CURRENT TRENDS AND PROSPECTS FOR DEVELOPMENT OF NON-INVASIVE BRAIN STIMULATION

S.A. Polevaya[1], *S.B. Parin*[1], *A.I. Fedotchev*[2*]

[1] National Research Lobachevsky State University of Nizhny Novgorod, 23 Prospekt Gagarina, Nizhny Novgorod, 603950, Russia;
[2] Institute of Cell Biophysics, Russian Academy of Sciences, 3 Institutskaya St., Pushchino, Moscow Region, 142290, Russia.

* Corresponding author: fedotchev@mail.ru

Abstract. This review analyzes current trends in the development of traditional (open-loop) methods of non-invasive brain stimulation, as well as promising directions for the development of closed-loop methods of adaptive neurostimulation. The main focus is on studies using non-invasive magnetic and electrical stimulation, as well as acoustic and audiovisual stimulation. The possibilities and prospects for using these technologies as a tool in carrying out a wide range of rehabilitation procedures are analyzed. The results of the authors' own research in this direction are presented.

Keywords: non-invasive brain stimulation, closed-loop adaptive neurostimulation, transcranial magnetic and electrical stimulation, acoustic stimulation, audiovisual stimulation, rhythmic processes of the body, automatic modulation.

List of Abbreviations

EEG – electroencephalogram

Introduction

One of the most promising and rapidly developing areas of neurophysiology is the creation, improvement and clinical testing of non-invasive methods of brain stimulation, including transcranial magnetic and electrical influences, acoustic and audiovisual stimulation. To date, the range of conditions for the successful use of these methods is extremely wide, as are the specific characteristics of the therapeutic effects used.

It is known that transcranial magnetic stimulation of the brain is widely used in the treatment of neurological and psychiatric diseases (Burke *et al.*, 2019; Gonsalvez *et al.*, 2021), in cognitive science for long-term modulation of the activity of the stimulated area of the cerebral cortex (Bakulin *et al.*, 2020; Begemann *et al.*, 2020), during cognitive rehabilitation of patients with focal brain lesions (Kalantarova *et al.*, 2020; Draisma *et al.*, 2020; Khrulev *et al.*, 2022), as well as in the treatment of symptoms of post-traumatic stress disorder (Kan *et al.*, 2020). Transcranial electrical stimulation is considered one of the most promising approaches to non-invasive modulation of neuroplastic processes in patients with movement disorders (Bakulin *et al.*, 2019; Stolbkov, Gerasimenko, 2021; Popyvanova *et al.*, 2022), to non-drug treatment of depressive disorders (Poydasheva *et al.*, 2020; Piccoli *et al.*, 2022; Hao *et al.*, 2023) and to the rehabilitation of patients with post-stroke aphasia (Belopasova *et al.*, 2020).

It is also known that specially organized acoustic influences are successfully used to correct psychosomatic disorders (Sekirin & Maybrodskaya, 2019), to strengthen mental health (Geiser *et al.*, 2020) and psychological rehabilitation of patients with impaired motor functions (Kotelnikova *et al.*, 2021), as well as to improve sleep and memory (Malkani & Zee, 2020; Wunderlin *et al.*, 2021; Stanier *et al.*, 2022). Audiovisual stimulation has even more pronounced therapeutic potential due to the participation of resonance mechanisms of brain activity, mechanisms of multisensory integration and neuroplasticity (Ashanina & Senik, 2018; Kotov *et al.*, 2020; Roy *et al.*, 2021). Thus, audiovisual influences are successfully used in the treatment of neurodegenerative diseases (Yang *et al.*, 2021), to enhance the adaptive capabilities of the body of athletes (Golovin *et al.*, 2018), to improve the functional state and health of a person (Korolev, Savchenko, 2018;

Sysoev *et al.*, 2018), in the prevention of overwork in students (Pats & Goryunova, 2018), in the restoration of motor and cognitive functions after severe traumatic brain injury (De Luca *et al.*, 2021).

An analysis of the literature shows that two main lines of research can be distinguished in the area under consideration. One of them includes methods of non-invasive brain stimulation based on the traditional approach, in which the stimulation parameters are set in advance and remain unchanged during the course of stimulation. Another line has been formed relatively recently and includes methods of adaptive neurostimulation with feedback from the current physiological parameters of a person. In recent years, the number of publications in both lines of research has been rapidly increasing, which makes it necessary to identify the most promising directions for further development of these lines of non-invasive brain stimulation.

