**Psychiatr. Pol. ONLINE FIRST Nr 80: 1–16**
Published ahead of print 25 September 2017
www.psychiatriapolska.pl
ISSN 0033-2674 (PRINT), ISSN 2391-5854 (ONLINE)
DOI: https://doi.org/10.12740/PP/OnlineFirst/76040

# Can brain-derived neurotrophic factor (BDNF) be an indicator of effective rehabilitation interventions in schizophrenia?

Renata Markiewicz[1], Małgorzata Kozioł[2], Marcin Olajossy[3], Jolanta Masiak[4]

[1] Department of Psychiatric Nursing, Medical University of Lublin
[2] Chair and Department of Medical Microbiology, Medical University of Lublin
[3] 2nd Department of Psychiatry and Psychiatric Rehabilitation, Medical University of Lublin
[4] Independent Laboratory of Neurophysiology, Chair of Psychiatry, Medical University of Lublin

**Summary**

The increasing body of evidence implies that brain-derived neurotrophic factor (BDNF) is the most common neurotrophin in the nervous system, playing an important role as an effectiveness indicator for rehabilitation interventions in schizophrenia patients. Currently, with the modern laboratory and instrumental diagnostic methods it is possible to diagnose deficits influencing the level of patient's functioning and use them as a basis for establishing individual re-adaptation programs for schizophrenia patients considering various forms of the therapy in different environments. Based on the PubMed and Scopus search tools a review of the available literature was performed and the paper presents current results of studies analyzing a relationship between selected rehabilitation interventions used in schizophrenia patients and changes in BDNF levels (a correlation between BDNF levels and physical activity and EEG Biofeedback therapy). Out of 240 records identified in total, the ones concerning the subject matter of the paper were taken into account. Studies concerning use of the presented method appear to indicate usefulness of BDNF factor in evaluation of effectiveness of implemented rehabilitation interventions in this group of patients. Changes in neurotrophin levels may indicate a synergy of the central and the peripheral nervous system, and high BDNF levels depending on physical activity and a neuromodulating effect of the EEG Biofeedback therapy may indicate their effectiveness. Use of various neurorehabilitation methods may improve the social functioning in schizophrenia patients. Treating BDNF as a biological indicator of those processes may represent an interesting hypothesis.

**Key words**: BDNF, physical activity, EEG Biofeedback, psychiatric rehabilitation

## Introduction

Schizophrenia is a mental disorder of a multifactor pathogenesis affecting about 1% of the population [1]. This disorder is characterized by pronounced positive symptoms in the acute phase and pronounced negative symptoms in the post-psychotic phase. The listed symptoms are a consequence of dysfunctions in activity of various areas of the brain, mainly the frontal and temporal regions, limbic and central structures, and basal ganglia [1–4]. Dysfunctions in the prefrontal region most strongly affect processes associated with short-term memory, attention, emotions and executive functions [1, 5–8]. These anomalies have a strong influence on patients' quality of life and social functioning [1, 5, 6, 9–11].

Schizophrenia, as an illness with a varying course, requires multidirectional rehabilitation interventions, however, the basic form of therapy is pharmacological treatment [12]. When the acute psychosis is reversed, multidirectional, non-pharmacological activities are initiated [12, 13]. They are characterized by an extensive therapeutic range and focus on family, professional and social aspects. Both treatment stages are important, because they divide the whole rehabilitation process into early and delayed, accordingly [12, 14]. The early process aims at eliminating acute symptoms of the illness, restoring disrupted social relations, and reducing effects of chronization, the so-called defect and hospitalism [12–14]. The delayed period aims at compensation of diagnosed dysfunctions and establishing the scope of provided assistance. It includes: improvement in dysfunctions, increasing patient's social activity and facilitating their professional and family adaptation. Both stages are important and their integration and appropriate selection of influences facilitates compensation of deficits [14].

When establishing an individual therapeutic program for a patient, a scope of revalidation must be planned, considering not only influences such as: neurorehabilitation, psychoeducation, psychotherapy, and physical and artistic activities, but also personality predispositions of patients, their hobbies, illness duration, number of hospitalizations or their social and professional status. Only when the developed plan considers all those aspects, it is possible to achieve positive results in the whole treatment and rehabilitation process [15]. They will be visible not only in patient's daily life, but also confirmed by results of modern diagnostic tests, such as: f-MRI, PET, spectroscopy, the brain-derived neurotrophic factor (BDNF).

This paper is an attempt to demonstrate in a group of schizophrenia patients a relationship between selected rehabilitation interventions and the levels of the brain-derived neurotrophic factor (BDNF) on a basis of available publications and previous study results. The verified issues considered the effects of physical activity and the EEG Biofeedback therapy on the neurotrophic factor (BDNF) levels in schizophrenia patients.

## BDNF – brain-derived neurotrophic factor

The brain-derived neurotrophic factor (BDNF) belongs to a group of secretory polypeptides, so-called neurotrophins. Together with other proteins, including the nerve growth factor (NGF), neurotrophin NT/3 and NT/4/5 (proteins supporting

synapse development), it participates in neuron function and influences the function of the central and the peripheral nervous system [16–21]. BDNF, synthesized as glycosylated propeptide (pro-BDNF), is generated as non-glycosylated mature protein following its processing into a proteolytic factor [22–24]. The studies indicate that its highest level is present in the hippocampus, the amygdala, the neocortex and the cerebellum [23–27], and its main source are T and B cells, cells of the connective tissue and granulocytes [21].

BDNF binds to the tyrosine receptor kinase B, Trk-B, and the p75 receptor [28–29]. After activation and phosphorylation of tyrosine residues, the tyrosine receptor kinase B activates the process of intracellular cascade [30, 31] and initiates transcription factors influencing cell life, its growth and differentiation [32, 33]. The p75 receptor is not very well characterized and possibly is a common receptor for all neurotrophins. In its processing, it does not involve the kinase path, therefore, its activation at a certain level induces apoptosis and retrograde transport [30, 33–35]. It may appear that the p75 receptor is obsolete due to its negative effects; however, numerous reports suggest that at a certain stage its participation and mechanism promote axon growth and correct modulation of the Trk-B [36–38].

