

# Neuroplasticity, brain entrainment, cognition and intellectual functions amelioration through the complex integrative approach of biological regenerative medicine

## Abstract

Neurodevelopmental and neurodegenerative disorders along with other conditions causing mental health and cognitive intellectual decline are reaching epidemic proportions in all ages groups. Regeneration and neuroplasticity thought to be incompatible with advanced human mental abilities but last decades research showed promising results in various forms of brain changes. In spite of the increasing predominance and debilitating influence on patients, actual treatment strategies demonstrate limited efficacy in preventing, slowing, or stopping the progression of the disease. Thus, the research and development of modern therapies and complex approach are of deepest concern. The methods of management and therapies include application of behavioral therapies, neuropeptides, various forms of stem cell therapy including precursor stem cells (PSC), hyperbaric oxygenation, “first language” sound/light brain entrainment, transcranial direct current stimulation (tDCS), education and training centers, memory diet mode and diet. The complex therapy including integrative and physiotherapeutic approaches demonstrated reliably stable results and significant influence on the course of the neurodegenerative process and clinical symptoms.

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Dina Tullina,<sup>1</sup> Mike KS Chan,<sup>1</sup> Michelle BF Wong,<sup>1</sup> Garnet E Dupuis,<sup>2</sup> Dmytro Klokol<sup>3</sup><sup>1</sup>Stellar Biomolecular Research, Germany<sup>2</sup>Neuro VIZR, USA, Thailand<sup>3</sup>European Wellness Academy, Germany

**Correspondence:** Dr. Dina Tullina, MD, Stellar Biomolecular Research, Klosterstrasse 205, Edenkoben, Germany,  
Email [Dr.din@sbui-europe.com](mailto:Dr.din@sbui-europe.com)

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## Introduction

### Memory and intelligence

Memory overall means the ability to record (impregnation), save (retention) and reproduce our experience and learned information. It is one of the main cognitive processes. However, as was established experimentally, the processes of reproduction are highly associated with the activity of the temporal lobes.<sup>1</sup> The physiological basis of memory is trace reactions in the cerebral cortex - temporary nerve connections that arise between neurons under the influence of external stimuli. The reliability of memorization depends on the ability to concentrate, the frequency of repetitions, and individual characteristics of memory. By the nature of the predominant activity, various people can be dominated by figurative (visual, auditory, taste, olfactory, tactile), motor, or verbal-logical memory. These individual characteristics of memory can be both innate and acquired and fixed in the process of professional activity, and sometimes can be associated with the presence of a disease, for example, the dominance of tactile memory in the blind.<sup>1</sup>

According to the degree of reliability of retention,<sup>1</sup> short-term and long-term memory are distinguished meaningfully. The short-term memory gathers information about events that are happening at the moment and awakes physiological mechanism of memorizing them. Long-term memory is able to reproduce information acquired in the distant past, and by the mechanism associated with structural changes in the molecules of nucleic acids (DNA, RNA).<sup>1</sup> This information is more reliable than due to events of the recent past in age or painful memory disorders, and then – distant.<sup>1</sup> The ability to memorize and detect information, as well as the qualitative features of memory, individually fluctuate over a wide range; so that in some people visual,<sup>1</sup> in others, auditory memory predominates.<sup>2</sup>

Mnemonic deficits in case of mental illness can also vary in different ways.<sup>1</sup> Most often, memory impairments are associated with organic damage to the brain. In these cases, they are resistant and irreversible. However, they can occur in violation of other functions of mental functioning. For instance, impaired clarity of consciousness or concentration, impaired thinking in patients with the manic syndrome, impaired sealing and subsequent reproduction of information.

Intelligence is not an independent mental function - it is the cumulative result of all cognitive processes, as well as the level of abilities, potential capabilities of a person. The concept of intelligence also includes the possibility of creative self-realization and socially useful humanistically directed activities of the human person.<sup>1</sup>

The prerequisites of intelligence include mental processes that ensure the perception, accumulation, storage of information, as well as the analysis of acquired experience. Thus, in this sense, we are talking about the functions of memory, thinking, speech activity, which most often allows us to assess the intellectual capabilities of a person. The quantitative level of intelligence can be characterized using the IQ test (intellectual index), which assesses general awareness, understanding of the situation, arithmetic abilities, memory, vocabulary, degree of development of abstract thinking, etc. IQs above 100% indicate high intelligence and rapid development. In the range from 70 to 90%, there are borderline conditions corresponding to low intelligence, which, however, are not pathological. Indicators below 70% indicate intellectual underdevelopment. However, psychometric testing is a fairly formal procedure.<sup>1-10</sup>

A medical practitioner can draw up more detailed ideas about the state of the patient's intellectual sphere during the conversation. In such case, attention needs to be paid to the most diverse aspects of the human personality, and also to take into account the possibilities of

dissimulative behavior. In some forms of dementia, patients can have sufficient vocabulary and retain practical skills, so in a conversation on specific situational topics, you can miss the presence of disorders of abstract thinking and generally incorrectly assess the patient's condition.

In a number of diseases, the development of dementia can be accompanied by a violation of praxis, for this reason, when assessing the condition of the patient as a whole, one should pay attention to behavioral stereotypes and motor skills: articulation, the ability to write, depict simple figures, the ability to use everyday objects.<sup>2</sup>

## Neuroplasticity

Neuroplasticity is a brain power, which consists in the ability to change under the influence of experience, as well as restore lost connections after damage or as a response to external influences. This property is described relatively recently. Previously, it was generally accepted that the structure of the brain remains unchanged after it is formed in childhood.<sup>11</sup>

The brain consists of interconnected nerve cells (neurons) and glia cells. The learning process can occur by changing the strength of the bonds between neurons, the emergence or destruction of bonds, as well as the process of neurogenesis. Neuroplasticity refers to the processes of occurrence/destruction of bonds and neurogenesis.<sup>12</sup> During the 20th century, it was generally accepted that the structure of the brain stem and neocortex remains unchanged after completion of formation in childhood. This meant that the learning processes there can proceed only by changing the strength of the bonds, while the areas responsible for the memory processes (hippocampus and dentate gyrus) and preserving the ability to neurogenesis throughout life are highly plastic. This view is changing under the influence of new research, which claims that the brain retains its plasticity even after childhood.<sup>13</sup>

Neuroplasticity can manifest itself at different levels, starting with cellular changes in the brain, up to large-scale changes with the reassignment of roles in the cerebral cortex, as a response to damage to specific brain areas. The importance of neuroplasticity is broadly recognized by modern medicine, and also as a phenomenon used in the development of memory, learning, and restoration of a damaged brain.<sup>11-13</sup> One of the fundamental principles of neuroplasticity is the phenomenon of synaptic pruning: in the brain there is a constant process of destruction and creation of connections between neurons.

