Translingual Neurostimulation in Late Residual Stage Cerebral Palsy Children Treatment Affects Functional Brain Networks

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Abstract: Management of cerebral palsy is an actual problem of modern medicine. A new direction of neurorehabilitation, intensively discussed in modern science and practice, includes various types of electrical stimulation. Constant stimulation of the nervous system is one of the most popular ways to activate neural networks to activate the brain and initiate neuroplasticity processes. Participants in the experiment were children with cerebral palsy, spastic diplegia form at the age of 6 to 19 (n = 6) (mean age - 17,9 ± 5,6 years). All subjects underwent standard treatment, including massage, therapeutic gymnastics simulators, robotic mechanotherapy, etc., which lasted 20-25 minutes with neurostimulation of the brain (using a PoNS device). All subjects underwent a resting state functional MRI once before and twice - after neurostimulation course. Results indicate positive dynamics in all subjects: most of them learned walking without aids, obtained decreased muscle tonus and improvement in balance, coordination function were noted. Neurostimulation with the PoNS device combined with curative gymnastics (focused exercises), improves the efficiency of motor functions and the development of motor skills. Resting state functional MRI showed improvement in brain networks. If performed properly, it can be an auxiliary method of objective control of treatment effectiveness.

1 INTRODUCTION

In subjects with cerebral palsy, there are apparent violations of equilibrium, the position of motion, retention of the pose in space. Each function of the human body is based on well-organized complex neural networks, including numerous interconnected structures (cortex, nuclei, neural clusters) located in different levels of brain and spinal cord. Collaboration and synchronization of human performance in behavioral, cognitive and autonomic functions. This close integration is especially important in complex sensory and motor functions, such as vision, hearing, balance, gait, speech.

Neurorehabilitation of children with cerebral palsy is multicomponent and includes physiotherapy, special massage therapy, treatment, special limb treatment with different stitches, the use of fixing devices for walking, special, facilitating the motor activity of the child, and costumes. In modern medicine, the problems of rehabilitation of children with cerebral palsy are given particular attention. A new direction of neurorehabilitation, intensively discussed in contemporary science and practice, is the use of various types of electrostimulation, as well as their use in or in combination with existing procedures. The most common among them - are electrical stimulation of muscles and nerves, as well as the spinal cord. Electrical stimulation was used to treat spastic Erb-Duchenne paralysis in 1871. Since the treatment of patients with spasticity by electrical stimulation of the muscles and nerve structures, skin, subcutaneous, epidural electrodes, as well as peroneal implantations have been used (Morenko et al., 2015). Despite the positive results achieved by an integrated approach of treatment, the problem of rehabilitation of children with cerebral palsy in the late residual stage with persistent stereotypes remains unresolved.

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The issue of restoring muscle control and complex sensorimotor integration (balance, movement coordination, body retention in space) has not been given the necessary attention so far. Artificial stimulation of the nervous system is one of the most popular ways to activate neural networks to activate the brain and initiate neuroplasticity processes (Danilov et al., 2006).

