



Journal Homepage: - www.journalijar.com
**INTERNATIONAL JOURNAL OF
 ADVANCED RESEARCH (IJAR)**

Article DOI: 10.21474/IJAR01/5058
 DOI URL: <http://dx.doi.org/10.21474/IJAR01/5058>



RESEARCH ARTICLE

NONLINEAR STIMULATION TECHNOLOGIES TO ENHANCE THE EFFICIENCY OF THE THERAPY OF BRAIN DISORDERS AND EFFICACY OF COGNITIVE TRAINING.

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Manuscript Info

Manuscript History

Received: 03 June 2017
 Final Accepted: 05 July 2017
 Published: August 2017

Key words:-

Nonlinear brain stimulation therapy, brain training, the complexity of the brain structure and activity.

Abstract

The development and maintenance of the complex structure of neural networks and the activity of the brain we recently linked with a complexity of visual and other environmental signals accompanying the person during his life. From this theory, it follows that the simplification of dynamics of environmental signals may be associated with the abnormal development and aging of the brain, or may accelerate the already existing neurological pathology. The use of nonlinear stimulation therapy can improve the restoration of the structure and function of the brain, including in neurodegenerative pathology by regulating the potential of neuroplasticity. In psychological rehabilitation, it may produce effects via the brainwave entrainment helping to restore the dynamics of the neuronal activity. We substantiate the possibility of application of technologies of nonlinear stimulation of the brain to enhance the efficiency of the therapy of neurological disorders and to preserve the mental activity of aging persons. Programs of nonlinear stimulation of the brain in healthy individuals can be self-contained methods of the cognitive training, including stress conditions. Besides, we believe that elements of nonlinear visual and audio stimulation should also be applied in new modifications of the existing brain training techniques because that can significantly enhance the efficacy of training games and programs of the brain stimulation.

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Introduction:-

The development and maintenance of the complexity of a structure of neuronal networks and activity in the healthy brain we recently linked with the complexity of visual and other sensory signals of the environment and habitat of the person: with the acquired by him the experience of nonlinear stimulation (Zueva, 2015).

The theory of "fractality of sensations" (Zueva, 2015) implies that the simplification of the dynamics of environmental signals is associated with the abnormal development and aging of the brain, and can accelerate the already existing neurological pathology and age-related CNS diseases (Fig. 1).

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A deficiency in the fractal characteristics of the environment



Fig 1:- Hypothetical consequences of simplifying spatial-temporal structure of environmental cues

It also follows from this theory that the use of nonlinear stimulation therapy can contribute to the restoration of the structure and function of the brain, including in neurodegenerative pathology by regulating the potential of neuroplasticity.

The plasticity of the brain is the inherent property of the nervous system and predetermines its ability to evolve in response to the experience. The neural plasticity is maintained throughout a person's life (Dragoi et al., 2001; Eysel, 2009; Chen et al., 2011; Gilbert and Li, 2012; Sur et al., 2013).

It plays a significant role in the development of the CNS, the acquisition of new skills (Moucha and Kilgard, 2006), learning and memory (Black, 1998), and in the restoration after the injury (Merzenich, 2013; Nudo, 2011). A high plasticity of neural networks allows the brain to adapt to the quantitative and qualitative changes in sensory inputs (Katz and Shatz, 1996; Buonomano and Merzenich, 1998; Carcea and Froemke, 2013).

The potential of plasticity is the highest in children in the critical and sensitive periods of the early development. In these periods, the incoming information is crucially necessary for the correct formation of specific neuronal connections (Hubel and Wiesel, 1970; Hensch, 2005; Merabet and Pascual-Leone, 2010; Bengoetxea et al., 2012). If the neural network is not stimulated, in the adult brain the deficit of function served by this network will remain. The mechanisms of plasticity are changed with age (Gilbert and Li, 2012; Sur et al., 2013; Mahncke et al., 2006; Freiherr et al., 2013; Stein et al., 2014). The potential of neuronal plasticity declines throughout the lifespan depending on variables defined by genetic, biological, and environmental factors (Maya-Vetencourt et al., 2008; Pascual-Leone et al., 2011; Maya-Vetencourt et al., 2011; Maya-Vetencourt and Origlia, 2012).

The theory states an existence of a close link between the complexity of the networks, dynamics of the brain's activity and the complexity of environmental cues that surround a person during his life. That is, the human evolution in a complex environment and the genetic factors predetermine but do not guarantee a healthy structure and function of the brain and other body systems. The experience of fractal stimulation is a fundamental element in maintaining brain health.

Different changes of the local (circuit) and global (network) cortical plasticity occurring in aging and pathological conditions have been demonstrated in studies using transcranial magnetic stimulation (TMS), electroencephalogram (EEG) and functional magnetic resonance imaging (fMRI) (Pascual-Leone et al., 2011). These studies have shown that the excessive or insufficient plasticity may contribute to disorders of development and neurodegenerative diseases including autism spectrum disorders or Alzheimer's disease. Deficiency of plasticity sharply reduces the ability of a brain to adapt to changing requirements of the environment and can lead to the conversion of normally innocuous processes to pathogenic. On the other hand, excessive plasticity can make structural bonds in the system unstable (Pascual-Leone et al., 2011).

Today various ways to reactivate the plasticity of the adult and aging brain are actively studied to increase the effectiveness of treatment of neurodegenerative diseases. It was shown that a potential of the plasticity might be enhanced using several training techniques including programs of the repetitive physical and cognitive training.

Many techniques on reactivation of neuroplasticity are considered in the framework of the "Environmental enrichment" (EE) (Zueva, 2015; Maya-Vetencourt et al., 2008; van Praag et al., 2000; Mora et al., 2009; Baroncelli et al., 2010; Baroncelli et al., 2012; Alwis and Rajan, 2014), which represents the conditions, ensured higher levels of multisensory stimulation, physical activity and social interaction. Findings from studies that investigated the effects of enrichment in various neurological disorders demonstrated behavioral, morphological, and molecular effects of EE [for example, Alwis and Rajan, 2014]. Some training methods are aimed at the activation of regions and structures in the human brain that are remained partially intact by the disease (Serruyaa and Kahana, 2008). A learning of new skills and languages, intellectual interaction, physical training, learning to play musical instruments, computer games, and some others methods were used to try to slow down the age-related cognitive decline (see, for example, Kramer et al., 2004; Green and Bavelier, 2007).