## Cognitive impairment

Memory impairment (episodic or permanent condition) is one of the most common disorders that can significantly impair the quality of life of any person, especially a child. Cognitive decline or cognitive impairment is a pathological condition associated with the inability to fully preserve, accumulate and use the information received earlier in the process of perceiving the surrounding world with limitations performing mental functions and in skills such as communication, self-help, and social skills. It may include memory issues or language, thinking, judgment or behavior in general. Such situations will cause a child to learn and develop slower than a regular child.<sup>14</sup>

## Causes of memory loss: medical, emotional and age-related problems

There are different factors that can lead to involuntary memory loss in both young and old individuals. Many of these factors appear not due to poor memory performance, but due to the intervention of other cognitive abilities (e.g., attention) or certain substances (e.g., alcohol, barbiturates, anti-psychotic drugs).

a) Loss of memory due to health problems that are treatable in most cases: side effects of certain medications, unbalanced diets with

low levels of vitamins B6, B9 and B12 can lead to temporary memory loss, alcohol abuse, thyroid, kidney or liver disease, lack of oxygen in the brain (as in a stroke), consequences of traumatic brain injuries<sup>15</sup> (head injuries), oncology treatment (chemotherapy or radiation therapy), tumors or brain infections, emotional problems (e.g. depression) and anxiety (i.e., post-traumatic stress disorder - PTSD) as well as brain atrophy in the aftermath of cardiac arrest.<sup>15,16</sup> There are studies, which point to the possible mechanisms of memory decline due to the hypoglycemia-induced changes in regional brain volume.<sup>17</sup>

- b) Loss of memory as a result of stress, anxiety and other emotional problems: in addition, stress, anxiety and some consequences of strong emotions, such as anger, can cause forgetfulness. If we had a car accident, stress could make us lose our memories of what happened this morning. But, as a rule, these memory losses occur because we focus on threatening incentives, and remove less significance to what surrounds us. Thus, we can remember what caused us these strong emotions, but we can't recall all the events that happened during this time. This occurs in the case of post-traumatic stress disorder and obsessive-compulsive disorder. In these disorders, a person is so focused on an emotional episode or object of obsession that he ultimately does not remember anything, except for this stimulus.
- c) Memory loss with age and normal aging:<sup>18</sup> although forgetfulness and memory disorders do not occur exclusively in older people, it is true that these people are more susceptible to such problems. With age, learning ability and quality of memory can deteriorate even without any pathology. However, when these problems become more serious than usual, we can talk about mild cognitive impairment or, in more serious disorders, dementia.<sup>18,19</sup> The hormonal levels also play roles on the cognitive function especially was noticed in women of menopause<sup>20,21</sup> or during pregnancy period.<sup>22</sup>
- d) Memory loss as a result of emotional problems in older people: it is typical for older people to feel alone, losing loved ones, or not to feel useful when they retire. Given these changes, it is normal for some of the elderly to suffer from emotional disorders such as depression. Depressed older people are more likely to experience feelings of memory loss and confuse these symptoms with Alzheimer's disease or other memory problems.<sup>23</sup> Depression might lead to severe memory problems in both the elderly and young people, but in the case of elderly patients it is very important to conduct an appropriate differential diagnosis to exclude the presence of Alzheimer's disease. Despite the fact that memory problems in people suffering from depression may not be as relevant as with other pathologies, it is necessary to pay attention to the emotional problems that they suffer.
- e) Memory loss with mild cognitive impairment:<sup>24</sup> mild cognitive impairment is a disorder that leads to memory loss, but does not interfere with the person who suffers from it in its daily activities.<sup>24</sup> Some studies suggest that mild cognitive impairment may be<sup>25</sup> an early sign of Alzheimer's disease, although not all cases drive to Alzheimer's disease. There are many relation of neuropathology to cognition in persons even without cognitive impairment.<sup>26</sup>
- f) Memory loss due to dementia is one of the most important problems affecting the health of elderly, but it is not a normal consequence of aging. Dementia usually involves the onset of chronic cognitive problems, such as problems with memory, speech, behavior, etc. There are numerous types of dementia as example the episodic memory dysfunction in frontotemporal dementia<sup>27</sup> or dementia with Lewy bodies which lead to focal atrophy,<sup>28,29</sup> but the most

common form is Alzheimer's disease, mixed dementia and/or with vascular cognitive impairment.<sup>30</sup>

