Schizophrenia in childhood and adolescence

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REVIEW

Abstract

Schizophrenia is a disorder characterized by delay in neurodevelopment and by a central disorder of recognition (i.e. with generalized cognitive deficit). Connectivity impairments in the areas of the social brain and cerebellum are the "messenger" of abnormal CNS development in schizophrenia. Processes of neuronal reorganization in cortical and subcortical structures, aberrant forms of pruning, sprouting, and myelinization may play a major role in the pathogenesis of a schizophrenic breakdown. Models of neuroplasticity during adolescence can be connected with models of neurodevelopmental vulnerability and models of neurotoxicity to form an integrated approach in order to better understand premorbid adjustment, onset, and course of schizophrenia. The loss of plasticity and aberrant myelinization lead to a deterioration in cognitive functions, social dysfunction and, in individuals with specific genetic vulnerability, to expression of schizophrenia. This article discusses brain development in relation to the diagnosis of schizophrenia and the basic symptoms of childhood schizophrenia (with early and very early onset) and of adolescent schizophrenia.

CLINICIAN VIEW OF SCHIZOPHRENIA

The mental disorder, schizophrenia, is a polygenic conditioned, neurodevelopmental disorder of unknown, heterogenic etiology. It has trans-culturally similar symptoms and a prevalence of around 1%. The onset of the disorder is most frequent (75%) in adolescence and early adulthood, between the ages of 13 and 16 (15%); childhood onset schizophrenia (COS) between the ages of 10 and 13 (4%); and very early onset schizophrenia (VEOS) before the age of 10 (1%). Childhood schizophrenia is characterized by delayed neurodevelopment and central cognition disorders, also known as a generalized cognitive deficit. In the social case history, the "broken home" is found in high percentage (45%) of cases, and more often associated with a death experience (including death of parents). Additionally, poor or nonexistent relationships with peers are also described. At disease onset, depressive symptoms are often present together with an abnormal EEG and neurological soft signs [10]. Should schizophrenia occur in childhood, the prognosis, in comparison to adult patients, is much worse and social maladaptation is more significant. Adolescents, who have a good family background, better premorbid developmental achievements, favorable personalities and attitudes, less vulnerability and good social adaptation, have a much better prognosis. A poor prognosis is found in cases where patients have a family history which includes psychotic behavior, a dysfunctional family background, an early and

overt disease onset, and in cases where there are specific organic handicaps. Furthermore, it is necessary to recognize that in patients diagnosed with schizophrenia, there is increased risk of suicide and increased risk of premature death. The risk of suicide in schizophrenics is much higher than even bipolar affective disorder. The highest risk of suicide is in adolescents, who kteri maji nahled na their disease and in whom post-psychotic depression (PPD) has been diagnosed. The Schwartz group, from Israel, have prepared diagnostic criteria for PPD in adolescents which will be included in the DSM V [14].

Another question regards whether insensitivity to pain, which is associated with increased morbidity as well as mortality, may be a prodromal predictor of schizophrenia.

In childhood schizophrenia, more often than in adults, reclusiveness, obsessions/compulsions, and friendlessness occur during development of personal traits; prior to the illness, non-socialized behavioral disorders take place more often, with occasional occurrences of aggressiveness. Additionally, familial risk with genetic loading is significantly higher in 2nd degree relatives (psychosis, suicide, alcoholism) as well as in 1st degree relatives (psychosis, suicide, alcoholism and personality disorder) [10].

DIAGNOSTIC CRITERIA

For schizophrenia in preschool age

More common than the schizophrenia diagnosis, are prodromal symptoms of schizophrenia, which manifest as autism. Thinking disorders as well as perception disorders are difficult to prove and are evidenced by what is known as delusion fantasy syndrome.