We should note, however, that the efficiency of such programs and technologies is not yet high enough and does not receive the confirmation at a high level of evidence-based medicine. For example, the positive effect of virtual reality and physiotherapy techniques aimed at improving the gait dynamics, postural stability and the quality of life in Parkinson's disease was recognized as "weak" or "very weak" (Dockx et al., 2016).

It is important to note that in the adult brain, even the temporal opening of the window of an enhanced plasticity can be an attractive therapeutic strategy aimed to rewire damaged neural circuits (Zueva, 2015). We can expect that during the period of increased synaptic plasticity, the effectiveness of any existing (traditional, alternative or complementary) therapeutic strategies will be enhanced. We believe that the stimulation therapy with aperiodic fractal impulses of different modalities would provide a greater practical impact, than the use of repetitive incentives of the simple spatial or temporal structure.

Dynamics of physiological activity in a health and disease:-

The most of the natural objects are fractals. Examples include branching trees, the outline of mountain ranges and the seacoast, river beds, and a lightning branching (Mandelbrot, 1982; Feder, 1988; West et al., 1999; Crownover, 1995; Iannaccone and Khokha, 1996, for review see Taylor et al., 2011; Zueva, 2013; Zueva, 2015). Fractals are figures that, unlike the usual geometric shapes, not change their form with the change in scale, i.e., have the property of self-similarity or scale invariance. Fractal dimension is the fundamental property of fractals and estimates the complexity of the object. Static geometric fractals cannot describe the time-varying natural phenomena. However, the fractal concept is also applied to the description of complex processes occurring nonlinearly in time. The complex, fractal process is the process that has the self-similar dynamics in various time scales, just as the geometric fractal has the scale-invariant structure.

Nonlinear fluctuations of different parameters of the system are called noises (Sejdić and Lipsitz, 2013). Noises are classified according to their spectral density and conventionally described by a color system of abstract terms commonly used in the electronics and acoustics. Spectra are well approximated by the inverse power law $1/f^\beta$. Three of the most well-known types of noise are "white," "brown" and "pink" noise. White noise includes completely random, not correlated fluctuations with the spectral density of $1/f^0$ - uniform at all frequencies, and with a variance equal to infinity. The weakly correlated non-periodic dynamics characterize the brown (or Brownian) noise with the spectral density proportional to $1/f^2$. In the pink noise (also called a fractal or flicker noise), the spectral density corresponded to $1/f^1$. Pink noise is dominant in Nature and describes the dynamics of river floods, fluctuations in traffic intensity and climate data, the sounds of human speech, music, and many other phenomena (Halley and Inchausti, 2004; Storch et al., 2002; Vasseur and Yodzis, 2004).

The evolution of man on Earth has been occurring in a nonlinear world, in an environment characterized by a variety of fractal objects and processes (Halley, 1996). The natural noises with different dynamics affect the adaptation of living systems to environmental conditions and may determine the alteration of populations (Vasseur and Yodzis, 2004). Theoretical models have been created to explain the mechanisms of adaptation of organisms to the spectrum of fluctuations in environmental factors (Dey et al., 2016).

Dynamical systems are classified according to different criteria. By the existing random parameters, the systems are divided into stochastic (white noise is an example), deterministic (periodic and quasi-periodic oscillations), and deterministic-chaotic (fractal pink and brown noise) (for instance, González and Pino, 2000). In deterministic processes, the state of the dynamical system is entirely determined by the initial values and can be predicted for any time. For stochastic processes, knowledge of their behavior in a particular time interval allows determining only the probability characteristics of the behavior of the system in the other time range. In the stochastic system, there are an enormous number of operating factors that are comparable in the strength and period of their action, while the state of the deterministic-chaotic process is determined by the final number of factors (at least three).

The cause of the chaotic behavior of dynamic system believes to be the nonlinearity of its internal connections. Cognitive processes require interoperability between a variety of specialized local and remote areas of the brain (Castellanos et al., 2010). Nonlinear interaction of several regulatory systems and the complex impact of the environment, exhibited by on different time scales, produce a highly variable "noise" behavior of the parameters of physiological processes, which can be modeled as a $1/f$ process (the pink noise) (Sejdić and Lipsitz, 2013). It is logical that the distinguishing feature of normal physiological processes is the fractal complexity of their dynamics shown by many studies (Goldberger et al., 2002; Tan et al., 2009; Manor and Lipsitz, 2013). On the other hand, a typical feature of a loss of fractal dynamics in the pathology is a weakening of long-range correlations (Manor and Lipsitz, 2013; Peng et al., 2002; Hausdorff et al., 1995; Goldberger, 1997). It can lead to a Brownian noise (weakly correlated fluctuations instead of pink noise), the highly ordered behavior (deterministic oscillations at constant frequency) or the completely uncorrelated behavior (white noise) (see also Sharma, 2009).

The simplification of dynamics with aging and the loss of time-invariance have been shown for multiple physiologic processes including cardiovascular control and heartbeats, hormone release, gait dynamics, electroencephalographic oscillations (Lipsitz and Goldberger, 1992; Hu et al., 2009; Balasubramanian and Nagaraj, 2015). The reduction in the complexity of neural networks (Geula, 1998) and brain oscillations was observed in several neurological and psychiatric diseases (Li et al., 2008; Zhang et al., 2015; Liu X. et al., 2016; Yuvaraj and Murugappan, 2016). In patients with Alzheimer's disease (AD), the complexity of the EEG was reduced compared with healthy persons of the same age (Liu X. et al., 2016; Jeong, 2004; Dauwels et al., 2011; Vecchio et al., 2013). The abnormal EEG power density in the frequency range below 12 Hz in AD and mild cognitive impairment were associated with a change in the functionality of neural connections and long-range synchronization of cortical activity (Babiloni et al., 2016).