- g) Memory loss caused by Alzheimer's disease. In this disease, a protein called "amyloid beta" accumulates in neurons, forming senile plaques, until these neurons lose their viability. This leads to a gradual and severe memory impairment, problems with orientation (patients often don't know what day it is and where they are), difficulties in calculating and, in general, with performing everyday tasks.<sup>25-29</sup> According to the stage at which the patient is will be a deviation of the severity of the disease. In a mild stage, a person with Alzheimer's disease can show significant memory loss, get lost in a familiar place, move away from familiar activities and conversations, can forget dates, show symptoms of depression and hostility. In the moderate stage, cases of memory loss are most prominent, patients can forget names or things that happened a few minutes ago, have difficulty with shopping or cooking, may neglect personal hygiene, have speech problems or are aggressive, tend to forget the way, and ultimately, their daily lives become impossible without outside help. In an advanced stage, patients may have problems with eating or understanding simple information, they will not recognize relatives and friends, and they behave inappropriately in public. At this stage, the person becomes completely dependent.
- h) Impaired memory after a stroke. When a stroke occurs, a cerebral artery becomes blocked by a thrombus, or a brain substance is squeezed with blood flowing from a ruptured artery.<sup>31</sup> Often after a stroke, memory impairment can be observed. In the initial stage (immediately after a stroke), general memory disorders can be observed in the form of complete disappearance of memories of the period of time before the disease. In rare (with extensive strokes) cases, total transient amnesia can be observed, when patients cannot even recognize close people and other well-known concepts. Gradually, general phenomena pass away and memory disorders associated with the defeat of a particular part of the brain responsible for a specific component of memory come to the fore. Violations are very diverse. For example, modal-specific memory disorders can occur (difficulty in perceiving information by one of the analyzers), short-term memory worsens, and difficulties arise in reproducing previously acquired information. Very often there are problems with concentration (distraction) and deterioration in the motivational component of memory. In spite of the severeness of memory impairment after a stroke, due to adequate rehabilitation, the mental functions of the brain can recover almost in full over time. It was also confirmed that cerebrovascular disease highly lead to neurodegenerative disease cases.<sup>32</sup>
- i) Dysmetabolic encephalopathies. Occur in chronic pulmonary, hepatic and renal failure, prolonged hypoglycemia. It is also caused due to deep hypovitaminosis and intoxication. It has a benign course and, when the provoking factor is eliminated, it independently regresses.
- j) Alcoholism: impaired memory not only due to lesions in the structures of the brain, but also general disorders associated with the toxic effects of alcohol on the liver and concomitant hypovitaminosis;
- k) Brain structure: traumatic brain injuries<sup>33,34</sup> and/or brain tumors. And other neuropsychiatric conditions which might include hippocampal abnormalities and memory deficits like in Parkinson disease.<sup>35</sup>
- l) Congenital mental retardation is combined with genetic disorders

(for example, Down syndrome), and due to pathological conditions during pregnancy and childbirth.

- m) Violation of the motivational component of memory. The main core in the memorization process is understanding the meaning and need of these actions which constitutes motivation. The motivational component of memory is disturbed in conditions of depressive and asthenic conditions, when there is a general slowdown in mental processes. Especially severely reduced motivation in patients with schizophrenia.<sup>36</sup> And in patients with epilepsy where also were noticed delayed verbal memory retrieval,<sup>37</sup> on the contrary, the motivational component of memory is significantly enhanced where magnetic resonance volumetry documented focal brain atrophy in transient epileptic amnesia.<sup>38</sup>
- n) Memory disorders associated with consumption of drugs. In a study was discovered significant odds ratios for benzodiazepines (alprazolam, bromazepam, prazepam, clonazepam etc.), benzodiazepine-like hypnotics (zolpidem and zopiclone), antidepressants (fluoxetine, paroxetine and venlafaxine), analgesics (morphine, nefopam and tramadol), anticonvulsants (topiramate, pregabalin, levetiracetam etc.), antipsychotics (aripiprazole and lithium) and other drugs, such as trihexyphenidyl, ciclosporin and isotretinoin.<sup>39</sup> Cognitive decline in adults and old age affecting millions of people worldwide and characterized by progressive loss of memory, deterioration of mnemonic functions such as language, visuospatial skills, executive functions and others.

### Therapeutic strategies

Current therapeutic strategies are represented by the following main areas: compensatory (substitution) therapy aimed at overcoming the neurotransmitter deficiency; protective therapy: the use of neuroprotectors and neurotrophic factors; psychological correction (training) of cognitive functions. Symptomatic therapeutic effects of most of the therapies are considered proven, however, it would be advantageous to combine tools of Bioregenerative medicine with physiotherapy and brain entrainment to achieve reliably stable results or significant influence on the course of the neurodegenerative process itself. The methods of management and therapies include application of complex behavioral therapy, various forms of cell therapy including stem cells, PSC and neuropeptides, hyperbaric oxygenation therapy, transcranial direct current stimulation (tDCS), physical exercise and appropriate diet.

### Neuropeptides

The therapeutic role in the cognitive decline of neurotrophic factors (nerve growth factor, the main growth factor of fibroblasts, etc.) of peptides, which ensure the differentiation and functioning of neurons, is rather actively discussed by scientists. Currently, there is evidence on the role of dysfunction of neurotrophic factors in pathogenetically different diseases of the central nervous system. Therefore, the use of such substances seems to be theoretically justified in order to slow the progression of the pathological process, vascular and neurodegenerative, and stimulate recovery processes, including those associated with the formation of new synapses.<sup>40</sup>

One of the effective therapy with neurotrophic properties is MitoOrganelles CNS (MO CNS) (MF+<sup>TM</sup>)<sup>41,42</sup> which consisting of low molecular weight CNS peptides and free amino acids and used to treat dementias of various origins. The medicine is produced using standardized biotechnological techniques using enzymatic cleavage of purified CNS proteins and does not possess allergic or toxic properties. The effect of MO CNS on its final effect and its severity resembles the action of the nerve growth factor. In addition, MO CNS accelerated the process of acquiring new knowledge, whereas the introduction of

the nerve growth factor did not affect the ability to learn. MO CNS prevents the development of mnestic disorders, if applied directly after the injury, and stimulates the restoration of learning ability even if it is administered several months after brain damage.

Experimental data collected *in vitro* and *in vivo*, indicated the neuroprotective properties at the intracellular level which is one of the key moments in the pathogenesis of cognitive impairment and other neurodegenerative diseases. It was shown that the neuroprotective effect of MO CNS is due to the anti-apoptotic properties of its constituent peptides and the improvement of neuronal metabolism under the influence of amino acids. Unlike necrosis, an acute and passive process of cell death, characterized by an early disruption of the integrity of cell membranes and an increase in cell volume (which ultimately leads to cell death), apoptosis is an active process. Apoptosis, as a form of programmed cell death, is accompanied by histological changes, such as the formation of vesicles in the cell membrane and the condensation of chromatin. With apoptosis, characteristic biochemical changes can occur, in particular, fragmentation of internucleosomal DNA. In the experiment it was shown that against the background of the introduction of MO CNS, the number of cells with apoptosis-mediated chromatin damage is reduced. One of the mechanisms of the anti-apoptotic activity of MO CNS is associated with a decrease in the damaging effect of glutamate on neurons. This is due to the ability of the peptides that make up the drug to inhibit the release of glutamate caused by ischemia, agonistically affecting the presynaptic GABA-B receptors. MO CNS provides protection of neurons from delayed death, and this effect is dose-dependent.