2 MATERIALS AND METHODS

2.1 Neurostimulation

An innovative alternative method of using peripheral neurostimulation for neurorehabilitation was presented by Yu. P. Danilov at the World Congress on Psychophysiology in St. Petersburg in 2010. This method was developed at the University of Wisconsin, USA, in a laboratory headed by the famous scientist Paul Bach-Rita, one of the founders of the modern concept of neuroplasticity. In the laboratory of haptic communication and neurorehabilitation (TCNL), a device was developed for electro-tactile stimulation of human skin, and in the most densely innervated tactile region, the tongue (Danilov et al., 2008). Electrotactic stimulation of the tongue is, at the moment, the most effective and safest stimulation of the central nervous system. The tongue is the thinnest part relative to other surfaces of the skin, saturated with various types of mechanical, thermal and taste receptors, with the addition of free nerve endings. This zone has a maximum density of mechanoreceptors per unit area and has a minimum two-point discrimination threshold: 0.5-1 mm for mechanical stimulation and 0.25-0.5 mm for electrical stimulation (Danilov et al., 2007). Two main cranial nerves (branches of the trigeminal, 20,000-22,000 nerve fibers and the facial nerve, 3,000-6,000 nerve fibers) from the front surface of the tongue transmit nerve impulses directly to the brain stem structures. They activate the complex of the trigeminal nerve (mesencephalic, sensory and spinal) the largest nuclei of the trunk) and simultaneously along the branch of the facial nerve the adjacent nucleus of the solitary tract is stimulated. The cochlear nuclei, the structures of the medulla and the upper sections of the cervical spine (C2 and C3) are activated directly also. The reticular formation of the brain stem, the complex of vestibular nuclei and the ventral part of the cerebellum fall into the zone of secondary activation (Barbara et al., 2009). As you know, the brain stem area has a massive accumulation of neural nuclei (86), some of them are engaged in autonomous regulation (blood circulation, respiration), the other part - sensorimotor integration. It is not necessary to exclude the possible secondary activation of several common systems of neurochemical regulation of brain activity, the nuclei of which are located in the brain stem - noradrenergic, dopaminergic, serotonergic and acetylcholinergic. Descending paths regulating the activity of spinal cord motoneurons, namely: the trigeminal-spinal, solitary-spinal, and three vestibulo-spinal, directly involved in the regulation of the activity of the lower limbs and walking, come from the same area (Mitchele et al., 2009). Intensive rhythmic stimulation of existing neurons leads to the corresponding activation of synaptic contacts and axons, including the whole complex of pre- and postsynaptic neurochemical mechanisms (Ignatova et al., 2018). Phenomena such as long-term potentiation or depression of neural networks may underlie the effects observed when using electro-tactile stimulation of the tongue. Long-term potentiation (Long-term potentiation, LTP), as well as long-term depression (Long-term inhibition, LTI), is the enhancement or suppression of synaptic transmission between two neurons that persists for a long time after exposure to the synaptic pathway. LTP is involved in the mechanisms of synaptic plasticity, providing the nervous system of a living organism with the ability to adapt to changing environmental conditions (Patriat et al., 2013). Most neurophysiological theorists believe that long-term potentiation together with long-term depression underlies the cellular mechanisms of memory and learning (Lomo, 2003).

At the moment, the device for electrotactile stimulation is called PoNS (Portable Neurostimulator), and its use for stimulation of the brain in children with cerebral palsy is a new direction in neurorehabilitation. The matrix, in which are the electrodes of irregular shape; optimized to stimulate the most sensitive areas of language. The matrix itself includes 143 electrodes divided into nine 16 - electrode sectors (Fig.1). Within each segment, only one electrode is active at a given time, and the rest are grounded. Stimulation through one electrode occurs simultaneously in nine sectors. The electrodes are alternated with a frequency of 50 Hz. The incentive is a triplet of rectangular pulses of microsecond duration.

Regular stimulation from the PoNS device, activating vast areas of the brain, increases the efficiency of existing neural networks, increases the likelihood of the formation of new synaptic contacts (synaptogenesis), enhances the brain's innate ability to improve motor function. The goal of successful neurorehabilitation with such stimulation is to restore motor function or to teach new motor skills, achieved by combining specialized exercises with extensive brain activation using the PoNS device.

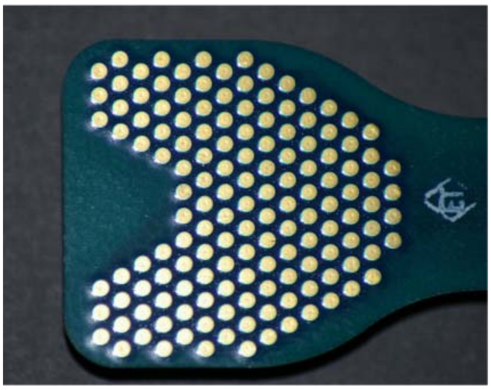


Figure 1: The PoNS device (Portable Neurostimulator), the close-up of the matrix.

Figure 2: The PoNS device (Portable Neurostimulator).