The BDNF factor is located (apart from the nervous system) also in the heart, skeletal muscles, smooth muscle cells, lungs, platelets and fibroblasts [39–42]. It contributes to stem cells development and differentiation, synapse development, regulation of neural circuits [27] and formation of memory pathways [20, 23, 24, 26, 27]. Its synergistic effect on the central and the peripheral nervous system is very important, because, according to the studies, BDNF contributes to neuron regeneration following various disorders, including ischemic stroke, posttraumatic disorder or toxic poisoning [43, 44]. Apart from the above-mentioned Trk-B receptor, the neuron growth and differentiation factor – NGF – also participates in those processes. Numerous studies emphasize a negative correlation between abnormal BDNF levels, Trk-B dysfunction and no BDNF–Trk-B signaling, and disorders – depression, schizophrenia, epilepsy, and Alzheimer's and Huntington's diseases [24, 45–49].

Mechanisms and effects of neurotrophins action in the human body are shown in Figure 1 at the end of the article.

## BDNF and pathophysiology of schizophrenia

Lack of a clear standard in approach to rehabilitation and monitoring of the schizophrenia course in patients prompted researchers to focus on laboratory parameters. The increasing body of evidence implies that the brain-derived neurotrophic factor (BDNF), as the most commonly known neurotrophin in the nervous system, plays an important role in pathophysiology of mental disorders, mainly depression and schizophrenia; however, its precise role is still not known in full [50]. It is known to cause changes in synapses in various regions of the brain [23–27], and influences the neuron function, their differentiation, and synaptic plasticity. Differences in activity of this factor result in disorders in cortical and synaptic circuits in the brain, and cause anomalies in synthesis of protein polypeptide chains (translation) and neuronal dysfunction [1, 51–54].

Researchers emphasize high significance of GABA, glutamate and dopamine in schizophrenia pathogenesis [1, 54]. They consider as important the effect of dopamine produced in dopaminergic neurons. Eight dopaminergic pathways are known, transmitting stimulation through neurotransmission. The four major pathways are: mesolimbic, mesocortical, nigrostriatal and tuberoinfundibular pathways [55].

Dopamine binds to receptors of different action profiles: receptor-$D_{1,}$ having a post-synaptic effect, and receptor-$D_{2,}$ having a pre-synaptic and post-synaptic effect. In normal conditions, dopamine levels are low [56], because the high dopamine level inhibits the respiratory chain, formation of free radicals, and induction of self-oxidation process [57]. This is confirmed by the dopamine hypothesis [58] assuming that to find the causes of schizophrenia, the following should be verified: 1) excessive activity of dopaminergic neurons, causing a psychotic state (positive symptoms) due to an increased dopamine production and excessive stimulation of $D_2$ receptors; 2) reduced activity of dopaminergic neurons, causing decreased stimulation of $D_1$ receptors resulting in development of negative (deficit) symptoms [58].

Excessive dopamine secretion observed in schizophrenia triggers biochemical processes adversely influencing normal cell functions. Those processes are associated with blocking synthesis of BDNF m-RNA that plays a protective role [1, 59–61]. Lack of a protecting factor with simultaneous inhibition of its expression results in loss of tyrosine hydroxylase, and in consequence, abnormal neuron function [60]. This conclusion is based on studies of Baquet et al. [62], who proved that mice in which BDNF expression in mid-brain and hind-brain does not occur, have lower levels of hydroxylase and clearly reduced expression of dopaminergic neurons in the substantia nigra. Tan et al. [63], verifying results obtained by Baquet et al., studied a group of schizophrenia patients, and additionally considered in the experiment dyskinesia or its lack. Their data indicate that patients with dyskinesia have lower BDNF levels versus those patients in whom dyskinesia was not observed [63]. The results of their studies probably confirm the decreased expression of dopaminergic neurons in patients with dyskinesia. Other researchers, Takahasi et al. and Durany et al., studied BDNF levels in the hippocampus and in the frontal part of the cingulate gyrus. However, their results differed. Takahasi showed higher BDNF levels in the analyzed structures, while in studies of Durany they were lower [1, 64, 65], compared to the control group. Hashimoto et al. [66] analyzed BDNF levels in the prefrontal region and found their significant reduction in schizophrenia patients versus subjects in a control group. The review of the above-mentioned studies indicates some problems with an unambiguous interpretation. They may result from many reasons – a post-mortem analysis of samples [1, 65], type of rehabilitation interventions, or a treatment process [67, 68].

An issue associated with the treatment process should be emphasized in particular. Erikson et al. [67] noticed that the chronic nature of the treatment process itself has a strong influence on the hippocampus volume. According to those authors, its reduction is frequently observed in patients treated for a long time, or completely untreated. Therefore, it should be reflected in changes in levels of parameters such as BDNF. Results obtained by Erikson et al. prove that clearly there is a relationship between lower brain volume, dendritic density and defective morphological and structural remodeling.

**Influence of physical activity on the BDNF levels in schizophrenia patients**

Physical activity is one of the aspects in the normally functioning body. Regular exercising influences metabolism and causes numerous changes in various systems. Those changes depend on a number of biochemical changes resulting from gasomediators (NO, CO, $H_2S$) distribution and processes initiated by them [69]. Processes associated with neurogenesis, angiogenesis and activation of brain regions associated with blood flow through the brain form a basis for functional and anatomical changes. Physical activity initiates secretion of many trophic growth factors – neurotrophins: the nerve growth factor (NGF), neurotrophins 3 and 4/5 (NT3, NT 4/5), and the brain-derived neurotrophic factor – BDNF. Those neurotrophins cooperate with cell receptors p75NTR and Trk-B, and facilitate cell proliferation, migration and differentiation [19,30].

Brain-derived neurotrophic factor is expressed when neurons are active, when energy processes and associated changes in potential occur. Those processes result in production of neurotransmitters facilitating remodeling of the synaptic network and formation of new branches. This process is only possible when a change in the action potential occurs, depending on an effective stimulation. Neural cells in which those changes do not occur, cannot remodel or modify, and their function becomes limited [22, 25, 27, 32]. This is confirmed in numerous reports, including studies of Mattson and Mennerick et al., implying that lack of energy processes results in reduction in cascade biochemical processes, inhibition of neurotransmitter production and a reduced synthesis of BDNF. Following an analysis of those findings it can be concluded that lack of transmission in the signaling pathways has a negative effect on formation of the neuron circuits [70–71]. Similar data is presented in reports of Mabuchi et al. [72] and Powers et al. [73]. They indicate that by inducing an inflow of sodium and calcium ions, activity of muscle and neural cells results in an increased transport of electrons, activation of metabolic processes in cells, intensified production of proteins and enzymes, stimulation of transcription, and an increase in number of vesicles containing neurotransmitters. The researchers are of the opinion that all those processes ensure cell viability, and the increased signaling causes production of glutamate, anti-apoptosis protein Bcl-2, antioxidant enzymes, and DNA enzymes [72, 73].

