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Anatomical changes of the CNS in the course of schizophrenia and recurrent depression a review of current knowledge

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Introduction and purpose of the study: Schizophrenia and recurrent depressive disorder are important mental disorders worthy of special interest in both the fields of psychiatry and neuroradiology. The studies presented in the following paper have made it possible to see a correlation between specific symptoms specific to the aforementioned disease entities and the location of pathological changes within the CNS.
Review methods: The article was based on a review of scientific papers available in the PubMed electronic database, in order to select the appropriate quality of scientific articles, appropriately selected keywords were used: "schizophrenia", "recurrent depressive disorder", "neuroimaging".
Description of the state of the art: Anatomical changes within the CNS are associated with various factors, such as genetics, environment or neurochemical interactions, which affect the development and course of the mental disorders in question. Neuroimaging techniques such as computed tomography (CT) and magnetic resonance imaging (MRI) allow us to detect pathologies in specific areas of the brain and correlate them with the clinical condition of the subject. In this way, we are constantly expanding our knowledge of the connections and neuronal loops that determine proper human functioning in society.
Summary: The diseases presented not only affect the functioning of the patient himself, but also affect his loved ones and the health care system. With the ability to observe the brains of patients with schizophrenia and recurrent depression, knowledge of its structure has expanded significantly. This is a key element in developing more targeted and effective therapies, both pharmacological and psychotherapeutic.

Keywords: schizophrenia, recurrent depressive disorder, neuroimaging

Introduction:

Schizophrenia and recurrent depression are two chronic mental disorders with complex etiology and pathogenesis. Previous studies suggest their multifactorial nature associated with a variety of factors affecting the evolution of the disease. In the case of recurrent depression, the physical state of the body as well as genetic, biological and cultural factors and psychosocial factors (traumatic, stressful life events, difficulties in interpersonal relationships) influence the disease [1].

Genetic, biological, environmental and pre- and perinatal factors as well as neurotransmission disorders in the CNS play a major role in schizophrenia [2]. The two conditions discussed above have a different course in terms of psychopathological symptoms. Symptomatic for schizophrenia are productive symptoms, i.e. so-called positive symptoms such as hallucinations, delusions, negative symptoms including shallowing of feelings, apathy and disorganization of thinking, cognitive disorders or affect disorders [3].

Most cases of schizophrenia occur before the age of 30, with men having a lower average age of onset than women. Recurrent depressive disorder, on the other hand, is characterized by repeated episodes of depression manifested by lowered mood, decreased energy and anhedonia [4]. Depressive disorders are a growing health and social problem, according to the World Health Organization (WHO), and are among the most common mental health problems worldwide. Figure 1 shows the percentage distribution of the prevalence of depressive disorders in each WHO region according to gender. Figure 2, on the other hand, illustrates the prevalence of these disorders by gender by age [5]. Neuroimaging studies indicate that there are structural differences in the central nervous system of those affected by these disorders compared to the healthy population. [6]