These symptoms are generally found in childhood schizophrenia:

- Unaware of their own identity in combination with perception deficits;
- Serious disturbances with regard to emotional relationship to people, social anxiety and withdrawal;
- Thinking disorders, which are focused, in children up to the age of 13, mainly on parents, myth figures, and animals; perception disorders, mainly auditory hallucinations, which occur in up to 80% of cases; magical and incoherent thinking with the loss of associations, not allowing interaction and confrontation between the internal and external world; disturbed contact with reality, not understanding context;
- Emotional disorders, without empathy, without interest and curiosity, social isolation or, the opposite, oversensitivity, irritability, and emotional incontinence;
- Abnormal illogical anxiety in younger children, in school age children anxiety often manifests with phobias, obsessions, and rituals;
- Speech disorganization with cognitive and social disorders – speech development retardation and communication defects [10].

Schizophrenia in adolescence

There is a typical alteration of emotional responses in adolescent schizophrenia. Adolescents keep a distance; they are reserved toward adults but also toward peers, and appear to be without emotional feelings. Their poor emotional control is manifest in increased irritation and affective lability, especially with regard to changes in previously well structured or highly ordered situations. Conflict with family members, as well as friends, are typical, as are learning problems. Thinking and perception deficits can be described as passing or fragmented. Delusions are bizarre and absurd, often omnipotent with a cosmic identity and re-birth (the so called phylogenic complex). Behavior is inadvisable, purposeless, and unpredictable, characterized by "foolish" and non-sense activity. Patients are not goal oriented and often abandon goals that have been set. The adolescent may have a shallow, with certain mannerism, interest in religion, philosophy and abstract themes, known as pseudo philosophy. Especially at the time of disease onset, in up to 70% of adolescents, depressive syndrome with suicide attempts and extreme social isolation are also present. Cenesthopathy and hypochondria with dysmorphophobic delusions, paranoid delusions and the syndrome of psychic automatism are also typical. Speech disorders, in terms of communicative ability is also significantly affected, speech is often interrupted, incoherent, and differentiation of the object mind and the "I" mind occurs [10].

For proper diagnosis, a minimum of 2–3 months of observation is usually necessary to confirm the permanency of the symptoms. In this period, asthenic syndrome is common, involving complaints of decreased psychic performance, difficulties in concentration, forgetfulness, headaches, insomnia, slowness, tiredness, false perceptions, "empty head", and bizarre fantasies. Day dreaming occurs leading to the inability to properly notice changes in the surroundings, sometimes referred to as Vondráček's sudden "life line break-down" [18].

Brain development and schizophrenia

Differentiation and proliferation of neurons begins in the early phase of conception. Differentiation includes the formation of dendrites, axons, synapses and preparation for neurotransmitter production. Neuronal activity increases up to the time of birth and then remains at this level of activity until the age of 12 – 15 months. The development of connections – making of functional circles – is formed by "conversation" among

neurons and occurs according to the "roadmap in the brain", which characterizes the development of anatomic connectivity (including the development of abnormalities in different neurodevelopment diseases) [15]. The development of neurons is accompanied by the formation of glia. Most glia cells are produced during the first year of life. Some are intended for myelinization of axons. During development, an extensive reduction of neurons occurs; overall about half of them case to exist. This means that the synaptic density decreases between the age of 2 and 10 years, by about 50% due to the neuron axonal retraction. Disturbances of pruning, in the period from birth to the age of 12–15 years, may be associated with the development of schizophrenia, as one of the conditions; however this is not the only condition. Although, dysfunction of developmental processes leading up to adolescence and early adulthood, can result in what is known as "unmasking" of an already existent "silent" lesion and the potential trigger for the onset of the disorder. In vulnerable adolescents, it is proposed that excessive pruning of dopaminergic neurons leads to mesocortical hypofrontality causing anhedonia and dysphoria. At the same time, anhedonia and dysphoria are important risk factors for the development of substance abuse. In turn, hypofrontality leads to a reduction in mesocortical feedback inhibition of the mesolimbic system, resulting in aberrant salience and positive symptoms.