The studies were conducted in patients with peripheral and central vestibular disorders (Badke et al., 2011; Chisholm et al., 2014; Bach-y-Rita, 2008; Wildenberg et al., 2013) multiple sclerosis, stroke (Wildenberg et al., 2011), TBI and spinal injuries (Joseph et al., 2011; Kublanov, 2008; Kublanov et al., 2018). The high efficiency of peripheral neurostimulation was shown in combination with specialized physiotherapy in restoring general motor control of the body, balance, walking, speech, eye movements, various aspects of sensorimotor integration. Additional studies, using functional MRI, unequivocally confirmed the presence of potent activation of the brain stem and the ventral part of the cerebellum during stimulation of the tongue, as well as the presence of long-lasting aftereffect, the preservation of foci of activity in the brain of subjects for hours and even days after the last stimulation (Efimtcev et al., 2018). Additional data analysis showed that simultaneously with the activation of the subcortical structures of the brain, the coefficients of communication between the cortex areas of the brain involved in integrative training processes also change (Petrenko et al., 2017).

2.2 Participants

This study involved six children with a cerebrally palsy, form of spastic diplegia. Patients with intact intellect, no seizures in anamnesis. All children obtained standard treatment, including massage, medical gymnastics with simulators, robotic mechanotherapy, hydrotherapy, and 10 daily sessions of physical therapy, which lasted for 20-25 minutes and neurostimulation of the brain (using the PoNS device). Patients underwent functional MRI of the brain before the start of and at the end of the course of treatment using neurostimulation. The patients were aged 8 to 14 years. Patients were evaluated by standard scales GMFSC Scale (gross motor skills), FMS (functional motor scale), Berg balance scale, the Ashworth scale (spasticity).

All patients underwent resting state fMRI at three timepoints - before the course of neurostimulation, within 3 days after the end of the course of neurostimulation, and in 1 month after neurostimulation. The parameters of the pulse sequence were: BOLD technique, repetition time (TR) - 3000 ms, echo time (TE) - 30 ms, spin rotation angle (FA) - 90°, FOV - 192 mm, matrix - 64 × 64, slice thickness - 4.5 mm, the number of slices - 29, the number of repetitions - 120, the scan time - 6 minutes. Patients were instructed to lie with their eyes open (do not sleep), without fixing their gaze. Thus, for all subjects, there were identical conditions of a state of rest, and this had a minimal impact on the visual and aural working networks of the brain.

Also, all patients underwent structural MRI with obtaining T1 and T2 weighted images and FLAIR (Fluid attenuated inversion-recovery) to exclude brain tumors and other pathological morphological changes. The T1-weighted gradient echo MP-RAGE (Magnetization Prepared Rapid Acquired Gradient Echoes) pulse sequence — a gradient echo with magnetization preparation and fast collection — was used to align fMRI images with the anatomical structures of the brain. The main feature of this sequence is its high resolution and isotropic voxel with a volume of 1.2 mm^3.

The parameters of the MP-RAGE pulse sequence were: repetition time (TR) - 2300 ms, echo time (TE) - 3 ms, spin rotation angle (FA) - 9 °, FOV - 240 × 256 mm, matrix - 256 × 240, slice thickness - 1.2 mm, the number of slices - 160, the number of repetitions - 1, scanning time - 9 minutes. Details of the parameters of all pulse sequences are presented in Table 1.

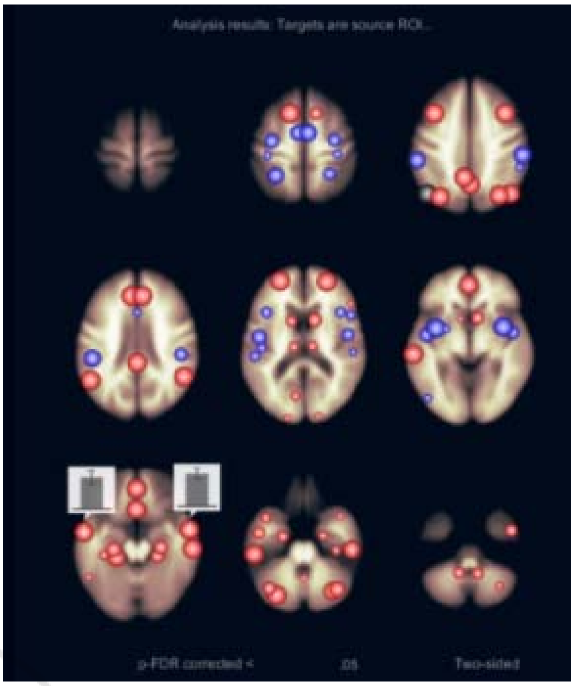
Table 1: MRI Examination Protocol.