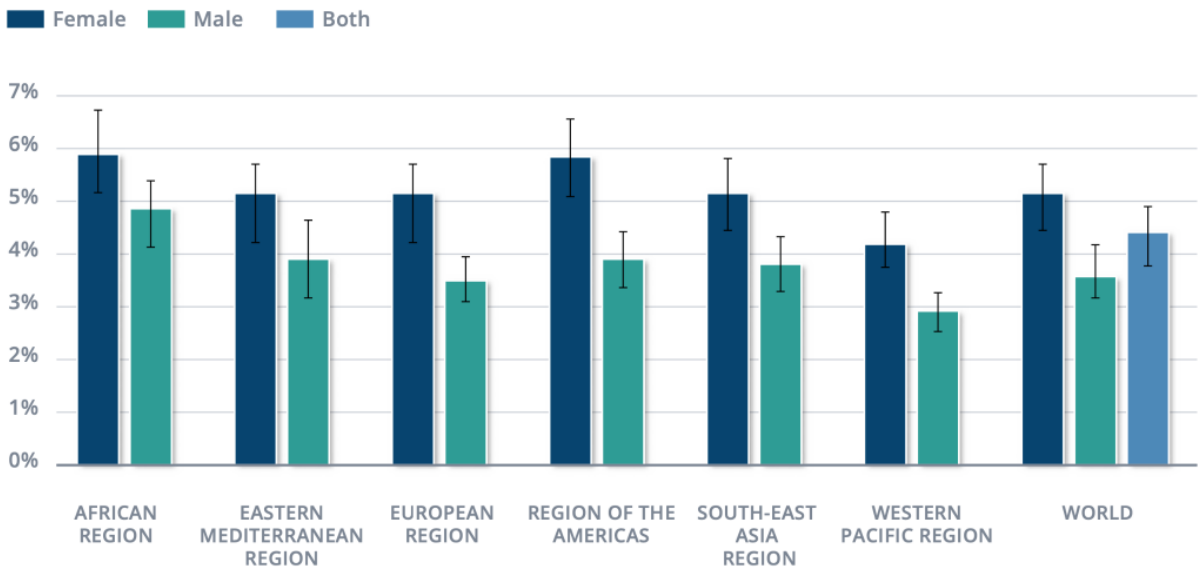

Figure. 1 Prevalence of depressive disorders (%) by WHO regions

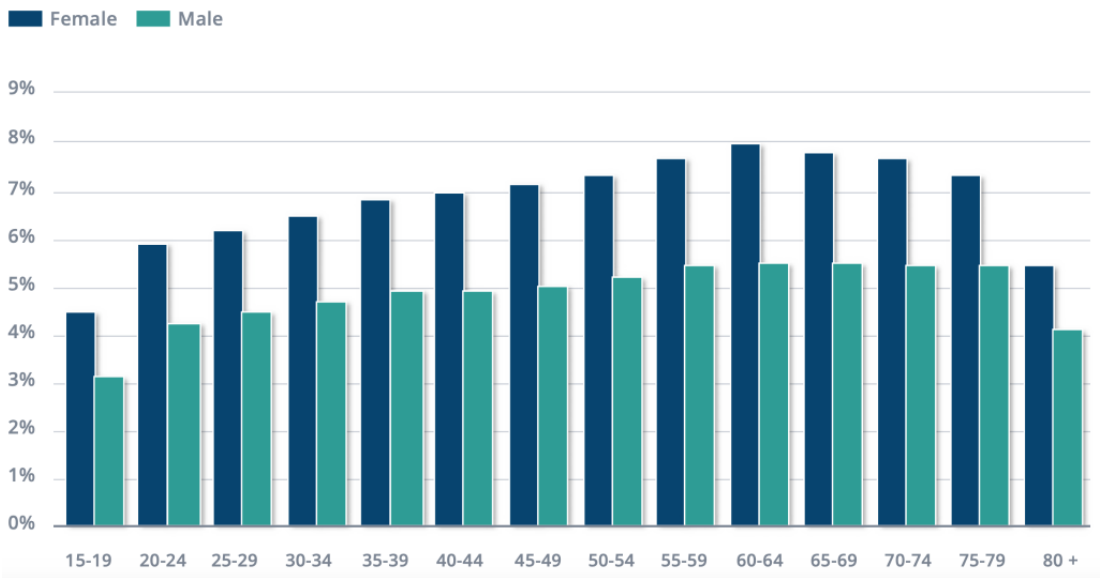

Figure. 2 Prevalence of depressive disorders by gender and age (%)

Objective: This paper aims to present the brain anatomical changes occurring in the course of schizophrenia and recurrent depression, which may explain the causes and mechanisms of many psychopathological symptoms of both disease entities.

Review methods: PubMed and Google Scholar databases were reviewed to identify publications on CNS anatomical changes in schizophrenia and recurrent depression. The literature search was conducted using relevant English keywords: "schizophrenia", 'recurrent depressive disorder', 'neuroimaging'.