Finally, the development of aberrant salience plays a role in both psychoses and cravings. The ontogenetic mechanisms involved in brain development are genetically vulnerable as well as vulnerable to harmful effects of the environment. Changes in genetic regulation modify these early changes and may transform the timing of neurodevelopment, which may contribute to premorbid cognitive impairment and to subsequent disturbances of neural connectivity and transmission, falling under the label of schizotype spectrum, and thus produce a common genetic background for **"social brain"** disorders [5].

Schizophrenic patients have a wide variety of disorders in understanding social, as well as emotional behavior, of other people, leading to the heuristic comprehension regarding the hypothesis that brain impairment leads to social dysfunction. This schizophrenia based hypothesis was already mentioned by Bleuler in his concept of "autistic alliance", which is *de facto* social dysfunction. Different interconnections of functional and structural maps lead to a set of symptoms, which were previously categorized under the term "psychosis." In psychotic disorders, including schizophrenia, disorganization of thinking and perception, the presence of an inappropriate affect, affective flattening, deficits in social perception and social cognition with loss of social cognitive abilities, combined with the associated social behaviors, ultimtely leads to the exclusion of the individual from society. Such changes in structural function are called as connectivity disturbances. Thus the developmental disturbance in synaptogenesis leads stepwise to decrease in connectivity. The onset of desease will manifest itself when this process reaches the critical point.

Thus the hypothesis of "social brain" reflects the interpersonal background of mental life. A child gains social skills through development according to predictable patterns; parents, and society, help lead the child's mind in a socially acceptable direction. Perceiving oneself arises from the social experience. The attitudes of others towards the child create feelings of a personal existence. Thus the individual mind is derived from collective opinion, words, and language of the social context. It is obvious that dysfunction of the "social brain" is present in many psychiatric disorders. It concerns brain areas, which include the prefrontal cortex, orbitofrontal cortex, cingulate, amygdale, temporal gyrus, and parietal association cortex. The primary cognitive deficit in schizophrenia (specifically expressed in the social sphere) is localized mainly in the cortex of the "social brain." With the assistance of neuro-imaging, fronto-temporal and fronto-parietal core "networks" have been discovered, and which, according to Burnse, are the reflections of neurons activating at the "moment of understanding" associated with social situations. It can be thought of as "social cognition at the cellular level" [3].

According to the neurodevelopmental theory, brain development disorder occurs because of interruption of dopamine afferentation to the dorsolateral and prefrontal cortex, with consequent disinhibition of limbic entries to the hippocampus. The "intrauterine dopamine Weinberger silence" is related to the development of cognitive functions during childhood and to vulnerability to the onset of psychosis in the 3rd decennium [10]. Cognitive deficit manifests already in childhood mainly as decreased capacity of working memory, disturbances of explicit memory, decreased concentration (with decreased ability to transfer concentration to new impulses and the prolongation of time reactions), impairment of executive functions (deficits of information processing and strategy formation) and decreased verbal fluency [13]. The level of cognitive functions can be determined by psychological examination (Raven-logic thinking, Wechsler – memory and learning ability, TMT – test of performance function, CPT – performance test, Stroop test, SAT ,VFT – vocabulary fluency test, WCT – card selection term creation test). These tests are useful measures of conceptualization, organized searching, use of feedback, targeting, keeping created concepts in mind, differentiation of categories, testing of new hypothesis and last, but not least, testing of impulse regulation. In healthy volunteers, adult men and women, functional magnetic resonance imaging (fMRI) during the WCT test demonstrated maximum activity in