Investigation of nonlinear dynamics of the time series of human EEG and MEG, recorded at rest, and during the performing of straightforward and complex tasks, and in various stages of sleep (Stam, 2005), allowed the identification of three basic patterns in the brain activity. The typical dynamics in resting healthy subjects were characterized by a high-dimensional complexity and fluctuations of the relatively low level in synchronization neural network. The hyper-synchronization with highly nonlinear (stochastic) dynamics was typical for epileptic activity. The dynamics of the brain activity in patients with encephalopathy and neurodegenerative changes was distinguished by an abnormally low level of spatial synchronization. Only average levels of the complexity in fluctuations of the brain activity due to the critical dynamics near the phase transition were associated with a normal data processing. At the same time, the states of high or low synchronization reflected violation in information processing and cognitive functions (Stam, 2005).

On the other hand, in the recent paper, the nonlinear features of EEG in resting condition and brain functional connectivity were studied in patients with acute thalamic ischemic stroke and healthy subjects (Liu S. et al., 2016). It was shown that patients had the greater mean Lempel-Ziv complexity (LZC) and Sample Entropy than the controls, which implied that the stroke group had the higher complexity of EEG dynamics. However, the stroke patients displayed a trend of weaker cortical connectivity, which suggests a functional impairment of information transmission in cortical connections. Therefore, the greater complexity does not always imply the better functional state. The average level of nonlinearity in the dynamics of the cortical activity (the deterministic-chaotic or fractal process) seems to be necessary for the optimal network's functionality. The fractal complexity of the behavior of the system lies in some optimal range between the stochastic and deterministic behavior that allows the system to respond quickly to changing environmental conditions (Sejdić and Lipsitz, 2013).

30 years ago, it was hypothesized that the normally functioning brain acts in a state of so-called "self-organized criticality" (Bak et al., 1987) – a physiological state, in which the system is spontaneously self-organized to be ready

to operate in a critical zone between order and randomness. Subsequent studies confirmed that the critical systems are associated with a fractal scaling and the presence of long-range correlations in space and time (Kitzbichler et al., 2009; Bilder and Knudsen, 2014; Timme et al., 2016). Kitzbichler and colleagues (Kitzbichler et al., 2009) proved the time-invariant behavior in two models of the critical dynamics of neural networks and human functional systems of the brain oscillating at low and higher frequencies, according to the data of fMRI and magnetoencephalography (MEG). The authors conclude that in the human brain, criticality is a property of an organization of the functional network at all physiological frequency intervals, and they called this phenomenon as a broadband criticality. In the recent work, several methods were used to analyze the neuronal avalanches in the 435 records of cell activity in dissociated rat hippocampal cultures, and in the cortical models of branching of neuronal avalanches (Timme et al., 2016). The results demonstrated that the neural systems operate at the critical point where their complexity is optimized, and the criticality maximises the complexity of neuronal activity.

Stimulation therapy and the dynamics of physiological rhythms:-

The brain is highly susceptible to the rhythmic external impacts, and it can synchronize waves of neuronal activity to the pace of the forcing signal (Srinivasan et al., 2006; Huang and Charyton, 2008). This property is used in certain disease conditions to stimulate the brain with factors of different physical nature (Serruyaa and Kahana, 2008; Sejdić and Lipsitz, 2013; Hummel and Cohen, 2005; Hallett, 2007; Cheng et al., 2014; Antal and Herrmann, 2016; Soderlund et al., 2016).

The spectral power of waves of cortical activity can be modulated with the help of non-invasive brain stimulation (NIBS), main types of which include TMS and transcranial electrostimulation - TES (for review see Krawinkel et al., 2015). TMS and TES seem to modulate not only the rhythm of the spontaneous activity of the brain but also human behavior (Marshall et al., 2011; Sauseng et al., 2013). Rhythms of the brain activity in different ranges are believed to control the timing of neuronal discharges and represent the fundamental principle of information processing (Engel et al., 2001; Valera et al., 2001; Buzsáki and Draguhn, 2004). In a recent analytical review of the current NIBS protocols, a link was demonstrated between the change in timing of impulses of neurons, axonal sprouting and human behavior (Krawinkel et al., 2015).

For different methods of stimulation therapy, efficiency and the duration of the positive results preservation after the treatment depend on many parameters, including polarity, frequency, and other characteristics of the impacts (for review see Serruyaa and Kahana, 2008). For example, studies have shown the significant dependence of the sign of the effect of intermittent impacts on the parameters of stimulation [Serruyaa and Kahana, 2008; Hallett, 2007; Cheng et al., 2014; Antal and Herrmann, 2016; Pascual-Leone et al., 1994; Huang et al., 2005]. In the regime of the repetitive TMS, the use of frequencies equal to or below 1 Hz causes an inhibitory effect, but rates over 5 Hz induces the excitatory action (Hummel and Cohen, 2005; Pascual-Leone et al., 1994). On the other hand, for some neurological and psychiatric diseases, selective attenuation of oscillatory activity in distinct frequency bands was shown (for review see Krawinkel et al., 2015). For example, clinical symptoms of Parkinson's disease (PD) and behavioral disorders were associated with changes in brain activity in the beta range (Levy et al., 2002; Kühn et al., 2008; Crowell et al., 2012; Heinrichs-Graham et al., 2014). In schizophrenia, the weakening of the working memory and other cognitive functions were associated with an abnormal rhythm of the oscillations in the gamma range (Johannesen et al., 2005; Uhlhaas et al., 2008; Sun et al., 2011; Andreou et al., 2014). Changes in the activity of the alpha-range were observed after stroke and traumatic brain injury (TBI) (Tecchio et al., 2005; Westlake et al., 2012; Laaksonen et al., 2013).

It is well known that the flickering light and pulses of sound signals may affect the activity of the brain waves (Adrian and Matthews, 1934; Barlow, 1960). The "brainwave entrainment" means the capacity of the brain to synchronize frequencies of its oscillations with the rhythm of the external stimuli. The modulation of frequency and the increase in the spectral power of oscillations occur in the frequency range of the conducted sensory stimulation. The use of different imaging methods made it possible to detect also a dependence of the metabolism and blood flow in the brain from the frequency of light flashes or sound pulses (Srinivasan et al., 2006; Fox and Raichle, 1985; Sappey-Marinié et al., 1992). In some works, flickering visual stimuli have been used for targeted changes in the activity of the cerebral cortex and improving episodic memory (Williams et al., 2006; Williams, 2001). For example, flickers at the frequency 9.5-11.0 Hz (with an interval of 0.5 Hz) before the demonstration of a monosyllable word, facilitate its storage and recall in the young and older adults (Williams et al., 2006; Williams, 2001). In cognitively healthy older adults, the remembering of words and long-term memory were improved significantly only after the exposure to flickers with a frequency close to 10.2 Hz, but not below 9.0 or above 11.0 Hz (Williams et al., 2006).