CNS changes - Schizophrenia.

In the course of schizophrenia, there are neuroanatomical changes in individual CNS structures. The most common of these are observed in the frontal lobe, temporal lobe and transparent septum as well as in the hippocampus, ventricular system, cerebellum and thalamus.

In addition, changes involving the area of white and gray matter and a reduction in the thickness of the layer covering the surface of the cerebral hemispheres - the cerebral cortex - have also been observed. Depending on the functions performed by specific anatomical parts of the brain and the abnormalities present in them in imaging studies, it is possible to see a differentiated clinical picture in people diagnosed with schizophrenia.

Lesions localized in the temporal lobe can cause perceptual disturbances in the form of auditory hallucinations. On brain MRI imaging in patients with schizophrenia, a noticeable reduced volume of the left hemisphere within the superior and middle cingulate regions is characteristic. In contrast, a defect in the area of the inferior temporal cingulate region affects both hemispheres of the brain [7].

The transparent septum, also known as the septum pellucidum, is a thin, transparent structure that separates the lateral ventricles of the brain. It is an anatomical area responsible for regulating emotion, memory and motivation, among other things. It is also an important element in the transmission of signals between the two hemispheres of the brain. There is a discernible link between the formation of this structure and the normal growth in fetal life of the corpus callosum and hippocampus. Detection of abnormalities in anatomical development lead to the occurrence of typical behaviors in schizophrenia, which include hallucinations and hallucinations, delusions, thinking and speech disorders, emotional and motor disturbances [8]. In addition, a dilated cavity of the transparent septum and bilaterally reduced volume of the amygdala and left posterior parahippocampus have been observed in imaging studies [9].

Special attention should also be paid to the hippocampus, which belongs to the limbic system. Regulation of emotions, maintenance of cognitive functions and proper memory are among its most important tasks. In patients affected by schizophrenia, we can observe a variety of changes in the hippocampus. These include:

1. Reduced volume - studies suggest that people with schizophrenia may have a reduced volume of this structure compared to healthy individuals which, as a result, may contribute to memory deficits and cognitive dysfunction.

2 Cellular structure abnormalities - brain imaging studies in patients show reduced neuronal density and also abnormal shapes of nerve cells. There are abnormalities in the transmission of nerve impulses between neurons in the hippocampus, resulting in a reduced number of synapses and abnormal function of neurotransmitters.

3 Changes in neural transmission - neurotransmitters such as glutamate, GABA, dopamine and others are crucial to hippocampal function. Disturbances in their synthesis and function can cause abnormalities in the processing of information reaching the hippocampus and interfere with the regulation of emotions.

4. impaired neuroplasticity - we define neuroplasticity as the brain's flexibility to both adapt and reorganize neural structures in response to diverse stimuli. Reduced neuroplasticity of the hippocampus affects learning ability, memory and cognitive function which translates into the clinical picture in a group of schizophrenic patients.

Moreover, patients with schizophrenic disorders also have difficulty recreating details of events, which leads to impaired episodic memory and may be associated with the subsequent breakdown of personality integrity [10].

Other changes involve the brain's ventricular system. This system is a system of spaces in the brain containing cerebrospinal fluid. There are several important aspects related to this system:

1. dilatation of the lateral ventricles - neuroimaging studies often reveal dilatation of the lateral ventricles with a particular focus on the right side. This is associated with an increased amount of cerebrospinal fluid located in these spaces.

2. changes in ventricle III and IV - the exact mechanisms of these changes and their relationship

with the pathogenesis of schizophrenia are still the subject of intensive scientific research. However, it is known that their purpose is to regulate and transmit neural signals between parts of the brain, especially between the cerebrum and cerebellum.

3. structural displacement - include pronounced vertical and horizontal shifts

in the structures of the ventricular system. These displacements may be related with abnormalities of brain development in the etiopathogenesis of schizophrenia [11].