the right dorsolateral prefrontal cortex, and lesser activity in thalamic nuclei [17]. There is minimum experience using the battery of these tests in children and also in adolescents, and these tests are difficult to access in general clinical practice in the Czech Republic. The WCST has become the instrument of choice in neuropsychiatric research on adult patients. This corresponds to the findings of Bromley, that clinical trials are investigating cognitive deficits and their eventual influence and improvement e.g. following therapeutic interventions; however, clinicians describe cognitive deficits by phenomena, not unified, and they often connect cognitive deficits with the occurrence of negative or depressive symptoms, some even with the occurrence of florid psychotic symptoms. Several interpretations of cognitive deficit may be differentiated: (i) information on learning, initiative and understanding, (ii) most common concept relates to the ability of attention concentration, (iii) others refer to "emptiness" without classification into any social structure, to social life or attempts to discover the individual identity disorder: (iv) another describes problems of daily "functioning" and (v) the last concept relates to learning and remembering. From the above, it is clear how different the neurocognitive or neurobiological concepts are from clinical ones. At the same time, in cognitive deficit therapy, according to the last findings of neuropsychopharmacology, clinicians should monitor responses to therapy and define patients, who will profit from treatment [2].

All of the above mentioned, identified and verified disorders support the hypothesis that in schizophrenia, disturbances in connectivity between the cortex and the deeper sub-cortical structures, take place. Interrupted connections between the amygdale and the cortex evoke positive schizophrenic signs, cognitive worsening, impulsiveness and "affective blindness." Horizontal connections between prefrontal cortex pyramid cells may be an anatomic substrate for working memory [13]. Dysfunction of this area related to working memory impairment has been discovered in that type of adolescent schizophrenia, where it continues to early adulthood [10, 15].

Neuro-imaging studies suggest volumetric differences and aberrant function in the prefrontal and temporal regions in schizophrenia patients compared to controls. Using structural neuro-imaging techniques, **volume reductions** in the amygdale, hippocampus, superior temporal gyrus, and anterior parietal cortex may represent vulnerability to schizophrenia. While volume loss in the prefrontal cortex, posterior parietal cortex, cingulate, insula, and fusiform cortex preferentially observed in schizophrenia may be critical for overt manifestation of psychosis.

Reduction in gray matter volume also occurs in healthy siblings of schizophrenics, mainly in the prefrontal and temporal areas, although it occurs bilaterally, it occurs more on the left side. The reduction can be considered to be a **family trait marker** specific for schizophrenia [8, 13]. Furthermore, abnormities in white matter in the amygdalo-orbitofrontal system and dysgenesis of the corpus callosum have been discovered, and it was shown that the decrease in the hippocampus is only about 10%, however the sub-regional maps reveal a different picture. Sub-regional maps showed heterogeneous changes with loss of hippocampus volume in both the anterior and posterior ends, while the body of the hippocampus gained in volume [12]. Examination by proton magnetic resonance spectroscopy (PMRS) allowed researchers to determine the decrease in the N-acetyl aspartate (NAA) – choline ratio in the left frontal cortex and to suggest that the reductions were responsible for verbal memory impairment. Working memory deficits in schizophrenic patients are once again being linked to GABA, where the inhibition synaptic transmission occurs [9].

Cortical dysfunction may therefore also be caused by an alteration in GABA neurons. They represent a subpopulation of cortical neurons, localized in prefrontal area, which directly control entries to excitatory pyramidal cells and to dopaminergic axons [10]. Disconnection together with increased dopamine activity is characterized by decreased function of GABA receptors (**GABA-R**), which are necessary for **neuron migration.** Different neuron migration causes different synaptic connections. Dopamine hyper-activation of left hemisphere in schizophrenic patients can then be related to verbal memory deficits and also related to perseverations, whereas disinhibition in the right hemisphere, specifically in temporo-hippocampal area, relate to visuospatial memory impairment.

In schizophrenics, there is a primary hypofunction of the glutamate system (mainly dysfunction of N methyl D aspartate receptors). NMDA receptors play a role in disturbance of memory, learning, long-term potentiation and synaptic plasticity. Decreased function of NMDA leads to cognitive impairment and to secondary dopamine neurotransmission dysregulation. Inhibition of synaptic GABA connections evokes disturbance of working memory. Decreased expression of GABA neurons in the prefrontal area is related to methylation, i.e. the **expression of neurons** can be **influenced epigenetically** [9].