Numerous studies are also devoted to various other aspects of light stimulation, but they do not enter into the scope of our discussion.

The therapies using stochastic (white) noise may improve gait disturbance and cognitive performance (for review see Sejdić and Lipsitz, 2013). The positive effect of the background audio noise was shown for the elderly (Priplata et al., 2003), patients with PD (Yamamoto et al., 2005; Pan et al., 2008) and other neurodegenerative disorders (Priplata et al., 2003; Soderlund et al., 2010). The using of vibrating sole for the treatment of the gait and postural dynamics in the elderly and patients with diabetic neuropathy, as well as in after-stroke patients demonstrated an increase in the fractal dimension of the inter-step interval (Ross et al., 2007; Costa et al., 2007). The basis of this effect is believed to lay a phenomenon of stochastic resonance. In physics, it is known that adding noise in nonlinear systems can enhance the detection of the subthreshold signal. The stochastic resonance phenomenon can explain the beneficial effects of a white audio-noise on cognitive performance in attention-deficit hyperactivity disorder (ADHD) and in inattentive persons (Soderlund et al., 2010; Sikström and Söderlund, 2007; Soderlund et al., 2007). The external noise has been assumed to introduce through the sensory system the internal noise in neural networks, and the induction of stochastic resonance in the neurotransmitter systems facilitates the task performance. Recently, the effects of the audio-noise therapy and a stimulant medication (methylphenidate) on the cognitive performance were compared in ADHD patients (Soderlund et al., 2016). According to numbers of correctly recalled points in the task on the visual-spatial distributed memory, the noise therapy (79-80 dB) rendered almost the same effect as the stimulant medication and somewhat enhanced its result in a joint application. Also, in the test for episodic memory, the noise therapy had even the higher number of correctly recalled words than methylphenidate.

The therapeutic potential of nonlinear technologies of the stimulation:-

Since the effects of NIBS and audiovisual stimulation depend on the stimulus frequency, and a variety of neurological and psychiatric disorders were associated with selective disturbances of oscillatory activity in specific ranges, the temporal structure of rhythmical impacts has to be of great importance for obtaining the desired effect.

We develop the conception the use of technologies of fractal and other nonlinear effects on the brain for normalization the complexity of the structure and activity of neural networks by reactivation of synaptic plasticity (Zueva, 2013; Zueva, 2015). In the earlier paper, for the first time, we drew attention to the importance of using the fractal structure of light flashes in the diagnosis and treatment of neurodegenerative diseases of the retina and the brain (Zueva, 2013). Later, Cheng and colleagues also noticed that fractal regimes are optimal in the stimulation therapy when used the intermittent impact of any modality (Cheng et al., 2014). However, the justification of the logic of the therapeutic use of the synchronizing rhythms to return the fractal dynamics of physiological processes, simply because such dynamics is inherent in a healthy system is not sufficient because it does not explain 'why' and 'what' underlies the expected positive effect of fractal stimulation. Then, the hypothesis was suggested and theoretically justified (Zueva, 2015), which states the existence of the relations of the complexity of neural connections, dynamics of the activity of the brain with the nonlinear characteristics of sensory cues. The theory of "fractality of sensations" postulates that the most significant result of evolution in a multiscale environment is not just a fractal characteristic of healthy functions. It is the emergence of the dependency of the complexity of neural connections and the activity of the brain on the dynamics of the environmental cues accompanying a person during his life (Fig. 2).

Positions set from the theory of "Fractality of Sensations"

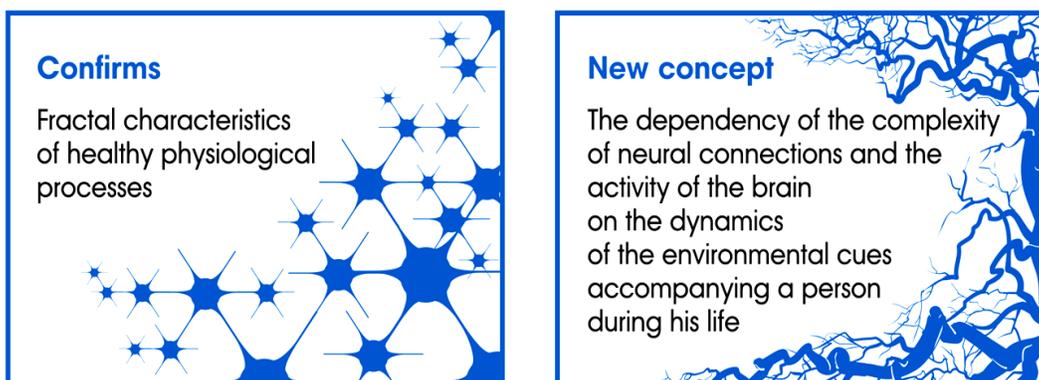


Fig 2:- Results of human evolution in a multiscale environment

Therefore, the benefits of fractal stimulation flow out not from typicality of nonlinear dynamics for healthy physiological processes but from an understanding of the need to maintain and restore a complex fractal dynamics using in particular situations the artificially created fractal environment.

It should also be noted the possible negative aspects of the use of regular (periodic) signals with deterministic dynamics. First of all, we cannot exclude the risk that periodic and quasi-periodic (deterministic) rhythms can worsen the already existent anomaly. It may occur because the fractal dynamics distinguishes robust, healthy systems, but the weakening of long-range correlations or the emergence of the periodic dynamics characterizes pathology. This thesis has been already underlined also by other investigators (Sejdić and Lipsitz, 2013; Cheng et al., 2014). On the other hand, even when the diseases of the brain are associated with the abnormal oscillations in a particular band of EEG, it is not the only characterization of a disease. The fluctuations of other physiological parameters or rhythms in the other EEG bands in the same patient may preserve the healthy fractal dynamics.