Negative symptoms play a key role in determining poor functional outcomes in patients with schizophrenia. Antipsychotic drugs, both first- and second-generation, have shown limited efficacy in treating this group of symptoms. Understanding the neural networks responsible for these symptoms may be key to developing new, more effective therapeutic approaches [12]. Damage or changes in the right hemisphere or both frontal lobes are responsible for the negative symptoms present in schizophrenia, which include apathy, abulia, or anhedonia [13]. A reduction in the volume of the temporal lobe often correlates with a reduction in the volume of the frontal lobe responsible for executive functions, planning, impulse control, and integration of sensory and cognitive information. Deficits in frontal lobe function cause patients to experience difficulties with non-verbal communication in the form of abnormal facial expressions, gestures and spatial orientation. It has been noted that these changes occur mostly in patients with severe disease and even catatonia [14]. With the decrease in volume in the frontal lobe, there is a concomitant increase in the connections between the described lobe in terms of the inferior frontal curve and the parietal lobe, as well as the temporal lobe, with a particular focus on the superior temporal and middle temporal regions. The above problem represents a significant diagnostic difficulty as well as the reason for numerous treatment failures in patients with predominantly negative symptoms [15].

Analogous to the changes in the structures described above, there is similarly a reduction in the volume of the cerebellum and also its cortex compared to the population of healthy individuals. Regulating balance mechanisms, muscle tension and coordination of motor activities, it forms one part of the hindbrain [16]. Reduced density of neurons contained in the cortical layer as well as a decrease in the number of Purkinje cells are among the abnormalities that we count among the changes present in the cerebellum of patients diagnosed with schizophrenia. As a result, they contribute to the presence of motor function deficits and balance disorders [8].

The thalamus is considered another area subject to abnormal modifications that can be visualized during neuroimaging. One of its functions includes the initial evaluation of stimuli and the transmission of signals between different brain areas such as the limbic system and prefrontal cortex. Of great importance is the neuronal connection of the hippocampus and the cingulate nucleus with the anterior thalamic nucleus and the nucleus accumbens. The noticeable asymmetry and deformation of the structure of the thalamus due to its reduced size is one of the anatomical defects within the boundaries of the interbrain. These changes determine reduced activity of the prefrontal cortex and also disturbances in the functioning of working memory. Modifications in the transmission of brain signals between the thalamus and other areas of the brain can also manifest themselves as so-called hyperreactivity. This means that existing connections between the thalamus and the motor and sensory cortex may operate at a higher intensity than physiologically. In some cases, auditory hallucinations or cognitive disturbances may then occur. Over-reactivity of the thalamus can also manifest itself through the appearance of perceptual disturbances, difficulties in processing information or problems with emotion regulation.

Schizophrenia spectrum disorders result from the simultaneous occurrence of neurodegenerative and neurodevelopmental processes . Intense degenerative changes have been observed in people treated for schizophrenia [17].

CNS changes - Recurrent depressive disorder

A breakthrough in the discovery of the correlation of mood disorders typical of depression with changes in the central nervous system is proving to be neuroimaging. Advances in medical technology are enabling clinicians to increasingly diagnose disease entities in all fields, including psychiatry. There are papers and studies confirming the validity and advisability of performing imaging studies in a group of patients suffering from depression. They allow early detection of changes in brain structures and adaptation of individualized targeted therapy. Another undeniable benefit of radiological imaging techniques is the possibility of functional evaluation of the CNS organs under study. Such techniques include proton spectroscopy, functional resonance based on the BOLD effect, as well as diffusion imaging and magnetization transfer evaluation. With these, we are able to determine the activity of individual brain structures. and also assess whether it is adequate. Stuart Oldham and Alex Fornito [18] describe the concept of network nodes, which are defined as special brain regions characterized by a large number of interneuronal connections that play a special role in information processing and integration. Evidence accumulated so far suggests that these nodes are formed already in the prenatal period, but undergo migration and development during childhood, adolescence, and early adulthood.