The obtained data indicate that one of the mechanisms of the neuroprotective effect of MO CNS is an increase in the plasticity of neurons due to the prevention of the destruction of their cytoskeleton. Thus, at the cellular level, the neuroprotective effect of MO CNS can be associated with preventing damage to dendrites. MO CNS reduces the severity of oxidative stress by acting on catalase and superoxide dismutase. Experimental data give grounds for the assumption of the ability of MO CNS to increase the density of synapses and induce neurogenesis in the hippocampal region.

The experience of using MO CNS showed that after the course of therapy there was an improvement in the patient's mental condition, manifested by an increase in activity in everyday life and severity reduction of behavioral disorders. The findings confirm the ability of MO CNS to slow down the progression of memory decline, since even after discontinuation of treatment, the condition of patients tended to improve.<sup>41-43</sup>

CNS is a complex of neuropeptides of the central nervous system playing an important role in the development of the higher nervous activity.<sup>43</sup> These processes include a set of conditioned and unconditioned reflexes, as well as higher mental functions that ensure adequate behavior according to the changing surrounding circumstances. CNS peptides are fundamental mediators of emotional and social behavior, speech and intellectual development.<sup>44</sup> The usage of CNS peptides on patients with autism spectrum disorder (ASD) showed the reduction of anxiety and significant impact on fear conditioning and extinction. Application of CNS peptides increased confidence and demonstrated a decrease of aggressive behavior and stress-reduced effects, improved communication issues, social recognition, recognition of facial emotions, more often patients looked for eye-contact discussion, become more aware on surroundings and environment.<sup>45</sup>

Individual manifestations of autism encompass a wide spectrum, from persons with severe disabilities, mute and mentally handicapped, spending time in monotonous manipulations, constantly waving their hands, to socially active, highly functional autists whose frustration

manifests itself in strangeness in communication, the narrowness of interests and verbose, pedantic speech. In all cases with autism, as an anomaly of mental development, there is its main manifestation - the unformed need for communication with others.<sup>45</sup> It is very important that after 4-6 months therapy patients become easier to sustain the conversation, obviously less repetitive motor features and ability to easily pick up and follow routine instructions. The positive effect on the improvement of higher mental functions also included the development of peer relationships, the clear presence of social or emotional reciprocity, progress on speech development and verbal communication.<sup>46</sup> Social skills are improving: greater eye contact appears, better following instructions, independent initiation of contact and communication. Less aggressive behavior: reduction of aggression in relation to others and to ourselves, reduced repetitive behavior. Visual contact improves: "Look into the eyes" and comprehension of what you say, the appearance of more attention to what the child sees.<sup>46,47</sup>

### Precursor stem cell therapy

A child with mental retardation understands those around him, later begins to talk and write than his peers. In his brain there is an educational ceiling, which he cannot overcome without special treatment. Introduced stem cells contribute to the renewal of the cellular composition of the brain, and conservative treatment helps to create the necessary neural connections.<sup>47</sup>

The comparatively slow progression of Alzheimer's disease at the outset is explained by the fact that the dying neurons of the brain are at least partially replaced by new ones, formed from intensively consuming progenitor cells. And when the stock of progenitor cells is exhausted, very rapid progression of the disease begins with the loss of brain functions, since there is nothing to replace dead neurons. Previously, it was thought that memory and intellectual decline could only be slowed down, that is, prolong the patient's life by reducing the rate of death of neurons of the brain.<sup>48</sup> In reality, nerve cells are perfectly restored, but this process is very slow. And once the nerve cells are restored, it means, theoretically, if you select the necessary medicine or chemical, you can force to grow new neurons in the brain, which will fill the losses and restore the lost functions, at least partially. The most potential origin of an extra number of progenitor cells is different types of stem cells.<sup>11,12,48</sup>

Stem cells have a significant impact on the treatment of slow intellectual development or cognitive decline as it leads to a great rise in growth factors amount in the brain structures. The main role in this is performed by the neurotrophic growth factor, which stimulates the growth of axons (neuron outgrowths, nerve fibers) and improves the transfer of impulses, signals and information between neurons. Due to the improvement of this process, the transfer of information from the damaged areas to other parts is switching, and as a result, the brain functions are substantially improved. Also, after the introduction of brain stem cells, there is an increase in the concentration of hematopoietic growth factors in the brain tissues - granulocyte colony-stimulating factor, erythropoietin, vascular endothelial growth factor, granulocyte-macrophage colony stimulating factor, stem cell factor and factor-1-alpha stromal cells. Stem cells also normalize the production of neurotransmitters.<sup>13,48,50</sup>

Experiments have shown that the effect of stem cells on hippocampal structures is carried out by indirect (associated with the release of the endogenous agonist) stimulation of adenosine receptors. Adenosine is a potent inhibitory neurotransmitter that inhibits the release of glutamate from presynaptic terminals. The final result of this process, as well as the above-mentioned effect of stem cells on the GABA-ergic system, is the inhibition of the release of glutamate from presynaptic terminals and the subsequent decrease in the intake of

calcium ions into neurons. This mechanism of action of stem cells can explain its ability to slow the progression of the neurodegenerative process and to influence excitotoxicity under conditions of ischemia.<sup>49</sup> Stem cells have the ability to accumulate in that area of the body where they have a special need, and replace damaged tissue. So the human body is restored, creating all the time new tissues and updating the cells. Cellular therapy is popular and gives a chance to cure many diseases, this also applies to Alzheimer's disease. The essence of this treatment is that the stem cells replace the damaged and are able to restore the function of the brain. Healthy Stem cells are able to synthesize substances that activate regeneration processes, new blood vessels appear, and nerve cells are regenerated.<sup>48,50,51</sup>

This entire process helps restore the functions of the brain and, therefore, eliminates all the neurological symptoms. The outcomes of the treatment are simply amazing, after the course of therapy, the brain atrophy ceases, and the patient is safely returned to the intellect and memory. The patient becomes socially adapted to everyday life. After all, with this disease there is a death of neurons in the brain, the consequence that entails, this extensive dementia. With dementia at a late stage: the patient after the treatment quite consciously could talk with loved ones. Of course the result is good, but it should be borne in mind that the patient turned with the neglected form of the disease. After years have passed, the patient is alive with stable condition. The disease was suspended with the noticeable positive outcome of stem cells therapy. As a result of the course "Alzheimer's disease treatment", many specific functions of the cerebral cortex are gradually restored.<sup>51</sup>

