories changed in details with time repeatedly (see also in next subsection). Up to date, elevated presynaptic DA synthesis, higher tonic (baseline) and phasic (stimulated) DA release and increased postsynaptic D2 receptor binding in striatum are described by multiple studies. In contrast, decreased extrastriatal D2 receptor binding has been observed in patients with schizophrenia especially in thalamus which can be associated with sensory gating abnormalities measured in schizophrenia (Hirvonen and Hietala, 2011). Studies on cortical D1 receptors yielded inconsistent data but authors suggested that increased receptors can be associated with individuals at genetic risk without symptoms of schizophrenia while it seems that receptors are decreased only in patients with developed schizophrenia who are chronically treated with antipsychotics (Hirvonen and Hietala, 2011). The *serotonergic* system is also implicated in the pathomechanism of schizophrenia as serotonergic neurons projecting from the dorsal raphe nuclei to the striatum and substantia nigra have modulatory effects on dopaminergic neurons. Moreover, direct serotonergic projections to the cortex are associated with negative symptoms of schizophrenia. Neurochemical and pharmacological evidences suggested that among 14 subclasses of 5-HT receptors, 5-HT2A receptor (with excitatory effect at cellular level and with integrating effect in cognitive and perceptual function at system level) has the most prominent role in the pathomechanism of schizophrenia while significance of changes of 5-HT1A receptor expression in schizophrenia are not clear. Elevated level of 5-HT and its metabolites with lower 5-HT2A receptor number were detected in the striatum and increased level of 5-HT1A was described in the dorsolateral prefrontal cortex of postmortem human brain tissues. In vivo studies suggested decreased 5-HT2A receptors and lower cortical serotonin binding were observed in drug-naïve patients with schizophrenia but results are not unequivocal (Shin et al., 2011; Thompson et al., 2009). Receptors of other neurotransmitters like *GABA* and *glutamate* are also altered in schizophrenia according to recently published studies. Deficient GABAergic function and decreased expression of subunit 1 of *N-methyl-D-aspartate (NMDA)* receptor (NR1) in cortical and limbic regions of postmortem samples from patients with schizophrenia were observed while elevated NR1 expression was demonstrated in patients with chronic antipsychotic treatment. The NMDA receptor hypofunction of schizophrenia was confirmed by NR1 knockout mice studies as well (Belforte et al., 2011).

THEORIES ON THE PATHOMECHANISM OF SCHIZOPHRENIA

Dopamin hypothesis

The theory of hyperdopaminergia in schizophrenia goes back to the 1960's based on indirect observations, that first antipsychotics are DA receptor antagonists and their clinical potency is associated with their ability to D2 receptor blocking; furthermore, amphetamine, which increases DA activity, can provoke psychotic symptoms. However, general hyperdopaminergia was not supported by studies that reported unchanged level of DA metabolites in cerebrospinal fluid or postmortem brain samples, in addition, negative symptoms of schizophrenia were shown to be resistant to typical antipsychotics (Davis et al., 1991). Instead of general hyperdopaminergia, researchers began to investigate dopmaniergic activity by different brain regions. Consequently, the DA hypothesis was reformulated as hyperactivity and hyper-responsiveness of D2 receptors in subcortical regions are responsible for psychotic symptoms, while deficient activity of DA functioning with hypostimulation of D1 receptors in the prefrontal cortex can play role in negative symptoms and cognitive impairments. Pharmacological experience with clozapine and aripiprazole called attention on additional role of D4 receptors and partial D2 agonism in development in schizophrenia but further studies did not provided clear results (Shin et al., 2011).

Serotonin hypothesis

The potential role of serotonin in schizophrenia was primarily supported by observations that lysergic acid

diethylamide (LSD) caused psychotic symptoms due to its assumed serotonergic effect. Later it was clarified that partial agonistic effect of LSD on 5-HT2A receptor is responsible for psychotic symptoms. Not independently from this evidence, atypical antipsychotics, such as clozapine, risperidone and olanzapine show higher affinity for 5-HT2A receptors than for D2 receptors (Arnt and Skarsfeldt, 1998). Regarding clinical aspects of 5-HT2A antagonism, now it is clear that it plays role rather in negative symptoms than in psychosis and treatment of whole schizophrenia spectrum symptoms require other receptor modulators than 5HT2A blocking. These findings resulted in different newer hypotheses, e.g. dopamine-serotonin hypothesis, serotonin-dopamine antagonism (SDA) hypothesis, etc. (Shin et al., 2011).

GABAergic and glutamatergic systems

The latest version of the DA hypothesis (postulated by Howes and Kapur) focuses on the modulatory effect of other neurotransmitters like GABA and glutamate on the DA system (Howes és Kapur, 2009). Possible role of dysfunctioning NMDA receptors in schizophrenia is supported by different experiences creating the NMDA hypofunction hypothesis (Belforte et al., 2011). For example, antagonists of NMDA receptors, such as phencyclidine (PCP) and ketamine have similar effects to positive, negative and cognitive symptoms of schizophrenia. The molecular relationship between NMDA receptors and the DA system has been demonstrated by in vivo studies where administration of ketamine for healthy individuals resulted in a significant increase of striatal synaptic DA level while regular ketamine abusers showed upregulated D1 receptors in the prefrontal cortex (Vollenweider et al., 2000; Nedergaard et al., 1988).