A cycle of biochemical transformations induced by physical exercises limits neural degeneration and increases BDNF production. Larsson et al. [74] emphasize that a type of exercises, duration and age of a person subjected to those influences are of importance in limiting changes. Physical activity also stimulates production of cytokines (signaling glycoproteins), produced in response to an energy crisis and microdamages in the muscle fibres [75, 76]. Their production is a beginning of muscle cells repair and regeneration, and inversion associated with reduction in levels of glycogen stored in muscles. The cells of the immune systems (neutrophils, macrophages, and pro-inflammatory cytokines TNF-α and IL-β) participate in this mechanism, as they rebuild the muscle tissue by involving transforming growth factor (TGF-β), platelet-derived growth factor (PDGF) and IL-6. IL-6 additionally stimulates expenditure of energy stored in the liver and in the adipose tissue [75].

Determining the type of physical activity appears to be questionable. Numerous reports emphasize a positive effect of long-term exercises of moderate intensity [75]. The authors explain this by a stable level of stimulation and a constant rate of regeneration allowing development of long-term potentiation memory pathways (LTP) consolidated by regular enhancement [76].

The recent progress allows stating that the levels of BDNF are also influenced by angiogenesis associated with physical activity. A process of blood vessel development with a contribution of the vascular endothelial growth factor (VEGF) is very important and depends on influences of numerous pro – and anti-angiogenic factors [77, 78]. In normal conditions, a balance between those factors is maintained [75].

It is clear that normal brain function, which is subjected to constant reorganization, influences cooperation between central and peripheral trophic factors. This relationship results from a two-directional synergism and is associated with functioning of various levels of nervous system. The first level initiates all biochemical processes in responses to stimuli from the environment. In consequence, the signaling pathway is activated, resulting in acquisition and remembering in a situation of consolidation and enhancement (LTP theory). The second level enables peripheral production of VEGF, which, after passing through the blood-brain barrier, stimulates neuron growth under the influence of irisin. This, in turn, induces proliferation and neurogenesis in the hippocampus The whole process involves immune cells, muscles and the liver. They have an important influence on the brain, which initiates production of VEGF through biochemical processes [76]. Recent studies report that stress also influences BDNF levels. Results obtained by Nelson imply that stress initiates the HPA (hypothalamic-pituitary-adrenal) pathway and causes release of glucocorticoids, mainly cortisol. Its intensification inhibits signaling associated with BDNF production thus limiting its expression. Other factors having an adverse effect on BDNF expression include an ageing process, various diseases, excessive psychosocial burden, sleep deprivation, or incorrect dietary habits [79].

Currently, reports on a relationship between the BDNF levels and physical activity in schizophrenia patients are scarce. Majority of publications focus on an analysis of that effect in groups of patients diagnosed with Alzheimer's disease, elderly persons, after stroke, or brain damage. Interesting results were obtained by Kim et al. [80], who attempted such analysis in a group of schizophrenia patients. They exposed the studied group to a cycle of exercises for 12 weeks, three times a week, with the activating program consisting of 25 minutes of physical exercise and 25 minutes of moderate exercise (walking). An analysis of their studies confirmed the effect of physical exercise on the increase in the BDNF levels, and additionally found a positive correlation between its increase and a condition of the cardiovascular system of the subjects.

A conclusion drawn by Kim at al. indicates that providing activating interventions is of importance in comprehensive treatment of schizophrenia patients, and may be an important component of non-pharmacological therapeutic influences [80].

## Brain wave modulation with EEG Biofeedback and BDNF

EEG Biofeedback is a therapy associated with modulation of brain waves, based on a feedback concerning physiological condition of the body. Effectiveness of this method is confirmed by numerous reports justifying use of this form of therapy in the psychiatric rehabilitation model [81–84]. Previous analyses indicate that regular trainings influence activity of specific brain regions [8, 49, 83, 88]. Modulation of brain waves, mainly beta-1, alpha and SMR wave, reduces cognitive deficits associated with memory, attention and executive functions [85]. Restoring of a normal activity in dysfunctional regions is the essence of the EEG Biofeedback therapy. Numerous publications, including studies of Trousselard et al. [86] and Scheinost et al. [87] confirm this relationship. The authors are of the opinion that regulation of the increased frequency of beta-1 wave has a positive effect on anxiety and stress levels, symptoms frequently accompanying schizophrenia [86, 87]. Similar conclusions are presented by Larsen who states that use of EEG Biofeedback is a desired direction in therapy of patients reacting negatively to pharmacotherapy and psychotherapy. It represents an alternative with a positive prognosis for rehabilitation [88].

Other authors, Birbaumer et al. and Mathiak et al., compare self-regulation of EEG Biofeedback to the process of learning and instrumental conditioning based on enhancing specific behaviors and rewarding. The authors state that those processes are a basis for an increase in the involvement of the dopaminergic system, and thus, for an increase in encoding the reward pathway [89–90].

Rota et al. reports interesting conclusions based on research, as they are of the opinion that EEG Biofeedback-based training to activate the frontal region of the right inferior gyrus has a positive effect on verbal functions. He observes that as a result of the training sessions there is a marked improvement in the functioning of Brodmann area 45, as confirmed by the fMRI study [91]. Similar positive effect was also observed by Ruiz et al., who emphasize a significant influence of therapy on perception of emotions in schizophrenia patients, and Naimijo et al. suggest their positive influence on executive function [92–93].

Using the description of Stoeckel et al. it can be said that "correctly selected neurotherapeutic methods are a precondition for improvement in cognitive functions and inducing a process for transformation of the brain function" [94]. Koush et al. [95] emphasize that "brain training" can be understood as a positively acquired behavioral feedback, which improves psychical function and develops brain functional network. Numerous reports emphasize an effect of NF on treatment. Research by Yuan et al. [96] implies that NF interventions improve the amygdala function in terms of receiving information from the hippocampus, hypothalamus, midbrain and temporal lobe. Restructuring of connections between the temporal regions of the cortex and the hippocampus and the amygdala results in transformation in form of enhancement in emotional regulation and reduction in schizophrenia symptoms. Similar results are presented by Gruzelier, who also emphasizes its effect on levels of fear [97].