Fei-Fei Zhang et al [19] indicate that damage to the network nodes highlighted earlier plays a significant role in the onset of major depression (MDD). Among MDD patients, the most common abnormality detected on MRI is lesions of the cortical-subcortical loop. Nodes of this loop include the frontal lobe, parietal lobe, thalamus, shell and hippocampus. The prefrontal cortex has an important function in handling working memory, planning actions and analyzing their consequences; it also inhibits violent emotional states flowing from the hypothalamus and limbic system. Its dysfunction can result in impulsive behavior, memory problems and loss of ability to solve new problems. Reduced divisibility of attention is also observed in patients with disorders of the prefrontal cortex.

Fei-Fei Zhang et al. also describe other changes in a number of brain anatomical structures that accompany patients with MDD, these include gray matter changes in the temporal lobe. White matter changes include reduced fractional anisotropy in the cingulate, hippocampus, parietal areas, inferior temporal lobe and superior frontal lobe. Considering the above data, it is noteworthy how many MRI changes involve the limbic system. It is responsible for regulating emotions, recognizing and interpreting emotions, and creating defensive reactions in response to stimuli. Thanks to it, a person is able to remember given reactions to the stimulus triggering them and use them in the future. Chengxiao Yang et al. paid particular attention to changes in the thalamus that can be visualized in MDD patients. The thalamus transmits most of the information to the right parts of the cerebral cortex, and is involved in processing emotions, arousal and the ability to relate observed stimuli to oneself. The cortico-thalamo-cortical loop of the neuronal network, of which the thalamus is a part, may be an important determinant of various psychiatric diseases, including depression. The medial-dorsal nucleus of the thalamus accumulates information flowing from the cortex, limbic system and striatum to match the appropriate action to the acting stimulus. At the same time, it also functions as part of the reward center by helping to send information from the ventral striatum to the prefrontal cortex. A study by Chengxiao Yang et al [20] suggests that dysfunction within the previously mentioned loop is a result of abnormal functioning of the thalamus. Also, Takamura et al [21] described the specific impact of dysfunction of the reward system seen in MRI studies, leading to anhedonia, or loss of the ability to experience pleasure, one of the axial symptoms of depression.

Adina S Fischer et al [22] specifically pointed out that neuroimaging may also allow us to isolate a group of patients who will respond better to antidepressant treatment and psychotherapy. This has to do with the functioning of the frontal cortex and prefrontal cortex. The greater the activity of the aforementioned areas, the greater the chance of a positive response to treatment. The explanation for this phenomenon is the cooperation between the prefrontal cortex and the limbic system, also known as the main coordinator of reward system functioning. Adequate functional connectivity between these centers makes it possible to optimally adjust the patient's response to an externally acting stimulus. The discovery of a link between the variable activity of areas of the central nervous system monitored by imaging studies and patients' response to treatment could provide an extremely important cue for clinicians in treatment planning. Depression, due to its recurrent nature, poses a huge challenge primarily to the patient himself, so the potential possibility of tests that can function as some kind of predictor in assessing response to treatment could significantly affect his comfort level, as well as how he prepares for pharmacotherapy and/or psychotherapy.

Recurrent depression (MDD) can emerge independently as a separate disorder or as part of bipolar affective disorder. In the course of bipolar affective disorder, anatomical changes occur in similar locations as in depression, but atrophy is more pronounced in the temporal horns of the lateral ventricles and the corpus callosum. In addition, the changes are more often scattered throughout the white matter [23]. Both of these disorders often co-occur together, which causes serious disruption in daily life.

Overview of changes occurring in the CNS - Schizophrenia and Recurrent Depressive Disorder

Analyzing neuroanatomical changes in the course of recurrent depression and schizophrenia, we can see both significant similarities and noticeable differences regarding abnormalities in the area of brain structures. In both diseases, we can find reduced brain volume both within individual brain lobes and within structures such as the hippocampus and thalamus. In recurrent depression, we primarily observe reduced gray matter volume in the temporal lobe, which may correlate with cognitive and emotional deficits. In schizophrenia, on the other hand, a number of changes are observed in the frontal and temporal lobes, transparent septum, hippocampus and thalamus manifested in the form of clinical symptoms such as auditory hallucinations and memory losses.