Therefore, we should not exclude that direct or indirect interference in it by periodic rhythmic brain stimulation may be dangerous. All this determines the need to study the effects not only incentives of nonlinear (non-periodic) dynamics, but also ordered periodic rhythms of certain frequencies to define the actual risk of adverse consequences and the conditions of their manifestation, or conversely, elimination. Fractal modulation of the fluctuations of stimuli in a targeted therapy might be a way to solve the problem (see also Cheng et al., 2014). In the maintaining the constant mean values of targeted stimulation frequency, its nonlinear modulation can be likely crucial to restoring the control of the fractal dynamics of brain oscillations, and their generators. Alternatively, as the initial step of the treatment, it may be first the restoration of the fractal dynamics of rhythms and the optimal level of phase synchronization between different brain areas. In this case, as the second phase of targeted therapy, the impact at the specific frequencies could be conducted.

The choice of the stimulation mode will be determined by possible limitations of this technology in humans related to the specificity of the disruption of the dynamics of physiological processes. For example, PD is characterized by the appearance of periodic fluctuations in intervals between steps, that is, deterministic walking dynamics instead of fractal dynamics in a healthy person (Goldberger et al., 2002; Manor and Lipsitz, 2013). Therefore, in patients with PD, it would be hazardous to use rhythmic stimuli with a constant stimulation frequency. Such a stimulation regime characterizes the traditional intermittent stimulation therapy. However, it can also be one of the factors of nonlinear stimulation when the mode of a rigidly defined carrier frequency is applied with a nonlinear modulation. Therefore, in PD and some other cases, it is advisable to use the nonlinear stimulation therapy regime with complex structured signals without a carrier frequency. In the same time, methods with carrier frequency can be helpful in targeted therapy in pathologies associated with selective changes in power and rhythm dynamics in particular EEG frequency bands.

Some studies provide indirect evidence proving that nonlinear effects on the brain can have the great prospects in the future therapeutic strategies. The recently published works documented the possibility of changing the gait dynamics (variability in the inter-step intervals) by synchronizing the walking with the rhythm of external signals. For example, in patients with PD, an interactive rhythmic audio stimulation restores the natural temporal structure of their steps $1/f$ – the pink noise (Hove et al., 2012). In healthy individuals, the possibility of the synchronization between the rhythm of steps and non-periodic sound pulses was also shown. The listening to white and brown fractal sound noises showed a shift of dynamics of a healthy person to the statistical properties of stimulating signals (Hunt et al., 2014; Rhea et al., 2014).

These studies on the synchronization of the gait dynamics with external forcing signals do not belong yet to the techniques of fractal therapeutics. In one study it was shown that under certain conditions, the new rhythm of walking was maintained until 15 minutes after the end of the experiment (Rhea et al., 2014), but we did not find any works that studied therapeutic effects of fractal therapy by the intermittent stimuli. However, it is important that the studies mentioned above (Hove et al., 2012; Hunt et al., 2014; Rhea et al., 2014) showed practical readiness of human physiological functions to synchronize with non-linear rhythms of the fractal structure, not just only with regular periodic rhythms.

The human brain contains the complex networks of anatomical connections providing the functional connectivity between brain regions. The highly synchronized electrical activity can be estimated with MEG and EEG. The

imaged coherence in the brain permits assessing the connectivity of the networked specific regions in the brain in neurological disorders. Phase synchronization is one of the fundamental principles of interneuron communications over long distances (Krawinkel et al., 2015; Valera et al., 2001; Hummel and Gerloff, 2005; Schoffelen et al., 2005). The brain has been assumed to be a complex network of dynamic systems with extensive interactions between local and more distant regions (Valera et al., 2001).

Varela and coauthors analyzed the multiscale integration mechanisms, which balances the distributed anatomical and functional organization of the brain, enabling the emergence of consistent behavior and thinking (Valera et al., 2001). According to their hypothesis, the formation of dynamic linkages, which is mediated by synchronization on multiple frequency bands, is the most likely candidate for the mechanism involved in the large-scale integration. The pathological conditions, such as the effects of a traumatic brain injury, violate the functional interaction between the local and remote regions of the CNS (Manjarrez et al., 2002). It is also known that cardiovascular system changes during aging, leading to reduced complexity of interactions between the various physiological control mechanisms of its dynamics (Balasubramanian and Nagaraj, 2015). The ability of external stimuli to synchronize the rhythm of the network activity in a variety of ranges refers to the known physics phenomenon of the synchronization of chaotic attractors. This phenomenon is observed when the correlation between two or more chaotic systems occurs (Boccaletti et al., 2002; Arenas et al., 2008).

As a peculiar influence close to fractal therapy, we may consider the music. Studies show that most musical compositions have a fractal dimension and the spectrum of pink noise (Bigerelle and Iost, 2000). Music is a complex and versatile stimulus for the brain that impacts many regions in the temporal, frontal, parietal cortex, in the cerebellum, and subcortical structures involved in the processing of auditory, emotional and motor information (see, for example, Lin et al., 2014). Numerous studies documented the psychological and physiological impacts of music on people, its effect on the functional activity of the brain (Yuan et al., 2000; Petsche, 1996; Jausovec et al., 2006; Nozaradan, 2014). The positive effect on the brain functions was demonstrated particularly for Mozart's compositions (Bigerelle and Iost, 2000; Hsü and Hsü, 1990; Hsü and Hsü, 1991; Jenkins, 2001; Hazard et al., 1998-1999). Regular music lessons may activate neuroplasticity, improve the structure and function of different areas of the brain (Särkämö et al., 2014), making music a potentially useful tool in neurological rehabilitation. Music therapy enhances the perception of speech in noise (Herholz and Zatorre, 2012) and other functions of the aging brain (Bhattacharya and Petsche, 2005). Musical training in childhood may reduce the effect of aging on the CNS (Strait et al., 2012; Kraus and White-Schwoch, 2014). In our previous article, we discussed some other aspects of this issue analyzing the role of music in the context of the theory of "fractality of sensations" (Zueva, 2015).