The best treatment results (up to 90% of cases) are achieved at the initial stages of the disease, with the appearance of the first neurological and psychic symptoms. Stem cells also participate in the treatment of concomitant diseases and conditions from other organs and systems, thereby facilitating the course of the underlying disease, and sometimes eliminating the cause of degeneration of the brain. In the late stages with significant development of the disease and severe mental disorders, the effect of treatment is to improve the quality of life (general condition, sleep, appetite, weight normalization).<sup>51</sup>

To summarize the mechanisms of stem cell therapy it most likely acts via the reduction of chronic systemic low grade inflammation in the brain, stimulation of neurogenesis in the hippocampus, function support to the neurons, beneficial influence on the neuronal oxidative metabolism, activation of the scouring reaction, normalization of neurotransmitter synthesis and synaptic transmission. Under the action of stem cells, which is confirmed by experimental data, there is an improvement in mnemonic functions for various types of damage. In addition to affecting neurons, Stem cells activate microglial elements, reduce the adverse effects of inflammation factors and affect the mechanisms of oxidative stress.<sup>49,50</sup> Furthermore, glucose transport through the blood-brain barrier is improved. Thus, stem cells therapy has an active multimodal effect directed to a number of key mechanisms of the neurodegeneration process. Another positive property of stem cells is the rapid onset of a positive effect and its long-term retention after the course of treatment.

According to the Global survey done by the Centers for Disease Control and Prevention on the average 1 in every 68 children in the USA, China and majority of the other countries have some form of autism spectrum disorder. As many as 60- 75% of children with ASD also have intellectual disabilities. About 30% never learn to speak, and many children even with early behavioral interventions still struggle to adapt. There are also no FDA-approved medications that improve the core symptoms of autism.

The PSC therapy showed improvement not only in children with autism spectrum disorder but also in adults sharing similar neuropsychiatric symptoms. The memory function is influenced by certain parts of the cerebral cortex, cerebellum, and limbic system.

But the main influence on this work is exerted by sites located in the temporal region of the left and right hemispheres. Another important brain structure that affects the memory process is the hippocampus. If the temporal region is damaged on the one hand, memory performance deteriorates, and if it is damaged on both sides, it stops completely.<sup>24,35</sup> The highest level of neuro elements important in Autism concentrated and produced by hypothalamus, amygdala and nucleus accumbens which is then distributed throughout the central nervous system.<sup>45</sup>

Before the beginning of neurogenesis, progenitor cells across the CNS secrete regulatory genes that subdivide every region into compartments and control their size as well as indicate cells destiny, growth and neuronal connections. The neurons produced by progenitor cells only at early to mid-embryogenesis and then move to the assignment sites.

Precursor Stem cells are specialized lineage-restricted stem cells.<sup>48,49</sup> Stem cells derived from hypothalamus will act accordingly to its origin function as they are already differentiated. The most significant transformation in cell number and synapses by reason of cell death and synaptic pruning take place during infancy, at the most active learning time. Synapse formation is linked with critical periods for the acquisition of sensorimotor functions, emotional competence and language abilities. The real issue doctors face is to fully understand details of physical, physiological, social and psychological changes in a person with ASD. The clinical experience shows that therapy with PSC is capable of bringing improvements in early childhood and adults with autisms.<sup>45,46</sup> The success of treatment depends on the prescription of the necessary types of cells. Every autism case has individual strengths and challenges, so there is no one size fits all approach to autism treatment and intervention. Each autism treatment plan is tailored to address the person's specific needs, as there are a number of medical and mental health issues that need to be addressed to have a better intervention plan.

The complex treatment is a dynamic process that often requires a reformulation of the protocol and repeated applications of live precursor cells, depending on the peculiarities of each case. Generally, full treatment with transplantation and complement therapy takes 3 to 4 days and it may take 4 to 6 months per course. Repetition within a year is about 2 to 3 times. The patient will discontinue treatment if no meaningful result is seen after the previous two treatments.<sup>42,46</sup> Within the first two weeks after treatment, children will show positive changes in their social and language development, and 2 to 3 months later, children will have eye contact, increase attention span, ability to respond to verbal instructions and develop meaningful speech. To ensure the improvement of IQ, language and social interaction, parent's involvement is crucial, proper plan and strategies at home during routine and daily activities are likely important elements of the success of the outcomes and their child's progress. It is also important to provide adequate nutritional support, speech and occupational therapy to the individual with Autism. Parents and therapists will carry out the intervention toward individualized goals for each patient, and work collaboratively to enhance the children social respondings, playing with toys, and communication.<sup>46</sup>

The clinical experience demonstrated that PSC are able to provide advantageous in childhood and also was revealed outstanding achievements in adults with autism, who were not treated in the past. Throughout the neurogenesis process the neural progenitor cells secrete regulatory genes which subdivide each brain region into departments and manage their size. Progenitor cells produce neurons at a time of early to mid-embryogenesis. Neurons gradually move to their target sites and transfer the legacy of transcription factors secreted by progenitor cells.

Parents and caretakers noted that after cell therapy, many of the treated children appear more invigorated, more energetic, and more relaxed. The hyperactivity is reduced, the memory is improved, and

the social interaction and awareness of the environment and people are enhanced. The teachers are also reporting much faster academic progress. Moreover, the child is reported to be more compliant and easier to teach. We have observed children three years of age with no speech prior to live cell therapy who within three months after cell therapy had speech emerging. At the age of five years old, the child showed normal intellectual performance and was being prepared for a normal school.<sup>46</sup> Live cells have positive effects by harmonizing the hormonal and immune systems, the revitalizing effects, the enzymes, the trophic factors – and also, the other substrates within the cells have had a positive regulatory effect on the genes somehow. What is manifested are improved cognitive and social skills in these children.<sup>45</sup> To maximize the efficacy of cell therapy a number of complementary therapies are used along with stem cell transplantation. Let us have a look at available options.