Although numerous reports verify a positive effect of the EEG Biofeedback therapy on activity of specific regions of the brain in patients with mental disorders, only a few

reports analyze a relationship between those effects and the level of BDNF. Assuming that the nervous system is plastic and has an ability for neuromodulation [98], and its normal function depends on two systems generating brain waves (the thalamocortical system where stimuli are processed and selected; and the septo-hippocampal system with the frontal lobes and the thalamus, where attention, concentration and memory are controlled), then a relationship between the NF therapy and the BDNF levels seems probable. This is implied by feedback loops (stimulating, inhibiting) connecting those two systems, activating the brain cortex through their cooperation. Their normal function depends on a stable neurophysiological regulation. The internal homoeostasis is disrupted by adverse stimuli. Stress may be an example here, as it influences structures and functions of those two connections. It "destabilizes loops", and in consequence, changes generation of brain waves. Therefore, when dysregulation represents the main problem, then an alternate corrective measure is to restore regulation. Using autoregulatory training techniques, Neurofeedback increases this stability, restores internal cohesiveness of neuroanatomic structures and stimulates formation of new neural circuits [98–100].

As reported by Angelakis et al. [101] and Becerra et al. [102], use of NF in elderly persons indicates a relationship between instrumental conditioning and brain activity. An increase in the alpha rhythm influences cognitive functions in the subjects, and in the future this may represent an interesting technique for their modulation and improvement. Also Wang et al. [103] obtained similar results, and confirmed improvement in working memory in those people.

Although reports clearly indicating that the EEG Biofeedback therapy influences changes in the BDNF levels are not available, previous research forms a basis for an assumption that they are correlated. The research in this direction in schizophrenia patients may be a useful tool for verification of usefulness of determination of this parameter as a biomarker in laboratory diagnostics during the EEG Biofeedback therapeutic process.

## Recapitulation

Schizophrenia constitutes a complex health issue, since its etiopathogenesis is multifactorial. A complex therapy facilitates social functioning and the quality of patients' lives. Its basic feature is pharmacological treatment, neurorehabilitation and psychotherapy. The effectiveness of rehabilitation is proven by scientific research, currently mainly focusing on gene analysis [104–106]. Chiefly, the MAO, COMT and BDNF genes polymorphism is subject to verification, as they have an impact on the course of the illness. The results of research papers in the field vary. Norton et al. [107] confirm that the MAO and COMT genes may be subject to epistasis, which may predispose one to the development of schizophrenia, Tybura et al. [108] do not confirm such a relationship.

The discrepancy also applies to the impact of gene polymorphism of BDNF and COMT gene. BDNF, being a protein in dopaminergic neurotransmission influences the neurocognitive functions. Its low level is mainly regulated by antipsychotics. In the case of deficit in catechol-O-methyltransferase (COMT), which participates in dopamine degradation, cognitive disorders occur, consequently leading to negative symptoms in

schizophrenia [109]. A conclusion may be drawn that low level of BDNF and decreased COMT level results in a deficit syndrome in this illness [110].

Such a conclusion is supported by the biogenic amine hypothesis claiming that disorders in the physiology and metabolism of biogenic amines, especially catecholamines (dopamine, norepinephrine) and indolamines (serotonin) may account for the cause and course of many mental disorders [111].

Regardless of the result of research in the field of psychiatric genetics, confirming in various aspects the multifactorial etiopathogenesis of schizophrenia, one is currently looking for neurorehabilitation methods, which following the inclusion in the intervention program could increase the level of social functioning among the patients and reduce the present deficits.

There are many interesting therapeutic interventions, including a positive neuromodulation physical activity effect and the EEG Biofeedback therapy. While seeking for laboratory biomarkers with a view of their effectiveness assessment, the BDNF seems crucial. The previous research has shown that its concentration constitutes the central and peripheral nervous system synergism index [76]. Many papers describe the relationship between BDNF and schizophrenia [60, 64–66], however, information clearly showing the direct correlation between the type of the EEG Biofeedback therapy and the increase in the factor concentration is rare. Research in this field is undoubtedly broadening knowledge. It seems justified to search for an answer to the question whether the selected rehabilitation interventions in schizophrenia influences the level of BDNF. In accordance with the Weber's law, stating that the reaction depends on the multiple changes in the stimulus, it may be possible [112].

## References


1. Favvali G, Li J, Belmonte-de-Abreu P, Wong A, Daskalakis ZJ. *The role of BDNF in the pathophysiology and treatment of schizophrenia*. J.Psychiatr. Res. 2012; 46: 1–11.
2. Niitsu T, Shirayama Y, Matsuzawa D, Hasegawa T, Kanahara N. *Associations of serum brain-derived neurotrophic factor with cognitive impairments and negative symptoms in schizophrenia*. Prog. Neuro.-Psychoph. 2011; (35): 1836–1840.
3. Weinberger DR. *Schizophrenia and the frontal lobe*. Trends Neurosci.1988;11: 367–370.
4. Harvey PD, Koren D, Rechenberg A, Bowie CR. *Negative symptoms and cognitive deficits what is the nature of their relationship?* Schizophrenia Bull. 2006; 32: 250–258.
5. Dickerson F, Boronow J, Ringel N, Parente F. *Social functioning and neurocognitive deficits in outpatients with schizophrenia: a 2-year follow-up*. Schizophr. Res. 1999; 37: 13–20.
6. Reichenberg A. *The assessment of neuropsychological functioning in schizophrenia*. Dialogues Clin Neurosci. 2010; 12: 383–392.
7. Green MF. *What are the functional consequences of neurocognitive deficits in schizophrenia?* Am. J. Psychiat. 1996; 153: 321–330.
8. Lawrie SM, Whalley HC, Abukmeil SS, Kestelman JN, Donnelly L, Miller P et al. *Brain structure, genetic liability, and psychotic symptoms in subjects at high risk of developing schizophrenia*. Biol Psychiatry. 2001;49(10): 811–823.