It seems to be essential to study the impact on the plasticity and the dynamics of the physiological activity not only of the intermittent incentives with dynamics invariant in time but also of static geometric fractals - images, invariant in space. These may include simple geometric fractals, fractal sets, simulated by computer programs, the pictures of natural objects and works of art, which observation could have a positive effect on visual function and brain activity. Some literature data confirms this possibility. For example, the plasticity of the fixation movements of human eyes was found during the observation of geometric fractals of varying complexity (Namazi et al., 2016).

The dynamics (timing) of saccadic eye movements shifted toward the dynamics of the observed image, and this effect was dependent on the fractal dimension of the presented visual stimulus. However, at first glance, unexpected results were obtained. The images with higher complexity (higher fractality) caused fixational eye movements with lower fractality, and the complexity of EEG was more reduced when observing the images with the higher fractal dimensions. On the other hand, it is known that the most pleasantly sounding music have the fractal dimension close to 1.4 (Hazard et al., 1998-1999). Pyankova (Pyankova, 2016) has reviewed the relationship between evaluations of aesthetic appeal and the complexity of objects of architecture, music, and painting with their fractal dimension. The literature data shows that the most aesthetic appeal have facilities with average fractal dimension: from 1.1 to 1.5. Looking at the dimension of the images in the previous work (Namazi et al., 2016) we can see that only the minimal level of complexity of one of three studied pictures (the Apollonian gasket) corresponded to the optimal fractal dimension. Therefore, one can assume that the complexity of the EEG dynamics and eye movements reduced when watching the images with excessive complexity taking into account the aesthetic appeal of the objects.

Probable effects of nonlinear stimulation therapy:-

Particular mechanisms of impacts of different regimes of TMS and TES on brain's functions are discussed in detail in many publications (Krawinkel et al., 2015; Marshall et al., 2011; Sauseng et al., 2013; Engel et al., 2001; Valera

et al., 2001; Buzsáki and Draguhn, 2004) and are not the object of our attention. We note an important fact, emphasized in several studies, that the improvement of oscillation power in particular ranges of the EEG spectrum correlated with the improvement of memory and patient behavior, for instance, in PD and schizophrenia (cited from Krawinkel et al., 2015).

Medical rehabilitation in patients with neurodegenerative pathology, TBI and some other clinical situations need solving problems associated with the disorder of the structure of neural networks and the deficit of brain functions provided by these networks. Also, stimulation therapy with stimuli of the complex structure can be used to restore the mental activity and correct the psycho-emotional state in situations not related to anatomical changes in nervous tissue.

In pathological conditions associated with a deterioration of the structure of neural networks and connectivity of the brain, the effect of nonlinear impacts on the brain, apparently, will be mediated through changing a potential of neuronal plasticity. Activation of the synaptic plasticity, in our opinion, might play a dominant role in mediating the effects of intermittent nonlinear stimulation on restoring the structure and improving the mental performance of the individual. The argument indirectly confirming this hypothesis is that the repetitive modes of stimulation and repetitive sessions of NIBS are more effective regimens than continuous exposure (cited from Krawinkel et al., 2015). It provides the evidence that the stimulation therapy may activate synaptic plasticity in the affected area through the mechanisms of long-term potentiation.

Experimental studies have shown that for animals, the reactivation of neural plasticity by different ways influence behavior and cognition through the modulation of various signaling pathways (Cassilhas et al., 2011). On the other hand, the response to exercises was demonstrated to be so massive that it was almost impossible to note a single signaling pathway by which exercise exerts its effect (cited from Hamilton and Phodes, 2015).

The technologies of nonlinear stimulation in a psychological rehabilitation and healthy subjects can contribute the restoration of dynamics of neuronal activity using the brainwave entrainment mechanisms (Adrian and Matthews, 1934; Barlow, 1960). One can suppose that the recovery of a fractal complexity of the electrical activity of a brain will help to improve cognitive abilities. The arguments for this hypothesis are the studies (Krawinkel et al., 2015) mentioned above that showed significant correlations between the degree of recovery of brain oscillatory activity, mental performance, and human behavior. It can be expected that the treatment effect of the stimulation with will be better for sensory stimuli that are adequate to the visual and auditory systems (Adrian and Matthews, 1934; Barlow, 1960; Williams, 2001; Williams et al., 2006).

The complex-structured optical signals can have an adequate effect on the suprachiasmatic nucleus and the epiphysis - the structures involved in controlling the biological rhythms of the organism. Loss of control over fractal modulation of the rhythmic activity of the brain can be one of the concomitant factors of the pathogenesis of certain diseases associated with disruption of circadian rhythms. In particular, disturbance of the rhythm of sleep and wakefulness and other circadian disturbances are found in aging and age-related diseases, such as schizophrenia and AD (Bonaconsa et al., 2013). Taking these facts into account, one can specify the morning time as the most appropriate for the application of optic and audiovisual stimuli.

It is also important to note the role of internal noise in physiological systems (for example, internal retinal noise) for the proper functioning of sensory systems, in particular for the color sensitivity of cone photoreceptors (Rieke and Baylor, 2000) and tuning of the contrast sensitivity of the visual system (Anderson et al., 2000). The external noise introduces through the sensory system the internal noise in neural networks, and the induction of stochastic resonance in the neurotransmitter systems has been assumed to facilitate the cognitive performance (Ross et al., 2007; Sikström and Söderlund, 2007). Therefore, a phenomenon of stochastic resonance can also serve as one of the mechanisms for the rehabilitation of physiological functions and brain activity.

The brain's areas most sensitive to the nonlinear stimulation therapy seem to be the structures and cortical areas that belong to the particular sensory system and provide information processing of adequate stimulating signals. Note also that almost all sensory information, except olfactory, is first processed in the thalamus that creates projections to all areas of the cerebral cortex (Hubel and Wiesel, 1961; Sherman and Guillery, 1996; Barlett, 2013). The thalamus contributes to the multisensory plasticity (Röder et al., 2002; Kelly et al., 2014; Moro et al., 2015). Therefore, this structure can be sensitive to the non-periodic signals influences and mediate effects of the nonlinear

stimulation therapy. However, this assumption should be evidenced or rejected in future studies. It will be necessary to prove also whether the treatment with nonlinear signals can modify neurogenesis and synaptic plasticity in hippocampal regions associated with memory and learning, similar to effects of environmental enrichment described in animal research (Lu et al., 2003).