{Note: Epigenetics are concerned with changes in behavior of genes, and also with changes in genes due to our own behavior. Epigeneticians investigate actions other than mutations, which lead to changes in gene function. One of these is methylation. Methylation may increase or decrease gene expression, may turn it on or off, and can therefore work as an accelerator or a break.
Methyl groups control genes, which then influence prenatal and postnatal development, and in some disorders

so, that **other** reactions to stress situations occure only in adulthood. Temporary exposure, during the development, to anything which influences methylation can change an animal or a human being for the whole life; while the source for methyl groups are is exclusively from food.

Models of neuroplasticity during adolescence can be connected with models of neurodevelopmental vulnerability and models of neurotoxicity within an integrated approach in order to better understand premorbid adjustment, onset, and course of schizophrenia. From the perspective of psychosocial development, prominent developmental tasks have to be considered, which represent a major challenge to all adolescents, having, however, special risks for some adolescents. Patterns of psychosocial adaptation found during this developmental period must be considered as part of the long-term consequences. Neurobiological reorganization and psychosocial transformation are two sides of one developmental process which occurs during adolescence and young adulthood. Apart from different development of the gray matter, what is also identified, are structural abnormities in the white brain matter.

Myelinization influences oligodendroglia functions and thus, the connectivity,, quality of the myelin, and synaptic transmission. Postnatal myelinization is the most intensive between the age of 4 and 20 years and is accompanied by gradual axonal growth. During childhood and adolescence, active myelinization occurs between the cortex and hippocampus, and myelinization within the frontal and temporal lobes is being completed. The maximum volume of white matter in the middle years of adolescence occurs, myelinization in the frontal lobes and in the association areas is finalized during this time [10]. White matter then grows in volume until middle age. Slower development of white matter tracts in connection with age supports the hypothesis that **white matter abnormalities in schizophrenia reflect a neurodevelopmental disorder.** Australian group of Whitford, described, in patients having their 1st schizophrenia episode, a reduction of **white matter** volume in the fronto-temporal area and an increase in volume bilaterally in the fronto-parietal area [19].

Myelin and oligodendroglia in schizophrenics are abnormal and present a functional barrier to creation of cortical and cortico-subcortical connections.
Not only myelin is dysfunctional in these patients, but also the genes related to it and to **oligodendroglia. The** CNP gene is synthesized in the early stages of myelinization and probably plays a role in communication and in the signal transfer cascade. The MAG gene participates during the onset of myelinization. The GSN gene, or gelsolin, is necessary for the development of oligodendrocytes. Down regulation of gelsolin in schizophrenic patients may play a role in neuron and oligodendroglia dysfunction caused by **glutamate.** Genes related to glutamate transmission influence neuron differentiation and cell signaling. Communication between hippocampal neurons and immature oligodendrocytes has been clearly demonstrated. Probably, a fast excitation signal path exists, which with the help of transporters in oligodendroglia regulate glutamate concentrations and thus prevents its toxic effects which can lead to demyelinization. Hypo-glutamate, as well as hyper-glutamate conditions probably coexists in the brain of schizophrenic patients. Also, a decrease in neuron density in the cingulate gyrus has been described in schizophrenics, with increased linking ability of GABA receptors. A decrease in GABA inhibition may lead to an increase in glutamate activity and to hyper-excitation conditions. All these findings support the hypothesis that dysfunction of oligodendroglia with the consequent abnormalities with regard to myelinization, supported by the neurotoxic effects of glutamate with decreased GABA inhibition activity, contribute to the development of schizophrenic symptoms [10].