### Hyperbaric oxygenation therapy (HBOT)

Children with autism have been consecutively shown to have aggravated, or abnormal CNS circulation as a result of hypoxia. Defects include cerebral hypoperfusion and decreased perfusion in response to stimuli that under normal circumstances upregulates perfusion. In several studies the areas influenced by hypoperfusion correlated with brain regions which reliable for functionalities that are abnormal in autism. For example, specific temporal lobe areas associated with face recognition, social interaction, and language comprehension, have been shown to be hypoperfused in autistic but not in control children.<sup>52</sup>

Numerous research data demonstrated the significant correlation and induction of onset of autism-like disorders in cases of hypoperfusion of temporal areas as well as removal or damage of the amygdala, hippocampus, or other temporal structures with development of characteristics like unexpressive faces, little eye contact, and motor stereotypies occur. It was shown that viral infection of the temporal lobe also could lead to the development of autism both in adults and children. It is important to know if to treat hypoxia symptoms of autism would disappear.<sup>52,53</sup> The hypoxia combined with autism actually is not primarily apoptotic or necrotic to the neurons in temporal lobe but much lead to their functional changes.

The association is not predominantly to temporal neurons but associated with the altered function. It was shown that hypoperfusion contributes to defects by induction of hypoxia and also allowing for incorrect metabolite or neurotransmitter accumulation.<sup>1,37</sup> Theoretically the augmentation of perfusion through stimulation of angiogenesis should allow for metabolite clearance and restoration of functionality. Although not well defined, cell death may also be occurring in various CNS components of autistic children. If this were the case, it is possible that neural regeneration can be stimulated through the entry of neuronal progenitor cells into the cell cycle and subsequent differentiation. Theoretically, it is conceivable that reversing hypoxia may lead to activation of self-repair mechanisms. Such neural proliferation is seen after reperfusion in numerous animal models of cerebral ischemia. In 2018 the study published as a first reported case of simultaneous HBOT-induced symptomatic and 18Fluorodeoxyglucose PET documented improvement of brain metabolism in Alzheimer's disease and suggests an effect on global pathology in Alzheimer's disease.<sup>53</sup>

Hyperbaric oxygen therapy is a delivers a high concentration of oxygen at an ambient pressure higher than atmospheric pressure. It is well tolerated by most patients. It was documented that children with autism benefit from hyperbaric oxygen therapy,<sup>54</sup> as inhalation of air with higher oxygen concentration in condition of increased atmospheric pressure may help to elevate the blood saturation with oxygen, hence improves the oxygen delivery to the brain. Hyperbaric oxygenation therapy is reported to help improve cerebral perfusion,

reduce inflammation throughout the body and reintroduce oxygen and blood flow to influenced areas, inclusive the brain. Due to the data on the effectiveness and safety of hyperbaric oxygen therapy, the present meta-analysis suggested that hyperbaric oxygen therapy can be recommended as an effective and safe complementary therapy for the treatment of vascular dementia which is a common type of disease in the elderly.<sup>55</sup>

The indications of hyperbaric oxygen therapy also include:

1. chronic fatigue syndrome, weather dependence and migraines;
2. to enhance the recover after surgical operations and medical procedures, injuries and stress;
3. to improve brain function, memory, increase concentration.

After the HBOT session individuals usually experience fatigue relief, improved mood, increased stamina, general feel of improving well-being.

### First language light/sound brain entrainment

When examining mammals, including us humans, the long evolution (phylogenesis) of the organisms clearly illustrates that the Central Nervous System (CNS – brain and spinal cord) developed in a predictable sequence. This same sequence is fundamentally true and repeated in the short-term developmental life cycle (ontogenesis) of the human from conception to maturity. As a broad stroke, it goes like this. First is the development of the senses then movement and finally mental/cognition. So, the shaping of the concept has Sensory development as the basis of The First Language, Movement/Motor as The Second Language and Mental/Cognition as The Third Language. As you might easily guess Logic and Rational thinking manifests in The Third Language.

To better understand the “illogical” nature of the Light/Sound of First language, it would be simple to consider the First Language expression we call “music”. Near endless in form and style, music is a powerful communicator that does not require thought or cognitive analysis. A crafted song or perhaps a complete orchestral symphony is reliably capable of telling remarkable “stories” that are directly “known” without demanding logical review or rational analysis. In this “sense”, music is radically “illogical” and “irrational”.

It is only very recently that our technologies have begun to evolve into the stages permitting the manipulation of light that approximates the manipulation of sound. We are now entering the era of “optical music”. As such, the same charming allure known to music is forming its potential in light.

There may be some lessons to learn from very recent studies in the activities of the brain while experiencing an altered state of consciousness. There is a long history of subjective reports of altered or unusual types and qualities of induced altered conscious experience.<sup>56-58</sup> Cognition is typically radically shifted away from normal logical associations. Novel interpretations can bountifully present themselves while the sensory terrain can be modified in entirely unique fashions and connections between common stimuli can seemingly multiply endless in fractal-like patterns. Experiences may lose logical and rational references while still somehow all “making sense” in ways that approach revelation. These experiences seem to, in some ways, offer a consciousness “refresh” and a movement away from older habitual patterns of consciousness. This refresh may or may not result in an enduring benefit and depends on perspectives of reinforcement and intention.

A study at a Barcelona university (Center for Brain and Cognition, Universitat Pompeu Fabra, 2018) analyzed the brains of persons experiencing the 5-HT<sub>2A</sub> receptors pharmacological stimulation.<sup>59</sup> Instead

of the more conventional fMRI algorithms, the team employed and advanced analysis called “connectome-harmonic decomposition” in an effort to better understand the potential ability for the medicine to induce a positive “reset” of the brain away from various persistent mental problems such as depression and PTSD. The approach was attractive because recent research on the connectome (which is the theoretical map of all connections in the brain) suggests that mental illness, at least in part, may stem from unusual patterns of connectivity, and that the potential healing from the effects of 5-HT<sub>2A</sub> receptors stimulation comes from its ability to alter these maladaptive links.