Pulse sequence	Scan time	Parameters
T2 TSE (axial plane)	2 m. 30 s.	FOV – 220×220 mm, slice thickness – 4.0 мм, TR – 6000 ms, TE – 93 ms, matrix – 320×320, slice number – 27
T2 TIRM (axial plane)	4 m. 30 s.	FOV –199×220 mm, slice thickness – 4.0 мм, TR – 9000 ms, TE – 93 ms, matrix – 256×232, slice number – 27
MPRAGE	9 m	FOV – 240×256 mm, slice thickness – 1.2 мм, TR – 2300 ms, TE – 3 ms, matrix – 256×240, slice number – 160
BOLD FRMI (resting state)	6 m	FOV – 192×192 mm, slice thickness – 4.5 мм, TR – 3000 ms, TE – 30 ms, matrix – 64×64, slice number – 36

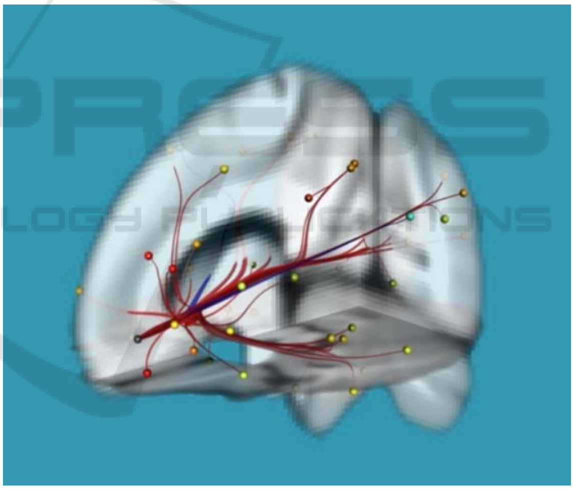
Statistical processing and evaluation of the results of neuroimaging studies of each patient individually and their group (rest fMRI data) was carried out using the software package CONN v.18 (Functional connectivity toolbox). The software was designed to determine the relationships between various brain regions, including the dynamic mode, statistical mapping of activation zones, identifying the structure of multiple rest networks and working functional networks of the brain. We used analysis based on the choice of the region of interest (ROI-to-ROI and Seed-to-Voxel), as well as analysis based on graph theory (Fig. 3).

3 RESULTS

The first patient before the course of treatment could walk using multi-support canes within the room, and used walkers for longer distances (500 meters or more), after the course of treatment he mastered walking using one single-support cane within the room and at school, for longer distances uses multi support sticks. Before the treatment, the second patient used multi-support canes for walking within



a)



b)

Figure 3: Graphical representation of the results of intergroup statistical analysis based on the choice of the zone of interest (ROI-to-ROI): a - maps with a schematic representation, combined with an anatomical atlas of the brain; b - 3D reconstruction of the map of positive and negative functional connections, combined with the anatomical atlas of the brain.

the room, and on the street, the patient could not stand on his own without support, after finishing the course of treatment he learned to walk independently on a flat surface (within the room), the patient can stand on his own without a support and on the street uses one single support cane. The third patient, before the start of the course of treatment, used a walker within the room to walk, a stroller was used at school and for longer distances. After completing the course of treatment, the patient has mastered multi-support canes within the room, the walker is using at school and can walk to the playground, and an active type stroller is used for longer distances. Before the treatment, the fourth patient walked using two single-support canes within the premises and on the street, could stand for several seconds without support, at the end of the course of treatment he learned to walk independently on a flat surface, he stands alone on the street, using one single-bearing cane on the street. The fifth patient, before the course of treatment, used multi-support canes for walking, at the end of the treatment course, he mastered walking within the premises, relying on one single-bearing cane, and using multi-support canes for longer distances.

One patient with the level of GMFSC development 4, before the course of treatment, could move around with the walker within the room, an active type of stroller was used at school and on the street. At the end of the course of treatment the patient learned to walk using multi-support canes within the room and at school for more long distance confidently uses walkers. Also, all patients showed a decrease in muscle tone and an improvement in balance and coordinating function. The equilibrium improvements estimated on the Berg scale ranged from 2 to 7 units (4.5 on average), and as a percentage of the initial state, the improvement was observed from 12 to 70% (31% on average) (Fig. 4).