Also in the **cerebellum**, a different architecture of synapses influences changes in neurotransmission which lead to cognitive deficit. Cognitive processes (e.g. planning, strategy formation, working memory etc.) are modulated by two-way interconnections between the cerebellum and prefrontal lobes. Decreased volume of the cerebellum in premature babies leads to significant worsening of performance of these children on cognitive tests and a more frequent occurrence of dyslexia [1]. Disturbances in connections between the prefrontal cortex and cerebellum have been clearly demonstrated in dyslexia [6]. An increased size of the cerebellum, in children and later in adults, has been linked to the better memory function, language operations, and overall IQ [7].

In isolated cerebellar diseases, disturbances of executive cognitive functions related to the planning, visuospatial working memory and verbal fluency disorders have been described. Based on these and other observations of cerebellum disorders, a new term has been introduced – **cerebellum cognitive affective syndrome** – which includes affective disorders, cognitive execution function disturbances, verbal and visual episodic memory impairment, and deficits in visuospatial working memory and speech abilities [11]. Neuropathology and cytoarchitectonic changes in limbic structures, the hippocampus, amygdale, septum, corpus callosum, cerebellum, temporal, and the frontal lobes, in the ventricular system together with the loss of plasticity and myelinization abnormalities are the markers of vulnerability in the individual at risk, same as the cognitive dysfunction and the social brain dysfunction [20]. Thus, **cognitive dysfunction and social dysfunction are considered to be a vulnerability marker and are significant in the prognosis of schizophrenia.** There-

fore, in order to improve the health state of patients, especially adolescents, beside of pharmacotherapy, there is a need of social rehabilitation, with synchronization of social rhythms and social interactions.

Another alternative to the cognitive dysfunction explanation, involves investigation of the **neurocognitive phenotype in schizophrenia.** The determinants of neurocognitive changes in schizophrenia are currently unknown. Bilder et al discovered that the presence of Met allel gene, COMT is connected with better performance in the speed and concentration domains, but not in the area of executive and sight-perception functions [10]. Polymorphisms of the gene for catechol-O-methyltransferase (COMT) relate to the regulation of aggressive behavior in schizophrenic patients. This observation needs to be viewed cautiously however; it is necessary to take into consideration not only the psychotic phenomena of the disease but also the impulsiveness and specific personality disorders of the patient. [16].

It can be expected that different types of polymorphisms for individual genes are the background for endophenotype dysfunction, which is clinically demonstrated by different symptoms, cognitive deficits, difficulties in concentration and neurotransmission dysregulation. Investigation of functional polymorphisms through complete genome scans did not establish an association with one or more genes, which could be related to schizophrenia; however candidate genes were discovered with various degree of probability for association with the schizophrenic etiology [15].

CONCLUSION

Early neurodevelopmental delay is not only a non-specific risk factor for the manifestation of psychiatric disorders in adolescence, but it is a strong specific predictor of the possible onset of schizophrenia.

Emotional disorders and bad psychosocial adaptation (mainly disturbances in interpersonal relationships with peers) are very often connected with the onset of schizophrenia, schizotypic and bipolar affective disorder, and anxious depressive disorder in adolescence. Still, delayed speech development and specific cognitive dysfunction are significantly different from those seen in healthy, control, children and are present only within the spectrum of schizophrenic disorders [4]. Primary cognitive deficit in schizophrenia is localized mainly in the cortex area of the "social brain" and neuro-imaging techniques have demonstrated changes in the size of various parts of brain – especially reduction – can be considered to be a family trait marker of schizophrenic disorder.

Thus cognitive dysfunction and social dysfunction should be considered to be vulnerability markers and are significant and important with regard to the prognosis of schizophrenic disorder. Neurodevelopmental polygenically conditioned neuropathological and cytoarchitectonical changes, disturbances in neurogenesis in myelinization and dysfunction of neurotransmission – cause disorders in synaptic connections, cognitive deficiency, and most often, first in adolescence – a full and complex manifestation of schizophrenic disorder.