9. Stahl SM, Buckley PF. *Negative symptoms of schizophrenia: A problem that will not go away*. Acta Psychiat. Scand. 2007; 115: 4–11.
10. Andreasen NC. *Negative symptoms in schizophrenia. Definition and reliability*. Arch. Gen. Psychiat. 1982; 39: 784–788.
11. Karakuła H. *Poszukiwanie wskaźników genetycznej podatności na schizofrenię*. Habilitation thesis, Medical University, Lublin; 2007.
12. Cechnicki A. *Rehabilitacja psychiatryczna – cele i metody*. Psychiatria w Praktyce Klinicznej, Via Medica. 2009; 2(1): 41–54.
13. Meder J. *Aktywny udział pacjentów w leczeniu farmakologicznym*. Warsaw; 1995.
14. Kabanow M, Wołowik G. *Rehabilitacja chorych psychicznie*. Warsaw: PZWL; 1974.
15. http://www.mz.gov.pl/zdrowie-i-profilaktyka/opieka-psychiatryczna/.
16. Traczyk W. *Diagnostyka czynnościowa człowieka*. Warsaw: PZWL; 1999.
17. Konturek S. *Fizjologia człowieka*, t. IV: *Neurofizjologia*. Krakow: Jagiellonian University Press; 1998.
18. Nolte J. *Mózg człowieka*. Wroclaw: Elsevier Urban & Partner; 2011.
19. Chao DL, Ma L, Shen K. *Transient cell-cell interactions in neural circuit formation*. Nat. Rev. Neurosci. 2009; 10: 262–271.
20. Lu Y, Christian K, Lu B. *BDNF: A key regulator for protein synthesis-dependent LTP and long-term memory?* Neurobiol. Learn. Mem. 2008; 89(3): 312–323.
21. Kalinowska-Łyszczarz A. *Neutrophins, cognition and multiple sclerosis*. NeuropsychiatriaiNeuropsychologia. 2012; 7(2): 51–56.
22. Mowla SJ, Farhadi HF, Pareek S, Atwal JK, Morris SJ, Seidah NG et al. *Biosynthesis and post-translational processing of the precursor to brain-derived neurotrophic factor*. J. Biol. Chem. 2001; 276(16): 12660–12666.
23. Lessmann V, Gottmann K, Malcangio M. *Neurotrophin secretion: Current facts and future prospects*. Prog.Neurobiol. 2003; 69(5): 341–374.
24. Lu B, Pang PT, Woo NH. *The yin and yang of neurotrophin action*. Nat. Rev. Neurosci. 2005; 6(8): 603–614.
25. Rodriguez-Tebar A, Dechant G, Barde YA. *Neurotrophins: Structural relatedness and receptor interactions*. Philos. T. R. Soc. B. 1991; 29:331(1261): 255–258.
26. Moretto G, Xu RY, Walker DG, Kim SU. *Co-expression of mRNA for neurotrophic factors in human neurons and glial cells in culture*. J. Neuropath. Exp. Neur. 1994; 53(1): 78–85.
27. Park H, Poo MM. *Neurotrophin regulation of neural circuit development and function*. Nat. Rev. Neurosci. 2013; 14(1): 7–23.
28. Barbacid M. *Structural and functional properties of the TRK family of neurotrophin receptors*. Ann. NY Acad. Sci. 1995; 766: 442–458.
29. Chao M, Casaccia-Bonnefil P, Carter B. *Neurotrophin receptors: Mediators of life and death*. Brain Res. Rev. 1998; 26(2–3): 295–301.
30. Kaplan DR, Miller FD. *Neurotrophin signal transduction in the nervous system*. Curr.Opin. Neurobiol. 2000; 10(3): 381–391.
31. Maisonpierre PC, Le Beau MM, Espinosa R. *Human and rat brain-derived neurotrophic factor and neurotrophin-3: Gene structures, distributions and chromosomal localizations*. Genomics. 1991; 10(3): 558–568.

32. Huang EJ, Reichardt LT. *Neurotrophins: Roles in neuronal development and function*. Annu. Rev. Neurosci. 2001; 24: 677–736.
33. Curtis R, Adryan KM, Stark JL, Park JS, Compton DL, Weskamp G et al. *Differential role of the low affinity neurotrophin receptor (p75) in retrograde axonal transport of the neurotrophin*. Neuron. 1995; 14(6): 1201–1211.
34. Michaelsen K, Zagrebelsky M, Berndt-Huch J, Polack M. *Neurotrophin receptors TrkB.T1 and p 75NTR cooperate in modulating both functional and structural plasticity in mature hippocampal neurons*. Eur. J. Neurosci. 2010; 32(11): 1854–1865.
35. Bibel M, Barde YA. *Neurotrophins: Key regulators of cell fate and cell shape in the vertebrate nervous system*. Gene. Dev. 2000; 14(23): 2919–2937.
36. Geetha T, Jiang J, Wooten MW. *Lysine 63 polyubiquitination on the nerve growth factor receptor TrkA directs internalization and signaling*. Mol. Cell. 2005; 20(2): 301–312.
37. Bentley CA, Lee KF. *p75 is important for axon growth and Schwann cell migration during development.* J. Neurosci. 2000; 20(20): 7706–7715.
38. Harrison SM, Jones ME, Uecker S, Albers KM, Kudrycki KE, Davis BM. *Levels of nerve growth factor and neurotrophin-3 are affected differentially by the presence of p75 in sympathetic neurons in vivo*. J. Comp. Neurol. 2000; 424(1): 99–110.
39. TimmuskT, Palm K, Metsis M, Reintam T, Paalme V, Saarma M et al. *Multiple promoters direct tissue-specific expression of the BDNF gene*. Neuron. 1993; 10(3): 475–489.
40. Yamamoto H, Gurney ME. *Human platelets contain brain-derived neurotrophic factor*. J. Neurosci. 1990; 10(11): 3469–3478.
41. Okada S,Yokoyama M, Toko H, Tateno K, Moriya J, Shimizu I et al. *Brain-derived neurotrophic factor protects against cardiac dysfunction after myocardial infarction viva a central nervous system-mediated pathway*. Arterioscl. Throm. Vas. 2012; 32(8): 1902–1909.
42. Garcés MF, Sanchez E, Torres-Sierra AL, Ruíz-Parra AI, Angel-Müller E, Alzate JP et al. *Brain-derived neurotrophic factor is expressed in rat and human placenta and its serum levels are similarly regulated throughout pregnancy in both species*. Clin Endocrinol. 2014; 81(4): 141–151.
43. Pantazis NJ, ZaheerA, Dai D, Zaheer S, Green SH, Lim R. *Transfection of C6glioma cells with glia maturation factor upregulates brain-derived neurotrophic factor and nerve growth factor: Trophic effects and protection against ethanol toxicity in cerebellar granule cells*. Brain Res. 2000; 865(1): 59–76.
44. Tabakman R, Lecht S, Sephanova S, Arien-Zakay H, Lazarovici P. *Interactions between the cells of the immune and nervous system: Neurotrophins as neuroprotection mediators in CNS injury.* Prog. Brain Res. 2004; 146: 387–401.
45. Villoslada P, Genain CP. *Role of nerve growth factor and other trophic factors in brain inflammation*. Prog. Brain Res. 2004; 146: 403–414.
46. Goldstein B, Young LT. *Toward clinically applicable biomarkers in bipolar disorder focus on BDNF inflammatory markers and endothelial function*. Curr. Psychiat. Rep. 2013; 15(12): 425.
47. Harte-Hargrove LC, Maclusky NJ, Scharfman HE. *Brain-derived neurotrophic factor-estrogen interactions in the hippocampal mossy fiber pathway: Implications for normal brain function and disease*. Neuroscience. 2013; 3(239): 46–66.
48. Xiong P, Zeng Y, Wu Q, Han Huang DX, Zainal H, Xu X et al. *Combining serum protein concentrations to diagnose schizophrenia: A preliminary exploration*. J. Clin. Psychiat. 2014; 75(8): 794–801.
49. Ninan I. *Synaptic regulation of affective behaviors*. Neuropharmacology. 2014; 76: 684–695.