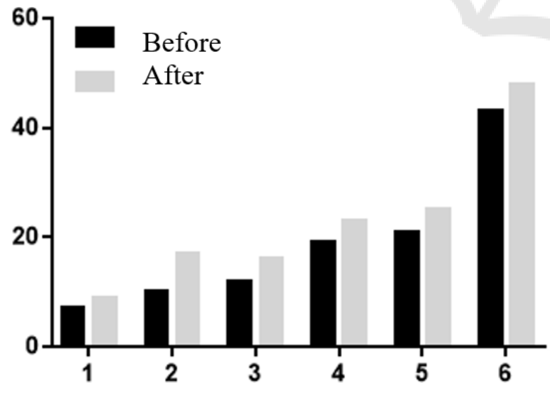
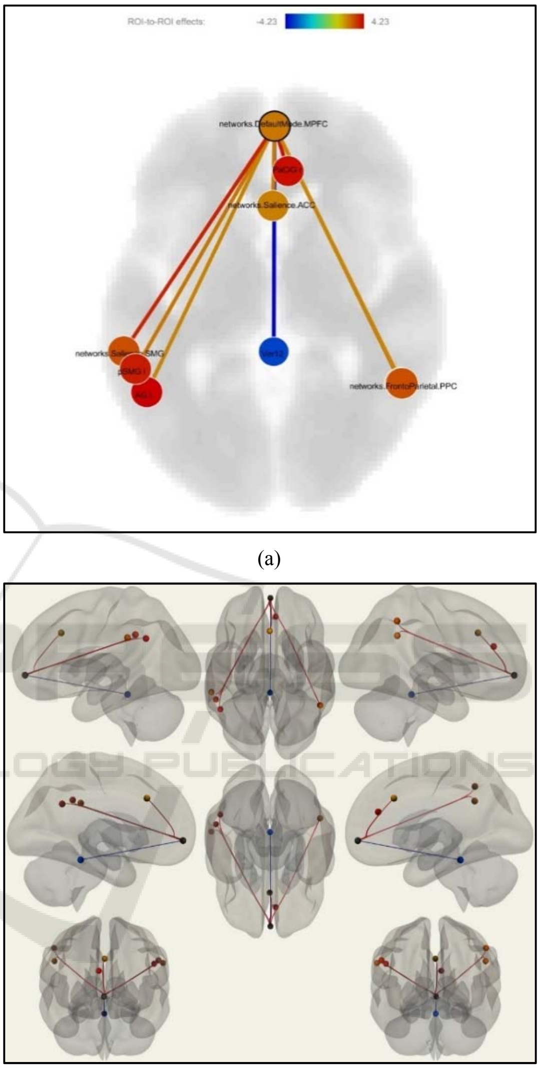


Figure 4: Berg scale (patients data).

As the result of intergroup statistical analysis (two-sample t-test, comparing the resting state in the first and second timepoints), we noticed the enhancement of the functional connections (FC) and the interaction of the MPFC with the posterior parietal cortex on the right, frontoparietal cortex, anterior sections of cingulate cortex (ACC), supramarginal and angular gyri on the left. All of them are parts of a default mode network (DMN). At the same time, we found decreased FC of MPFC and the cerebellar worm (p FDR-corr. <0.05) (Fig. 5, Table 2).



(a)

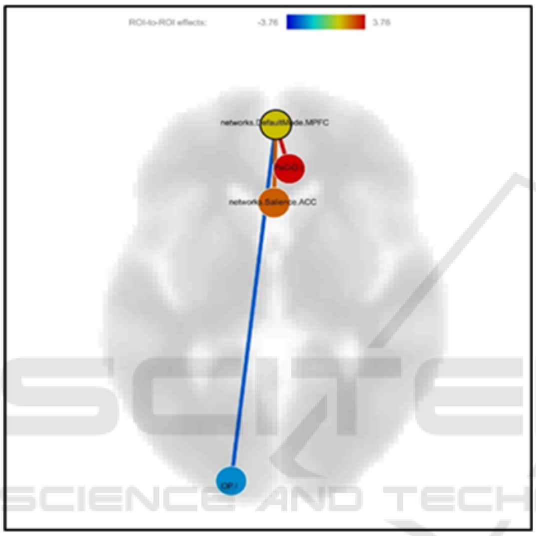
(b)

Figure 5: The result of a group comparison of patients in the second and first timepoints. The areas of statistically significant differences are shown: increase and decrease of the functional connectivity in diagram (a) and on the 3D model (b) (cont.).