Neurodevelopmental model

Environmental factors in combination with predisposing genes appear to be important for the etiology of schizophrenia. It means that heritance of vulnerability genes create the condition for the development of schizophrenia but genes themselves do not cause manifestation of schizophrenia. Early life traumas, like prenatal infections, maternal malnutrition, obstetric complications in combination with vulnerable structure of neural circuits determined by predisposing genetic variants can result in abnormal fetal brain development through synaptic changes (Bale et al., 2011; Nagai et al., 2011; Faludi and Mirnics, 2011). Moreover, as development of brain is not finished until the birth, environmental factors, like child abuse and neglect, war trauma, loss of parents etc. can have similar interacting effect with genetic predisposition in childhood and adolescence too (Larson et al., 2011). The crucial role of disrupted brain development in schizophrenia is supported by numerous abnormalities of early intellectual, neuromotor and neurocognitive performance in individuals later diagnosed with schizophrenia (Tenyi, 2011). The neurodevelopmental model can give an alternative explanation for conflicting results of studies investigating genetic factors by themselves and for time of first manifestation of schizophrenia. Prospective birth cohort studies suggested that altered brain development and fetal stress exposure can be associated through epigenetic modifications (Bale et al., 2011).

FUTURE PERSPECTIVES

In the early era of schizophrenia research newer concepts usually had to refute previous theories and acceptance of new hypothesis was built on explanation of weak points of its predecessor. These ancient models were postulated by dominant characters of psychiatry and their concepts forcedly provided basis for interpretation of central nerves system function, all psychiatric disorders, classification, therapy etc. Later, with development of neurobiological science, more and more complex models were born but not with totally refuse of earlier models, rather completed them with previous valuable results. Up to date we have learned that regulation systems at different levels in the human organism are so sophisticated that two results can be contradictory on the surface but it does not necessarily mean that one of them can be refused – rather our presupposition or methods was wrong. For example according to our knowledge schizophrenia has a significant genetic component but first SNP association studies failed to identify genetic risk factors for schizophrenia. However, we cannot conclude that schizophrenia has not genetic background, moreover that genes cannot be excluded either which's SNPs provided conflicting results. Rather it means that investigation of SNPs has to be completed with other components, like copy number variants or combination of sequence analysis and epigenetics or gene expression profile. Typical example of complex models is the neurodevelopmental concept in which environmental factors with genetic, epigenetic and further molecular mechanisms are combined. Taken together, schizophrenia research and

evidence based, up to date neurobiology has already perfectly met and every blockages are eliminated from their relationship for making comprehensive molecular biological studies. Indeed, parallel with 'winning break' of molecular research, clinical aspects have been relegated to the background at the expense of right interpretation of complex models. We like to emphasize that neurobiological data cannot be interpreted without correct and exact description of phenotypes. Furthermore, it seems that a universal concept of pathomechanism cannot be applied for schizophrenia as a syndrome, rather it is suggested that different subtypes of schizophrenia should be matched with special combinations of assumed pathomechanism components. For example identification of a special subgroup of schizophrenia can be associated with one special genetic variant combined with maternal viral infection during pregnancy while another subtype can be linked to damaged brain development due to drug consumption in adolescence. Although numerous examples exist for investigation of schizophrenia subtypes separately, most of them use subtypes according to the DSM-IV or the ICD diagnostic systems with five and six subtypes. However, regarding failure to find specific relationship between subtypes and pathomechanism, application of more sophisticated phenotype characterization is required such as the Composite Diagnostic Evaluation System (CODE) (Ban, 2007). This complex diagnostic system was a priori developed for testing a hypothesis relevant to the association between 'processing of mental events' and 'signal transduction' in the central nerves system making appropriate environment for molecular research (Ban, 2007). Our research group has begun to revise and validate the Hungarian version of this instrument for schizophrenia in cooperation with the author (Thomas Ban) and first experiences are very promising.

In conclusion, schizophrenia is a complex mental disease covering diverse neuroscientific fields. Increasing body of evidence revealed important details of pathomechanism but there are still numerous missing links in the picture. However, molecular biological methods cannot provide relevant results without sophisticated phenotypic description, thus development of complex diagnostic systems are recommended.

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A szkizofréniakutatás kezdetei és perspektívái

A szkizofrénia komplex pszichiátriai zavar változatos klinikai megjelenéssel. A szkizofréniával kapcsolatos ismereteket a kezdetekben elsősorban a klinikai megfigyelések alapján alkotott elméleti hipotézisek jellemezték megfelelő idegélettani vizsgálódási lehetőségek hiányában, a modern tudományos érában a molekuláris szinten mérhető, idegtudományos adatok kerültek előtérbe; míg a klinikai kép elemzése háttérbe szorult. Ugyanakkor mára egyértelművé vált, hogy a legkorszerűbb molekuláris biológiai mérések eredményeit sem lehet korrekt módon értelmezni komplex, adekvát fenotipizálási eszköz nélkül. Jelen áttekintő tanulmányban a szkizofréniakutatás legfontosabb eredményeit foglaltuk össze, valamint felhívjuk a figyelmet egy komplex diagnosztikai rendszerre (CODE), amely a napjainkban széles körben elfogadott fejlődéselméleti modell méltó klinikai partnere lehet.

Kulcsszavak: szkizofrénia, epidemiológia, etiológia, patomechanizmus