In both depression and schizophrenia, changes related to the brain's ventricular system have been observed, particularly concerning the dilation of its lateral ventricles. Changes in ventricles III and IV may affect the regulation and transmission of neural signals associated with the pathogenesis of depression. In schizophrenia, on the other hand, the structural shift in the ventricular system may be related to the abnormalities of brain development and neural transmission that occur.

Referring to the analogy of CNS changes between schizophrenia and relapsing depression, both of these disease entities also experience reduced volume within the frontal lobe. This results in dysfunction of executive and cognitive functions, impaired planning, impulse control and also integration of sensory information. Moreover, in the context of depression, reduced volume of the frontal lobe can manifest itself through apathy and reduced psychomotor drive belonging to some of the main negative symptoms. In schizophrenia, the noticeable differences seen in the structure of the frontal lobe can translate into difficulties in non-verbal communication as well as problems with memory, especially episodic memory.

Reduced hippocampal volume in the course of schizophrenia and recurrent depression, can generate memory deficits and cognitive dysfunction. Given the abnormalities in the transmission of neural signals and impediments to the brain's adaptation to environmental and therapeutic changes associated with neurochemical dysfunction of the hippocampus, we suspect that these changes occurred in the course of depression. Nevertheless, difficulties related to the reconstruction of details of events and impairment of episodic memory are typical of changes in the hippocampus following schizophrenia.

Summary

Continuous advances in technology related to imaging of the central nervous system and the constant advancement of knowledge in the field of neuroradiology have become fundamental elements that complement the diagnosis of these psychiatric entities as well as enable a comprehensive understanding of their symptomatology. Both recurrent depression and schizophrenia show analogous structural and functional changes occurring in the CNS. Discrepancies in the localization and nature of the changes can lead to a diverse spectrum of clinical symptoms as well as a multidimensional course of these diseases.

References:

1. Miernik-Jaeschke M, Namysłowska I. Zaburzenia depresyjne u dzieci i młodzieży. Medycyna Praktyczna https://www.mp.pl/pacjent/pediatria/choroby/psychiatria/81302,zaburzenia-depre syjne-u-dzieci-i-mlodziezy (dostęp: 23.11.16).

2. Rybakowski J. Etiopatogeneza schizofrenii – stan wiedzy na rok 2021. Psychiatria Polska. 2021; 55(2): 261-74. https://doi.org/10.12740/PP/132953

3. Kaniewska-Mackiewicz E. Codzienne wyzwania osób z rozpoznaniem schizofrenii. Zeszyty naukowe WSG, seria: Edukacja – Rodzina – Społeczeństwo. 2022; 40(7): 277-304.

4. Cierpiałkowska, L. Psychopatologia. Dodruk. Warszawa: Scholar, 2022.

5. Depression and Other Common Mental Disorders: Global Health Estimates. Geneva: World Health Organization https://www.who.int/publications/i/item/depression-global-health-estimates (dostęp: 3.01.17).

6. Dam S, Batail JM, Robert GH, Drapier D, Maurel P, Coloigner J. Structural Brain Connectivity and Treatment Improvement in Mood Disorder. Brain Connect. 2024; 14(4): 239-251. https://doi.org/10.1089/brain.2023.0063

7. Antonova E, Sharma T, Morris R, et al. The relationship between brain structure and neurocognition in schizophrenia: A selective review. Schizophr Res. 2004; 70(2-3): 117–145. https://doi.org/10.1016/j.schres.2003.12.002

8. Gałecki P, Szulc A. Psychiatria. Wyd. 1. Wrocław: EDRA; 2023. p. 170-176.

9. Liu-Xian Wang, M.B., Ping Li, M.B., Hong He, M.B. et al. The Prevalence of Cavum Septum Pellucidum in Mental Disorders Revealed by MRI: A Meta-Analysis. J Neuropsychiatry Clin Neurosci. 2020; 32(2): 175–184. https://doi.org/10.1176/appi.neuropsych.18030060

10. Callicott JH, Weinberger DR. Functional MRI in Psychiatry. W: Moonen CTW, Bandettini PA. Red. Functional MRI, Berlin, Heidelberg, New York, Barcelona, Hong. Kong, London, Milan, Paris, Singapore, Tokyo; 2000. p. 501-512.