The novel algorithmic analysis seeks out evidence of combinations of harmonic waves in the brain (hence the now accepted term “connectome harmonics”). These connectome harmonics are used to decode brain activity. This approach was first introduced in Nature Communications, 2016 and is a very progressive approach to brain imaging and analysis.<sup>60</sup> The “waves” of connectome-harmonics express in a manner that is universal and the same as the harmonic waves produced as sound from a musical instrument however in this case, the instrument is the brain. While influenced by compounds acting through 5-HT<sub>2A</sub> receptors, the brain produces a harmony of functional waves across many areas of the brain and these harmonious waves were not random. The research team call this expression “repertoire expansion” as areas in the brain that do not usually connect do so during these episodes. The activity presents the probability that the brain undergoes some sort of reorganization process and not simply some random or indiscriminate haphazard behavior. The study did observe that this unique activity did substantially slow down as the effects diminished however there did appear to be degree of reorganization that remained and persisted. As such, the residual reorganization effects may have a relationship to claims of relief from pre-existing distressful mental states.

Appreciating the potential of deeply rooted sensory communications that do not rely on higher cognition characteristic of mental logical/rational processing, the Neuro VIZR relies on signaling approaches that may be considered illogical and irrational in a positive interpretation.<sup>61,62</sup> Furthermore, such signaling can be presented in light/sound compositional designs that permit the brain to shift in and out of degrees of stable/unstable behaviors and the possibility of a “repertoire expansion” as waves of reorganizational connectome harmonics wash through the terrains of brain activity. We may come to accept that novel and enjoyable forms of light/sound Brain Engagement have the capacity to guide the brain into very attractive positive neuroplastic experiences.<sup>61-63</sup>

### Transcranial direct current stimulation (tDCS)

This is a highly effective therapeutic method based on stimulating brain cells with a weak direct current. Micropulses of small power contribute to the development of nerve tissue and the creation of new connections between nerve cells.<sup>64</sup> tDCS can improve or restore motor, mental, and speech functions, normalize the functions of the pelvic organs, and reduce the lesions of the brain in patients with stroke and traumatic brain injury in the acute period. The tDCS method gives brilliant results with delayed speech and mental development in children. Selectively stimulating the weakened zones of the brain responsible for the formation of speech, motor activity and mental development by microcurrents, it is possible to achieve a substantial or complete restoration of their functionality.<sup>64,65</sup>

The essence of the process: tDCS allows you to restore the disturbed functioning of the nervous system, helps to improve vital skills and abilities. The action of tDCS is directed directly to the cause of the development of the disease, and not to its external manifestations. The microcurrents used in the method are similar to the natural impulses of the brain, and therefore the treatment is safely and gratefully perceived by the body and is suitable even for babies.

Many years of experience and our own experience have allowed us to achieve great efficiency for all children, a protocol for each child is written individually.<sup>66</sup>

Among the conditions that may possibly benefit from the tDCS are:

- delay in mental and psycho-speech development in children;
- motor and partially sensory alexia, any speech disorders;
- hyperactivity disorder, attention deficit, impulsivity;
- head injuries and their consequences;
- vascular diseases of the brain (including symptoms such as ataxia, aphasia);
- consequences of neuroinfections;
- impairment of visual and auditory functions (nystagmus, strabismus, sensorineural hearing loss);
- neurological disorders: fears, aggressiveness, tics, psychogenic enuresis<sup>66</sup>

With increased muscle tone: tDCS activates the corresponding zones of the cerebral cortex, which leads to selective relaxation of spasmodic muscle groups.<sup>67</sup> In cases of disorders with hyperactivity<sup>67</sup> tDCS minimizes the manifestations of the hyperactivity associated with many diseases, including hydrocephalus. The method is aimed at eliminating the primary disease, it corrects, and first of all, the damaged work of the nervous system and through this eliminates the manifestations of hyperactivity. When will the result be? The maximum effect is 2 months after the end of the course, when damaged and new nervous tissue has already recovered. The course can be repeated after a certain time. It was shown that the effectiveness of the method would be much higher if patients concurrently undergo brain entrainment and engagement therapies. The positive clinical effect of tDCS correlates with improved electroencephalographic indicators of the functional state of the brain and memory improvement.<sup>68</sup> A visual analysis of routine EEG shows a decrease in the severity of slow-wave and high-frequency activity, there are signs of the organization of the main rhythm compared to the initial data in the form of the index grow and normalization of the amplitude of the regular alpha rhythm, improvement of the cortical reaction during standard functional tests.

Whereas single or multiple sessions of transcranial direct current stimulation (tDCS) on the prefrontal cortex over a few weeks improved cognition in Alzheimer’s disease patients, effects of repeated tDCS over a longer period and main neural correlates stay to be elucidated. tDCS improved global cognition assessed with Mini-Mental State Examination and language function assessed by the Boston Naming Test, but not delayed recall performance. Moreover, active tDCS prevented decreases in executive function at a marginal level. It was revealed that daily tDCS for 6 months might improve or stabilize cognition and in Alzheimer’s disease patients, suggesting the therapeutic potential of repeated at-home tDCS.<sup>68</sup>

In summary: tDCS of the brain is a progressive technique for stimulating the central nervous system through constant small currents, which favorably affects the brain and overall development. This therapy is suitable for children with a delay in psycho-speech development and is able to help as much as possible with autism. Therapy is highly effective, considered safe. It is painless, compatible with cartoons and other entertainment.

### Memory training centers

Targeted treatment plans focus on memory functioning, cognitive skills, and compensatory strategies that are applied for success

in independent living. Very often the basis for the development of forgetfulness is social exclusion, when an elderly person is ignored by relatives. It affects the loss of ambition, a person feels socially exhausted, loose interest in everything that made up his/her life yesterday. It ceases to strain the brain, reducing its leisure at best to watching television series until complete degradation.

The effectiveness of the applied methods and training is also confirmed by the diagnostics that all participants undergo before the start of classes and at the end of them. Not only general types of memory are improved, such as short-term, long-term, delayed and others, but also mechanical, visual, associative. Speaking of memory training, it is important to understand that it is almost impossible to train a specific ability by scribbling. Memory always develops in close connection with attention, perception, thinking, sense organs and other phenomena of human nature. Therefore, most exercises produce a complex effect on thinking, as well as memory as the main component of thinking.