REFERENCES:

1 Allin M, Mastsumoto H, Santhouse AM et al (2001).Cognitive and motor function and the size of cerebellum in adolescents born very pre-term. Brain.**124**: 60–66.
2 Bromley E. (2007). Clinicians' Concepts of the Cognitive Deficits of Schizophrenia. Schizophrenia Bulletin. **33**(3): 648–651.
3 Burns JK. (2004). An evolutionary theory of schizophrenia: cortical connectivity, metapresentation, and the social brain. Behav Brain Sci. **27**/6/851–85.
4 Cannon M, Dean K (2004). Childhood similarities and differences between schizophrenia anfd bipolar disorder. In: Schizophrenia: challenging the orthodox, edited by Mc Donald C, Schultze K, Murray RM, et al, Taylor, Francis UK. pp. 205–211.
5 Dunbar RI, Shultz S **(**2007) Evolution in the Social Brain *Science* Vol. **317**. no. 5843, pp. 1344–1347.
6 Eckert MA, Leonard CM, Richards TL, et al, (2003).Anatomical correlates of dyslexia: frontal and cerebellar findings. Brain. **126**: 482–494.
7 Frangou S, Chitins X, Williams SC (2004). Mapping IQ and gray matter density in healthy young people. Neuroimage. **23**(8): 800–805.
8 Gogtay N, Greenstein D, Lenane M, et al, (2007). Cortical brain development in nonpsychotic siblings of patients with childhood-onset schizophrenia. Arch-Gen-Psychiatry. **64**(7): 772–80.
9 Hashimoto T, Arion D, Unger T,(2008). Alterations in GABA related transcriptosome in the dorsolateral prefrontal cortex of subjects with schizophrenia. Mol. Psychiatry. **13**: 147–161.
10 Malá E (2005). Schizofrenie v dětství a adolescenci. Praha (ČR): Grada.
11 Mravec M,(2008). Mozočok: Štruktura, funkcie a jeho úloha při neuropsychiatrických ochoreniach. Psychiatrie. **12** (1): 17–26.
12 Nugent T, Herman DH, Ordonez A, et al, (2007). Dynamic mapping of hippocampal development in childhood onset schizophrenia. Schizophr-Res. **90** (1–3): 62–70.
13 Ross RG, Wagner B, Heinlein S.et al, (2008). The stability of inhibitory and working memory deficits in children and adolescents who are children of parents with schizophrenia. Schizophr-Bull. **34** (1): 47–51. .
14 Schwartz-Stav O, Apter A, Zalsman G, (2006). Depression, suicidal behavior and insight in adolescents with schizophrenia. Eur-Child-Adolesc-Psychiatry. 15 (6): 352–9.
15 Šťastný F, Balcar JV, (2008).Schizofrenie jako genetická porucha synaptického spojení. Psychiatrie **12** (Suppl.2): 29–38.
16 Volavka J,(2008). Vztah mezi COMT a agresí: pohyblivý cíl? Psychiatrie **12** (2): 72–73.
17 Voltz HP, Gase C, Hager F, et al, (1997). Brain Activation During Five Stimulation with the Wisconsin Card Sorting Test A Functional MRI Study of Healthy Volunteers and Schizophrenics. Psychiatry Res. Neuroimaging Sec **75**: 145–157.
18 Vondráček V (1967). Speciální psychiatrie. Praha (ČR): SPN Publishers.
19 Whitford TJ, Grieve SM, Farrow TF, et al, (2007).Volumetric white matter abnormalities in first-episode schizophrenia: a longitudinal, tensor-based morphometry study. Am-J-Psychiatry. **164** (7): 1082–9.
20 Whyte MC, Whalley HC, Simonotto E, (2006). Event-related fMRI of word classification and successful word recognition in subjects at genetically enhanced risk of schizophrenia. Psychol-Med. **36** (10): 1427-39.