11.Meduri M, Bramanti P, Ielitro G, et al. Morphometrical and morphological analysis of lateral ventricles in schizophrenia patients versus healthy controls. Psychiatry Res. 2010; 183(1): 52-58. https://doi.org/10.1016/j.pscychresns.2010.01.014.

12. Aristotle N. Voineskos, Colin Hawco, Nicholas H. Neufeld i wsp. Functional magnetic resonance imaging in schizophrenia: current evidence, methodological advances, limitations and future directions. World Psychiatry. 2024; 23(1): 26-51. https://doi.org/10.1002/wps.21159

13. Marder SR, Umbricht D. Negative symptoms in schizophrenia: Newly emerging measurements, pathways, and treatments. Schizophr Res. 2023; 258: 71-77. https://doi.org/10.1016/j.schres.2023.07.010
14. Walther S, Vanbellingen T, Müri R, et al. Impaired pantomime in schizophrenia: Association with frontal lobe function. Cortex 2013; 49(2): 520-527. https://doi.org/10.1016/j.cortex.2011.12.008
15. Selemon LD, Goldman-Rakic PS. The reduced neuropil hypothesis: a circuit based model of schizophrenia. *Biol Psychiatry*. 1999; 45(1): 17-25. https://doi.org/10.1016/s0006-3223(98)00281-9
16. Bochenek A, Reicher M, Anatomia człowieka. Wyd. VI Warszawa, PZWL; 2018. p. 210.
17. Murray R, Bhavsar V, Tripoli G, Howes O. 30 Years on: How the Neurodevelopmental Hypothesis of Schizophrenia Morphed Into the Developmental Risk Factor Model of Psychosis. Schizophr. Bull. 2017; 43(6): 1190–1196. https://doi.org/10.1093/schbul/sbx121
18. Oldcham S, Fornito A. The development of brain network hubs. Dev Cogn Neurosci. 2019; 36: 100607. https://doi.org/10.1016/j.dcn.2018.12.005
19. Zhang FF, Peng W, Sweeney JA, Jia ZY, Gong QY. Brain structure alterations in depression: Psychoradiological evidence. CNS Neurosci Ther. 2018; 24(11): 994–1003. https://doi.org/10.1111/cns.12835
20. Yang C, Xiao K, Ao Y, Cui Q, Jing X, Wang Y. The thalamus is the causal hub of intervention in patients with major depressive disorder: Evidence from the Granger causality analysis. Neuroimage Clin. 2023; 37: 103295. https://doi.org/10.1016/j.nicl.2022.103295
21. Takamura M, Okamoto Y, Okada G, Toki S, Yamamoto T, Ichikawa N, et al. Patients with major depressive disorder exhibit reduced reward size coding in the striatum. Prog Neuropsychopharmacol Biol Psychiatry. 2017; 79(Pt B): 317-323. https://doi.org/10.1016/j.pnpbp.2017.07.006
22. Fischer AS, Hagan KE, Gotlib IH. Functional neuroimaging biomarkers of resilience in major depressive disorder. Curr Opin Psychiatry. 2021; 34(1): 22-28. https://doi.org/10.1097/YCO.0000000000000662
23. Solaro C, Gamberini G, Masuccio FG. Depression in multiple sclerosis: epidemiology, aetiology, diagnosis and treatment. CNS drugs. Feb 2018; 32(2): 117-133. https://doi.org/10.1007/s40263-018-0489-5