Classification of neurocognitive impacts and technologies that use them:-

Mentioned above methods of stimulation therapy and environmental enrichment can be attributed to the techniques of neurocognitive impacts. Neurocognitive technologies (NCTs) are the non-medication technologies of effects on the human brain by stimuli of physical nature that promote positive changes in the structure of neural connections, brain activity, mental abilities and human behavior, that is, produce neurocognitive effects. Neurocognitive impacts we can divide into "passive," "conditionally passive" and "active" by the degree of conscious participation of the person himself in their consequences (Fig. 3).

"Passive" neurocognitive technologies:-

"Instrumental" methods of stimulation therapy are referred to the "passive" neurocognitive influences, including phototherapy, audiovisual stimulation, TMS and TES, mechanical vibration and other techniques. We attribute the nonlinear stimulation therapy by complex-structured stimuli also to the "passive" neurocognitive impacts.

"Conditionally passive" neurocognitive technologies:-

To this sort of neurocognitive effects, one should refer all kinds of works of art including works of painting and sculpture, architecture, music, and others. We classify influences of this sort as "conditionally passive," because aesthetic pleasure at the contact of man with art arouses a sense of co-belonging, and thereby may stimulate the activity of the brain.

"Active" neurocognitive technologies:-

The "active" impacts are often considered in the framework of the environmental enrichment and art-therapy. They include cognitive and physical training programs, computer games, language and new skills learning. Methods of art-therapy include learning to play (and the practical playing) musical instruments, singing, painting, drawing, and other creative activity. The "activity" of these influences is that, in contrast to "passive" or "conditionally passive" exposures (stimuli of complex dynamics or contemplation of works of art), a direct involvement of a person in the creative process stimulates the creative thinking. For example, observations showed that attracting older people with dementia to drawing and using other types of art therapy can help to reduce cognitive decline and correct their behavior (Noice et al., 2013; Bolwerk et al., 2014).

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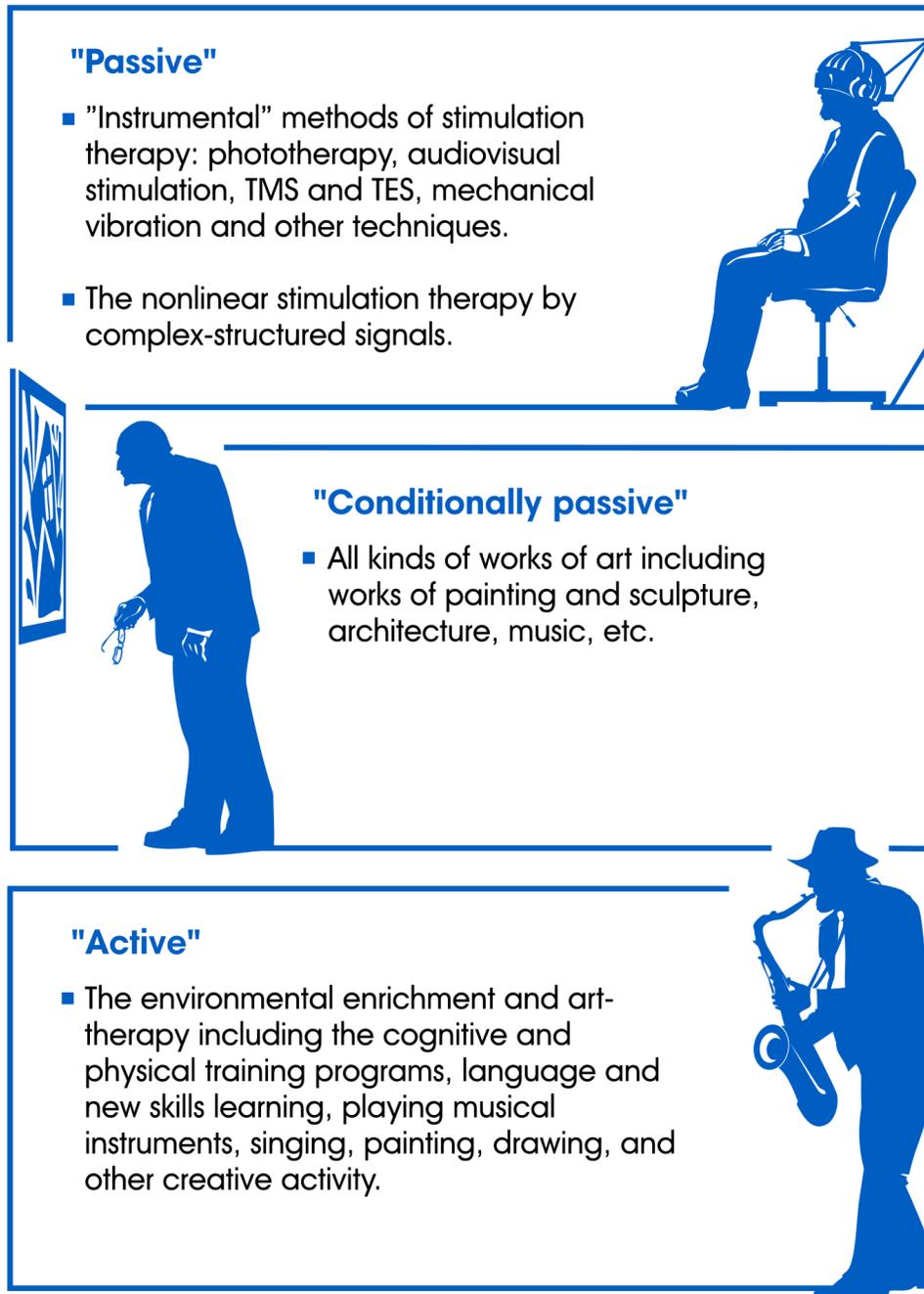


Fig 3:- Classification of neurocognitive technologies by the degree of conscious participation of the person himself in their impacts: "Passive," "Conditionally Passive," "Active"

All sorts of NCTs have their own merits. However, their therapeutic potentials are not the similar. Therefore, it seems to be appropriate to use the particular combinations of the different techniques in various clinical situations. "Active" NCTs may be more efficient than "conditionally passive" influences, but they are not always available to the patient for various objective and subjective reasons. Besides, in many situations, the effectiveness of restoring cognitive functions using only "active" and "conditionally passive" NCT can be inadequate. For instance, it has

recently been proven that virtual reality technologies and physiotherapy have a weak effect on the gait dynamics in PD [33].