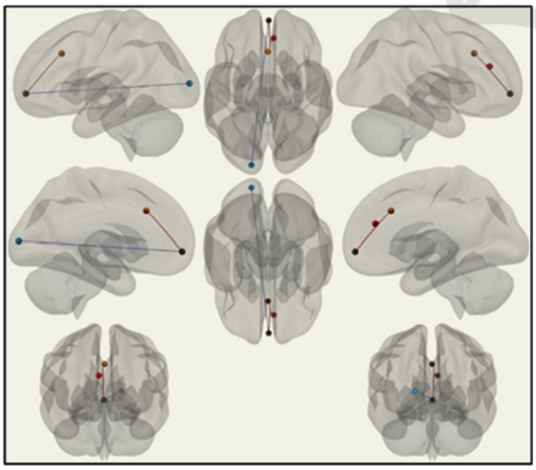
When performing intergroup statistical analysis (two-sample t-test, comparing the state of rest in the first and third timepoints), the changes were less expressed. The MPFC FC with the paracingulate gyri on the right and the ACC intensified even more, and the FC with the posterior occipital cortex on the left decreased (p FDR-corr. <0.04) (Fig. 6, Table 3).

Table 2: The results of a group comparison of patients in the second and first timepoint.

Brain area	Hemis phere	T	Voxels	% of atlas	Volume mm³	MNI coordinates (x,y,z)
atlas.Ver12 (Vermis 1 2)		-4.23	41	87	328	1,-40,-11
atlas.PaCiG r (Paracingulate Gy*ght)	r	3.96	213	16	1704	7,37,23
networks.Salience.SMG (L) (-60,*,31)	l	3.73	416	44	3328	-60,-39,-31
atlas.AG r (Angular Gyrus Right)	r	2.98	630	43	5040	54,-50,-17
atlas.pSMG l (Supramarginal Gyr*eft)	l	2.63	431	41	3448	-55,-46,33
networks.Salience.ACC (0,22,35)		2.52	147	6	1176	0,21,-15
atlas.AG l (Angular Gyrus Left)	l	2.42	334	35	2672	-50,-56,30
networks.FrontalParietal.PPC (R)*,45)	r	2.37				52,-52,32



(a)



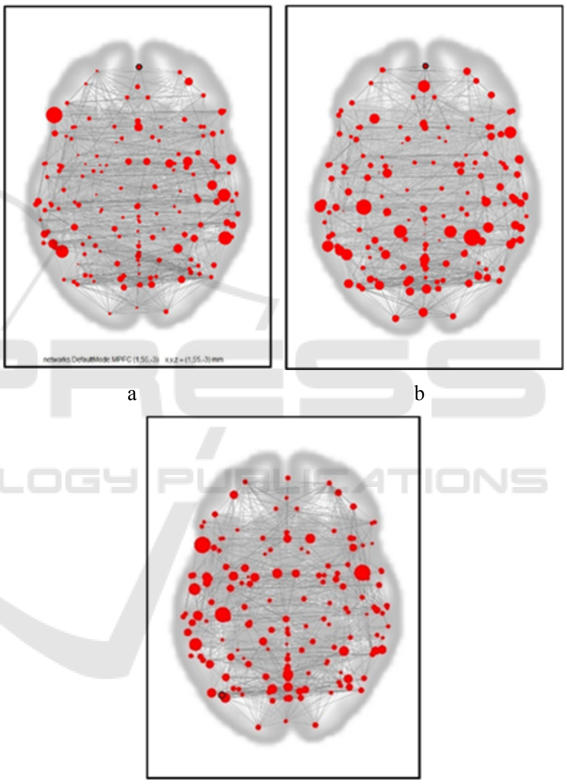
(b)

Figure 6: The result of a group comparison of patients in the third and first timepoint. The areas of statistically significant differences are shown: increase and decrease of the functional connectivity in diagram (a) and on the 3D model (b).