50. Martinowich K, Lu B. *Interaction between BDNF and serotonin: Role in mood disorders*. Neuropsychopharmacol. 2008: 33(1): 73–83.
51. Pezawas I, Verchinski BA, Mattay VS, Callicott JH, Kolachana BS, Straub RE et al. *The brain-derived neurotrophic factor val66met polymorphism and variation in human cortical morphology*. J. Neurosci. 2004; 24(45): 10099–10102.
52. Pang PT, Teng HK, Zaitsev E, Woo NT, Sakata K, Zhen S et al. *Cleavage of pro BDNF by tPA/plasm in is essential for long-term hippocampal plasticity*. Science. 2004; 306(5695): 487–491.
53. Nawa H, Takahashi M, Patterson PH. *Cytokine and growth factor involvement in schizophrenia-support for the developmental model*. Mol.Psychiatr. 2000; 5(6): 594–603.
54. Lewis DA, Hashimoto T, Volk DW. *Cortical inhibitory neurons and schizophrenia*. Nat. Rev. Neurosci. 2005; 6(4): 312–324.
55. Girault JA, Greengand P. *The neurobiology of dopamine signaling*. Arch. Neurol.-Chicago. 2004;6: 641–644.
56. Eisworth JD, Roth RH. *Dopamine synthesis, uptake, metabolism and receptors: Relevance to gene therapy of Parkinson's disease*. Exp. Neurol. 1997; 144: 4–9.
57. Asanuma M, Miyazaki I, Diaz-Corrales FJ, Ogawa N. *Quinone formation as dopaminergic neuron-specific oxidative stress in the parkinsonism*. Acta Med. Okayama. 2004; 58: 221–233.
58. Abi-Dargham A. *Do we still believe in the dopamine hypothesis? New data bring new evidence*. Int. J. Neuropsychoph. 2004; 7(1): S1–S5.
59. Hyman C, Hofer M, Barde YA, Juhasz M, Yancopoulos GD, Squinto SP et al. *BDNF is a neurotrophic factor for dopaminergic neurons of the substantia nigra*. Nature. 1991; 350(6315): 230–232.
60. Sauer H, Fischer W, Nikkhah G, Wiegand SJ, Brundin P, Lindsay RM et al. *Brain-derived neurotrophic factor enhances function rather than survival of intra-striatal dopamine cell-rich grafts*. Brain Res. 1993; 626(1–2): 37–44.
61. Weickert CS, Hyde TM, Lipska BK, Herman MM, Weinberger DR, Kleinman JE. *Reduced brain-derived neurotrophic factor in prefrontal cortex of patients with schizophrenia*. Mol. Psychiatr. 2003; 8(6): 592–610.
62. Baquet ZC, Bickford PC, Jones KR. *Brain-derived neurotrophic factor is required for the establishment of the proper number of dopaminergic neurons in the substantia nigra pars compacta*. J. Neurosci. 2005; 25(26): 6251–6259.
63. Tan YI, Zhou DF, Zhang XY. *Decreased plasma brain-derived neurotrophic factor levels in schizophrenic patients with tardive dyskinesia: association with dyskinetic movements*. Schizophr. Res. 2005; 74 (2–3): 263–270.
64. Takahashi M, Shirakawa O, Toyooka K, Kitamura N, Hashimoto T, Maeda K et al. *Abnormal expression of brain-derived neurotrophic factor and its receptor In the corticolimbic system of schizophrenic patients*. Mol. Psychiatr. 2000; 5(3): 293–300.
65. Durany N, Michel T, Zöchling R, Boissl KW, Cruz-Sánchez FF, Riederer P et al. *Brain-derived neurotrophic factor and neurotrophin 3 in schizophrenic psychoses*. Schizophr. Res. 2001; 52(1–2): 79–86.
66. Hashimoto T, Bergen SE, Nguyen QL, Xu B, Monteggia LM, Pierri JN et al. *Relationship of brain-derived neurotrophic factor and its receptor TrkB to altered inhibitory prefrontal circuitry in schizophrenia*. J. Neurosci. 2005; 25(2): 372–383.
67. Erickson KI, Prakash RS, Voss MW, Chaddock L, Heo S, McLaren M et al. *Brain-derived neurotrophic factor is related with age related decline in hippocampal*. J. Neurosci. 2010; 30(15): 5368–5375.