In such cases, the role of “passive” NCT that uses the complex-structured signals have to increase primarily. In our opinion, “passive” nonlinear neurocognitive impacts may have the greatest therapeutic effectiveness among all sorts of NCTs. We believe that the effect of the nonlinear stimulation (primarily with visual, audio and other sensory signals) will be mediated by an optimization of the neuroplasticity potential in various neurological and psychiatric disorders, the traumatic brain injury and stroke. In healthy subjects and for mitigation of psychological problems, these techniques should contribute to the restoration of neuronal activity via the brainwave entrainment phenomenon.

The effect is expected to be provided by low-intensity stimuli that are adequate for the human experience in the natural environment. However, future studies should identify ranges of efficient and inefficient areas of variation in some parameters of stimulation such as frequency and color for optical signals. Possible limitations of this technology can be related to the specificity of the disruption of the dynamics of physiological processes in patients.

Areas of application of technologies of nonlinear impacts on human:-

It is likely that visual stimuli may play a greater role in comparing to other sensory modalities in therapeutic stimulation providing a high opportunity to influence via the visual system to all the brain.

We have recently created the first LED generator of flickers with fractal dynamics (Zueva M.V., Spiridonov I.N., Semenova N.A. and Rezykh S.V. RF Patent N 0002549150, 25.03.2015). In this device, the time-invariant (self-similar) sequence of flashes with the adjustable complexity is programmed. With this photo-stimulator, we carried out the pilot study of the effects of dynamic visual fractals on the electrical activity of the retina of healthy rabbits (Zueva M. an oral report on the 2nd International Conference on Brain Disorders and Therapeutics, Oct. 26-28, Chicago, USA. “The theory of “fractality of sensations”: possible applications in brain therapy and future research”). The fractal stimulation enhanced the amplitudes of scotopic responses of the retina while reducing their latency that pointed to an increase in the efficiency of synaptic transmission from the photoreceptors to bipolar cells. This LED device for stimulating therapy is only the example of one of the possible options for implementing the idea. Other versions of NCTs of nonlinear impacts can use different principles of programming of complex-structured signals. In future studies, it is necessary to evaluate the real effects that these technologies have and to justify the selection of optimal stimulation parameters for various clinical situations with the help of modern methods of electrophysiology and neuroimaging.

One of the prospective areas of the application of nonlinear signals of various dynamics may be the rehabilitation after the TBI and stroke, and neurodegenerative diseases of the brain and also of the retina. It should be noted that with neurological and psychiatric disorders and especially when structural changes, any non-pharmacological interferences cannot be considered as an alternative to the traditional treatment strategy. They may have only the additional meaning. However, their supplementary role in the therapy of these disorders can turn out to be significant, since one can expect that even in the brief period when the plasticity is enhanced, the effectiveness of any pathogenetically adequate treatment would be strengthened.

The stimulation with incentives with fractal non-periodic dynamics should be, probably, regarded as a physiologically relevant way of normalization of neuronal activity and cognitive function not only in pathological conditions. These techniques can be useful in healthy individuals in a variety of situations when they can also promote the social impact and a significant economic effect. The most promising areas of application the technologies of nonlinear impacts on the brain of a healthy person seem to include the following fields:

First, under normal physiological human aging, the loss of the memory and some other cognitive functions occurs. Nonlinear stimulation techniques may be useful for maintaining a high level of mental activity and long-term preservation of healthy cognitive functions of older people, promoting the mental longevity. Secondly, such techniques might be used for the recovery of cognitive functions and critical thinking when working or residence in extreme and stress conditions, including for support of the population in the conflict zones and in the long-time scientific expeditions. Thirdly, techniques of stimulation with non-periodic incentives of different dynamics may be helpful to increase and recover cognitive and physical performance after severe physical or psychological loads in

athletes. The application of technologies of nonlinear stimulation may be practiced in the centers on psychological rehabilitation and psychological training.

The use of nonlinear modes of stimulation in these situations may be the key factor improving the efficiency of correction of the human cognitive performance by restoring the fractal complexity of the activity of the brain. The role of NCTs, adapted for these purposes, will consist not of treatment, but of training of the brain that may facilitate the process of rehabilitation. We expect that the recovery of the complex dynamics will contribute to maintaining of cognitive functions.

Conclusion:-

We justified that nonlinear therapy with non-periodic light stimuli and stimuli of another nature should be taken into account as a physiologically adequate way helping the recovery of cognitive functions in brain diseases advantageously complementing the therapeutic strategy and medical rehabilitation. The hypothesis assumes that technologies of nonlinear brain stimulation may be prospective for the improving the outcome of a treatment of neurological disorders, TBI and strokes of the brain by promoting the recovery of the structure and function of the brain through the reactivation of neuroplasticity.

The usefulness of these technologies should also be studied for the strengthening of the efficiency of psychological rehabilitation, the slowing down of cognitive impairment in elderly, and for accelerated recovery after severe physical and mental stress.

In the spectrum of NCTs, different variants of mono- and multimodal stimulation with complex-structured signals should be considered as well as their combinations with white noise, music therapy, and other treatment options.

As medical technologies, the NCTs can complement and enhance the capabilities of the standard therapeutic strategy. However, it is assumed that they can have independent significance as simulators of the brain when used in psychological rehabilitation programs.

The visual and audio nonlinear stimuli, if they will be applied in new designs of the well-known contemporary brain training technologies have the prospects to significantly enhance the efficacy of these training games and programs of the brain stimulation.

Conflict of Interest:-

The author declares that there is no conflict of interest regarding the publication of this paper.

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