Table 3: The results of group comparison of patients in the second and first timepoint.

Brain area	Hemisp here	T	Voxels	% of atlas	Volume mm³	MNI coordinates (x,y,z)
atlas.PaCiG r (Paracingulate Gy*ght)	r	3.76	102	8	816	7,37,23
networks.Salience.ACC (0,22,35)		2.74	250	10	2000	0,22,35
atlas.OP l (Occipital Pole Left)	l	-2.66	171	6	1368	-17,-97,7

When performing analysis based on graph theory, global efficiency has become more expressed at the second and third timepoints, compared to the first timepoint (p FDR-corr.<0.05 for each time point) (Fig. 7).



a b

c

Figure 7: The result of the analysis based on graph theory at different timepoints: a – the first timepoint (before the course of treatment), b – the second timepoint (immediately after the course of treatment), c – the third timepoint (delayed study).

4 DISCUSSION

The simultaneous combination of TLNS with specialized exercises allows to influence all components of motor activity: central (cortical), subcortical (basal ganglia, cerebellum, brain stem), spinal cord centers. Thus, multilevel neurostimulation allows activating not only muscle control (decrease in tone) but also such complex sensorimotor functions as balance and movement coordination when walking, which, in combination with physical rehabilitation, helps to master and develop new motor skills quickly.

The positive effects persisted (or decreased, but slightly) during the many months of interruption (up to one year) between the courses of therapy, which is confirmed by our fMRI study. It shows that the dynamical changes in brain during the course are obvious, and there were also improvements a month later, though they were not so significant compared to the second one, the clinical condition of the patients confirms this fact. They did not have negative dynamics. This allowed us to consistently improve the symptoms, being studied, with each subsequent course, i.e. neurostimulation gives to rehabilitation a cumulative (accumulative) effect.

It is traditionally considered that a child with cerebral palsy reaches half of its potential to develop motor skills by the age of 5 years and the maximum possible development by 7 years. The potential achieved remains at the same level or may even worsen with age. In our experiments, all children were over the age of 7 years. These results can significantly expand both the scope of this technology in the rehabilitation of children with cerebral palsy and improve the prediction of the effectiveness of the therapy used for older children.

Brain TLNS enhances the effect of physical rehabilitation, activating vast areas of the brain, increases the efficiency of existing neural networks, increases the likelihood of new synaptic contacts (synaptogenesis), enhances the brain's innate ability to improve motor function. The fMRI data alone confirms that the human brain is plastic at any age and is capable of an amazing reorganization, the mechanisms of which we are just beginning to explore. The dynamics of changes in DMN and functional connections between the first and second timepoints turned out to be more vivid than between the first and third timepoints. That probably indicates a delayed rehabilitation effect.

5 CONCLUSION

Taking into the attention the limited and minimal intensity of training, the main task of the study was limited to the formation of new motor skills. The patient in 10 sessions had to form a new motor skill, consolidate it and use it in everyday life. Based on these considerations, it is clear why the index of general motor control (FMS scale) has statistically significantly improved. Since the development of motor control skills was the task of training, besides general improvement in functional connectivity, certain parts of motor neural networks improved their level of functional activity as a result of neurostimulation. This technique is innovative in the field of neurostimulation, non-invasive, safe and easy to use. Indeed, the daily 20-minute stimulation of the tongue for two weeks increases the innate ability of the brain to improve motor function, contributes to the formation of new motor skills.

The use of neurostimulation using the PoNS device, in combination with therapeutic exercises (targeted exercises), can improve the efficiency of the recovery of motor functions and the development of motor skills.

The use of resting state functional MRI allows to obtain data without having to perform special tasks for children, which simplifies the method of objective monitoring, as well as it provides better and more detailed information about the functional state of the brain than with task-based fMRI. This pilot study data allows to consider the fMRI technology as the objective tool for the neuro-electrostimulation mechanisms investigation. The data could also form new treatment techniques of the non-invasive multi-electrode neck neural structures neurostimulation application for treatment of the psychiatric and neurological disorders, exactly – disorders accompanied by the neurodegeneration (Alzheimer disease, Parkinson disease, dementia), consequences of the brain traumas, neurotoxic actions, depressive and anxiety disorders, strokes.

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