68. Palomino A, Vallejo-Illarramendi A, Gonzalez-Pinto A, Aldama A, González-Gómez C, Mosquera F et al. *Decreased levels of plasma BDNF in first-episode schizophrenia and bipolar disorder patients*. Schizophr. Res. 2006; 86(1–3): 321–322.
69. Wang JF, Li Y, Song JN, Pang HG. *Role of hydrogen sulfide in secondary neuronal injury*. Neurochem. Int. 2014; 64: 37–47.
70. Mattson MP, Maudsley S, Martin B. *BDNF and 5-HT: A dynamic duo in age-related neuronal plasticity and neurodegenerative disorders*. Trends Neurosci. 2004; 27(10): 589–594.
71. Mennerick S, Zorumski CF. *Neural activity and survival in the developing nervous system*. Mol. Neurobiol. 2000; 22(1–3): 41–54.
72. Mabuchi T, Kitagawa K, Kuwabara K, Takasawa K, Ohtsuki T, Xia Z et al. *Phosphorylation of cAMP response element-binding protein in hippocampal neurons as a protective response after exposure to glutamate in vitro and ischemia in vivo*. J. Neurosci. 2001; 21(23): 9204–9213.
73. Powers SK, Jackson MJ. *Exercise-induced oxidative stress: Cellular mechanisms and impact on muscle force production*. Physiol. Rev. 2008; 88(4): 1243–1276.
74. Larsson E, Nanobashvili H, Kokaia Z, Lindvall O. *Evidence for neuroprotective effect of endogenous brain-derived neurotrophic factor after global forebrain ischemia in rats*. J. Cerebr. Blood F. Met. 1999; 19(11): 1220–1228.
75. Zembroń-Łacny A, Ostapiuk-Karolczuk J. *Udział cytokin w metabolizmie mięśni szkieletowych*. Sport Wyczynowy. 2008; 10–12: 526–528.
76. Ziemba A. *Rola aktywności ruchowej w zapobieganiu zaburzeniom poznawczym*. Aktualności Neurologiczne. 2014; 14(3): 175–180.
77. King A, Balaji S, Keswani SG, Crombleholme TM. *The role of stem cells in wound angiogenesis*. Advances in Wound Care.2014; 3: 614–625.
78. Zielonka TM. *Angiogeneza – część I. Mechanizm powstawania nowych naczyń krwionośnych*. Alergia Astma Immunologia – przegląd kliniczny. 2003; 8: 169–174.
79. Nelson DH. *Regulation of glucocorticoid release*. Am. J. Med. 1972; 53(5): 590–594.
80. Kim HJ, Song BK, So B, Lee O, Song W, Kim Y. *Increase of circulating BDNF levels and its relation to improvement of physical fitness following 12 week of combined exercise in chronic patients with schizophrenia: A pilot study*. Psychiat. Res. 2014; 220(3): 792–796.
81. Hammond D. *What is Neurofeedback*. Journal of Neurotherapy 2006; 10(4): 25–36.
82. Fovet T, Jardri R, Linden D. *Current issues in the use of f MRI-Based Neurofeedback to relieve psychiatric symptoms*. Curr. Pharm. Design. 2015; 21(23): 3384–3394.
83. Yucha C, Mantgomery D. *Evidence-Based Practice in Biofeedback and Neurofeedback*. Association for Applied Psychophysiology and Biofeedback; 2008.
84. Coben R, Linden M, Myers TE. *Neurofeedback for autistic spectrum disorder: A review of the literature*. Appl. Psychophys. Biof. 2012; 35(1): 83–105.
85. Cantor DS, Stevens E. *QEEG correlates of auditory-visual entrainment treatment efficacy of refractory depression*. Journal of Neurotherapy 2009; 13(2): 100–108.
86. Trousselard M, Canini F, Claverie D, Cungi C, Putois B, Franck N. *Cardiac coherence training to reduce anxiety in remitted schizophrenia, a pilot study*. Appl. Psychophys. Biof. 2016; 41(1): 61–69.
87. Scheinost D, Stoica T, Saksa J, Papademetris X, Constable RT, Pittenger C et al. *Orbitofrontal cortex neurofeedback produces lasting changes in contamination anxiety and resting-state connectivity*. Transl. Psychiat. 2013; 30(3): 250.
88. Larsen S, Sherlin L. *Neurofeedback: An emerging technology for treating central nervous system dysregulation*. Psychiat. Clin. N. Am. 2013; 36(1): 163–168.

89. Birbaumer N, Ruiz S, Sitaram R. *Learned regulation of brain metabolism*. Trends Cogn. Sci. 2013; 17(6): 295–302.

90. Mathiak KA, Koush Y, Dyck M, Gaber TJ, Alawi E, Zepf FD et al. *Social reinforcement can regulate localized brain activity*. Eur. Arch. Psy. Clin. N. 2010; 260(2): 132–136.

91. Rota G, Sitaram R, Veit R, Erb M, Weiskopf N, Dogil G et al. *Self-regulation of regional cortical activity using real-time fMRI: The right inferior frontal gyrus and linguistic processing*. Hum. Brain Mapp. 2009; 30(5): 1605–1614.

92. Ruiz S, Lee S, Soekadar SR, Caria A, Veit R, Kircher T et al. *Acquired self-control of insula cortex modulates emotion recognition and brain network connectivity in schizophrenia*. Hum. Brain Mapp. 2013; 34(1): 200–212.

93. Naimijoo P, Rezaei O, Feizzadeh Z. *Neurofeedback training in schizophrenia: A study on executive functioning*. European Online Journal of Natural and Social Sciences. 2015; 4(1): 106–116.

94. Stoeckel L, Garrison K,Ghosh S, Wighton P, Hanlon CA, Gilman JM et al. *Optimizing real time fMRI neurofeedback for therapeutic discovery and development*. Neuroimage – Clin. 2014; 5: 245–255.

95. Koush Y, Rosa MJ, Robineau F, Heinen K, Rieger SW, Weiskopf N et al. *Connectivity-based neurofeedback: Dynamic causal modeling for real-time fMRI*. Neuroimage. 2013; 1(81): 422–430.

96. Yuan H, Young KD, Phillips R, Zotev V, Misaki M, Bodurka J. *Resting-state functional connectivity modulation and sustained changes after real-time functional magnetic resonance imaging neurofeedback training in depression*. Brain Connectivity 2014; 4(9): 690–701.

97. Gruzelier J. *A theory of alpha/theta neurofeedback, creative performance enhancement, long distance functional connectivity and psychological integration*. Cogn. Process. 2009; 10: 101–109.

98. Raudzis D. *Biofeedback*. Master thesis, Opole University of Technology, Faculty of Physical Education and Physiotherapy, Opole; 2009.

99. Smyk K, Smyk K. *Teoria i praktyka terapii neurofeedback*. Training materials of AKSON Medical Education Center; 2015.

100. Othmer S, Othmer SF, Kaiser DA, Putman J. *Endogenous neuromodulation at infraslow frequencie*s. Semin.Pediatr. Neurol. 2013; 20(4): 246–260.

101. Angelakis E, Stathopoulou S, Frymiare JL, Green DL, Lubar JF, Kounios J.*EEG neurofeedback: A brief overview and an example of peak alpha frequency training for cognitive enhancement in the elderly*. Clin. Neuropsychol. 2007; 21(1): 110–129.

102. Becerra J, Fernández T, Roca-Stappung M, Diaz-Comas L, Galan L, Bosch J et al. *Neurofeedback in healthy elderly human subjects with electroencephalographic risk for cognitive disorder*. J. Alzheimers Dis. 2012; 28(2): 357–367.