It is documented and necessary to highlight the issue of stigmatizing individuals with memory and intellectual impairments as well as their relatives and caregivers. Empirical research has shown that autistic people and parents of autistic children are frequently stigmatized. The manifestations of health-related stigmas are culturally determined, especially in developing countries.

An education center is a place where children with autistic are provided with special education and children's parents are taught the strategies for capturing their children's attention and promoting communication. By applying these strategies during the day, the children were offered many opportunities to learn to interact with others. It also to help children acquire new skills and overcome a wide variety of developmental challenges. The employed behavior analysis program is often offered for autistics. The program trains a child to develop verbal communications, develop and imitate social skills, and reduce stereotypic behavior. The motives for negative behavior and why it persists are noted, and through appropriate reward, the behavior is not reinforced or modified. This program might be highly intensive, and speech therapy is often incorporated. These entirely will not be adequate without looking into the biological parameters and needs of the child.

### Behavioral therapy

The treatment of productive psychopathological disorders and behavioral disorders acquires special significance in connection with the fact that it is these manifestations of the disease that make patients difficult for examination, rehabilitation and especially for care. With respect to patients with mild dementia, we can talk about achieving stable stabilization of the state at the level of the initial manifestations of the disease. Thus, this category of patients managed to delay the progression of the disease for several years to the stage of clinically pronounced dementia, i.e., to save the patient several years of independent and relatively high-quality life, and in some cases, disability.

### Memory Diet Mode and Diet

It is very important for patients with memory impairments to lead an active lifestyle, preserving it to very old age. Walking in the fresh air, hard work, playing sports and other active activities contribute not only to strengthening overall well-being and improving blood supply to the brain. Such activity is accompanied by the receipt and processing of a significant amount of information, which in turn contributes to the training of memory and attention. A positive effect on the mental abilities of a person has intellectual activity: reading books, solving crosswords, print and electronic media, other favorite activities and hobbies. Maintaining the patient's active communication

with relatives and friends, social activity is also very important for strengthening memory, developing its motivational component.

For people suffering from psychogenic memory impairments, a sparing day regimen, avoiding overwork at work and stressful situations, and correcting the psychological atmosphere at work and in the family are very important. It is also very important high-quality full sleep, corresponding to the individual norm, but not less than 7 - 8 hours a day.

The diet of patients with memory impairments<sup>69</sup> should be balanced, contain a sufficient amount of proteins, fats and carbohydrates, vitamins and minerals. Since the human brain absorbs around 20% of all the energy produced in the body, diets with an immensely low calorie content significantly reduce its performance. Fatty varieties of sea fish are very important: salmon, herring and others. They contain plenty of iodine and polyunsaturated fatty acids, inclusive omega-3, which are part of the composition of all nerve cells and improve mental abilities. Whole-grain cereals (cereals, whole grain bread), nuts, tomatoes, broccoli, pumpkin seeds are also useful. Drinking regimen is very important. It is advised to drink at least two liters of water per day. Dehydration is very harmful to the function of the nervous system.

### Prevention

The leading role in the prevention and preservation of intellectual abilities is played by maintaining a healthy lifestyle:<sup>70</sup> giving up bad habits, playing sports, timely treatment of somatic diseases (especially cardiovascular, nervous and endocrine).

It is also very important to observe a rational mode of work and rest, the normal duration of sleep. Eventually, it is in a dream that the whole work of the brain occurs on sorting the received information, its fixation in long-term memory. Normal sleep must be around 7 to 8 hours per day.<sup>71</sup> Another important aspect of the prevention of memory impairment is the preservation of normal social activities such as participation in public life and the provision of at least minimal work activity. Communications with family and friends are helpful. Intellectual activities also have a positive impact on a person's mental abilities: reading books, print and electronic media, solving crosswords, having a hobby.

### Conclusion

As a result of complex treatment: motor activity is activated, the range of motion is improved, movements become conscious, directed, more intensively develop new motor skills (sitting, crawling, rolling over, walking, etc.), muscle tone normalizes, restore the functions of the brain and, therefore, eliminates all the neurological symptoms. It was shown the increase in activity in everyday life and a decrease in the severity of behavioral disorders. The findings confirm the ability of complex therapy to slow down the progression of memory decline, since even after discontinuation of treatment, the condition of patients tended to improve. In addition to the mnemonic changes it was noticed the reduction of anxiety and significant impact on fear conditioning and extinction, confidence increased, also was demonstrated a decrease of aggressive behavior and stress-reduced effects, improved communication, social recognition, recognition of facial emotions, more often patients looked for eye-contact discussion, become more aware on surroundings and environment.

Following PSC therapy in short period patients learnt to regulate their own behaviors independently and act appropriately in different environments such as home, school, and community based situations. After 5 months patients differentiated between appropriate and inappropriate behaviors, accurately monitor and behave appropriately. After 6 months become more fluent with the self-management, some

of the implementation responsibilities shift from teachers, families, and other practitioners to the learners themselves.

Children become able to attend playgrounds and have meaningful communications in a manner that they weren't previously. They also demonstrated much less repetitive behavior compare to the beginning of treatment. After second time treatment patients are able to manage anxiety, mood problems, attention deficits, depression, control anger, and developed social skill, demonstrated less rigid behavior. At the same time PSC therapy managed patient's problems with seizures, gastrointestinal problems, dietary imbalances and disrupted sleep patterns.

Overall integrative therapy together with course of physiotherapy demonstrated following: improves cognitive functions of the brain: attention, memory, thinking; motor development; improves understanding of speech, clear pronunciation; the active vocabulary expands, children start talking, switch to phrases or sentences, use speech; increases interest in the environment, there is contact and a desire to communicate; improves cognitive interest, active attention, desire to learn; decreases in aggressiveness, fears, hyperactivity; eliminates hysterical manifestations are eliminated; normalizes muscle tone, reduces stimuli; improves mood, behavior; sleep normalizes; eliminates headaches.

In addition the other advantageous noticed in children with Autism Spectrum Disorder is the stimulation of the insufficient activity of the frontal lobes of the brain, responsible for intelligence, consciousness, initiative. As a result of treatment, the child begins to show greater interest in the world around him, finds cognitive interest, and normalizes speech and emotional development.

## Conflicts of interest

The authors declare that this article content has no conflict of interest.

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