103. Wang JR, Hsieh S. *Neurofeedback training improves attention and working memory performance*. Clin. Neurophysiol. 2013; 124(12): 2406–2420.

104. Mak M, Samochowiec J, Tybura P, Bieńkowski P, Karakiewicz B, Zaremba Pechmann L et al. *The efficacy of cognitive rehabilitation with RehaComprogramme in schizophrenia patients*. Ann. Agr. Env. Med. 2013;20(1): 77–81.

105. Bosia M, Bechi M, Marino E, Anselmetti S, Poletti S, Cocchi F et al. *Influence of catechol-o-methyltransferase Val158Met polymorphism on neuropsychological and functional outcomes of classical rehabilitation and cognitive remediation in schizophrenia*. Neurosci. Lett. 2007:417(3): 271–274.

106. Cavallaro R, Anselmettis S, Poletti S, Bechi M, Ermoli E, Cocchi F et al. *Computer-aided neurocognitive remediation as an enhancing strategy for schizophrenia rehabilitation*. Psychiat. Res. 2009; 169(3): 191–196.

107. Norton N, Kirov G, Zammit S, Jones G, Jones S, Owen R et al. *Schizophrenia and functional polymorphism in the MAOA and COMT genes: No evidence for association or epistasis*. Am.J. Med.Genet. 2002;114: 491–496.

108. Tybura P, Grzywacz A, Syrek S, Parus M, Samochowiec J. *Związki funkcjonalnych polimorfizmów genów kluczowych enzymów w metabolizmie amin biogennych z występowaniem schizofrenii paranoidalnej oraz ich wpływ na wyniki w PASS pod wpływem leczenia przeciwpsychotycznego*. Psychiatr. Pol. 2006:40(5): 913–923.

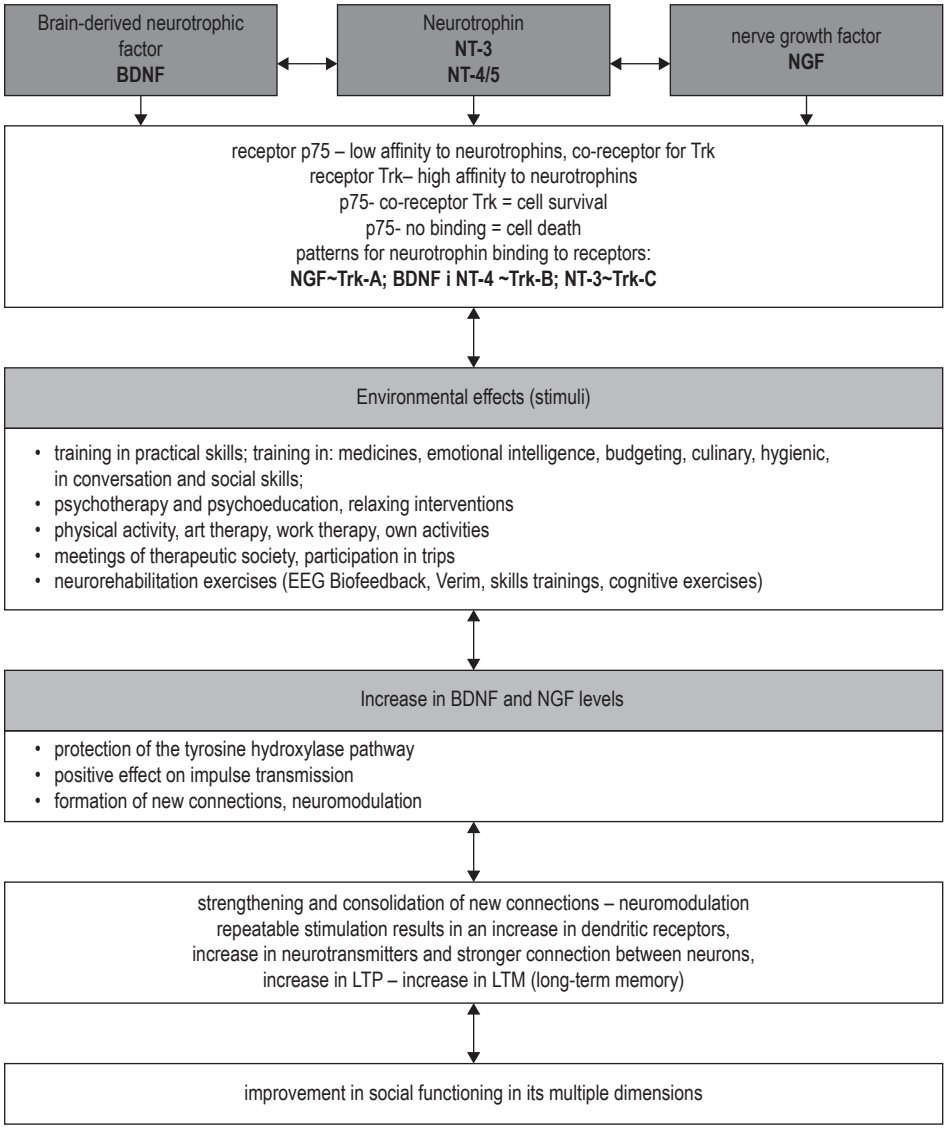
109. Li W, Kou C, Yu Y, Sun S, Zhang X, Kosten TR et al. *Association of catechol-o-methyltransferase gene polymorphisms with schizophrenia and negative symptoms in a Chinese population*. Am. J. Med. Genet. B.2012; 4: 370–375.

110. Pełka-Wysiecka J, Wroński M, Jasiewicz A, Grzywacz A, Tybura P, Kucharska-Mazur J et al. *BDNF RS 6265 polymorphism and COMT 4680 rs polymorphism in deficit schizophrenia in Polish sample*. Pharmacol. Rep. 2013; 65(5): 1185–1193.

111. Łoza B, Czernikiewicz A. *Amerykański słownik psychiatryczny*. Wroclaw: Elsevier Urban &Partner; 2003.

112. Bosia C, Osella M, Baroudi M, Corà D, Caselle M.*Gene autoregulation via intronic microRNAs and its functions*. BMC Syst. Biol.2012;6:131.

Address: Renata Markiewicz
Department of Psychiatric Nursing, Medical University of Lublin
20-124 Lublin, Szkolna Street 18




Source: developed on a basis of [30, 100, 103, 104].

Figure 1. **Mechanism underlying the effect of neurotrophins in the human body**