In this regard, the purpose of the presented review is to analyze current trends in the development of traditional methods of non-invasive brain stimulation, as well as promising directions for the development of adaptive neurostimulation with feedback. The main attention is paid to the consideration of studies using non-invasive magnetic and electrical influences, as well as acoustic and audiovisual stimulation. The possibilities and prospects for using these technologies as a tool in carrying out a wide range of rehabilitation procedures are analyzed. The results of the authors' own research in this direction are presented.

Development trends of traditional methods of non-invasive brain stimulation

One of the progressive trends is the use of combined effects. Thus, a combination of meditation or hypnosis procedures with transcranial electrical stimulation of the brain led to an increase in neuroplasticity and an increase in the clinical effectiveness of the combined interventions relative to their isolated effects (Rebello-Sanchez *et al.*, 2022). Transcranial alternating current stimulation combined with acoustic stimulation (40 Hz tone) was found to be a safe and easily tolerated treatment for cognitive function in patients with Alzheimer's disease, while separate use of electrical and acoustic stimulation was significantly less effective (Liu *et al.*, 2023).

A progressive trend in increasing the effectiveness of transcranial electrical stimulation with direct current is the use of small ring electrodes, which allows increasing the focality of stimulation (Poydasheva *et al.*, 2021). Other authors also point out the importance of spatial resolution and focality of transcranial magnetic stimulation, which allows differential stimulation of cortical areas when correcting cognitive functions (Numssen *et al.*, 2023).

Another trend in the development of traditional methods of non-invasive brain stimulation is the widespread use of functional brain imaging data. For example, it has been shown that rhythmic transcranial magnetic stimulation under the control of an electroencephalogram (Poydasheva *et al.*, 2019) or functional magnetic resonance imaging (Lagoda *et al.*, 2021) is a highly effective treatment for cognitive disorders. It is believed that the strong and long-lasting oscillations caused in the cerebral cortex by rhythmic stimulation may help restore the natural frequencies of neural activity in older people to those characteristic of younger and healthier brains (Qiao *et al.*, 2022). Particularly promising are individualized treatments in which the frequency and location of stimulation are adjusted according to pathological brain conditions identified by functional brain imaging (Chino *et al.*, 2023).

Despite the intensive development and noted research prospects, in general, existing traditional methods of non-invasive brain stimulation are characterized by a number of disadvantages, such as low efficiency, high variability and poor reproducibility of the results obtained (Janssens, Sack, 2021; Antal *et al.*, 2022; Schutter *et al.*, 2023). The reason for the listed shortcomings is the fact that when organizing these therapeutic interventions, empirically specified parameters are used, which remain constant during stimulation and do not depend on changes in the patient’s condition. This approach does not take into account the dynamic nature of the endogenous oscillatory activity of

the nervous system. In fact, stimuli are presented during different physiological microstates of the brain, leading to high variability in the effect of individual stimulus and to a weak overall stimulation effect (Bakulin *et al.*, 2021; Kasten & Herrmann, 2022). As a result, untimely applied neurostimulation may be ineffective or cause unwanted side effects (Zanos, 2019; Provenza *et al.*, 2019).

Overcoming these shortcomings is achieved in an intensively developing line of research - adaptive neurostimulation, in which feedback from the current physiological parameters of a person is used when organizing non-invasive brain stimulation procedures.

Trends and prospects for the development of adaptive neurostimulation with feedback

Adaptive neurostimulation methods use sensory influences that adapt to the current parameters of dynamic processes characteristic of a given patient using control feedback signals from various physiological parameters of the body (Lo & Widge, 2017; Oxley & Opie, 2019). The key feature of adaptive neurostimulation methods is that the adjustment of the parameters of the therapeutic effect, controlled by feedback signals from the patient's current physiological indicators, is carried out automatically, without the participation of his consciousness (Zhou & Miller, 2019; Tervo *et al.*, 2022). Compared with traditional brain stimulation methods, adaptive feedback neurostimulation can improve the effectiveness of therapy, eliminate the long initial period for programming and adjusting the stimulator, provide individualized treatment, and automatically maintain adaptive stimulation parameters (Hosain *et al.*, 2014; Prosky *et al.*, 2021).

Thus, the use of feedback from current human physiological parameters provides adaptive neurostimulation methods with a number of advantages. First, feedback signals modulate or adapt therapeutic interventions in response to physiological changes and thus provide more effective and efficient therapy (Sun & Morrell, 2014; Potter *et al.*, 2014). Secondly, thanks to the principle of feedback closure, the current dynamics of microstates of the nervous system are taken into account (Vosskuhl *et al.*, 2018; Dick & Nozdrachev, 2020; de Bock *et al.*, 2020; Hu *et al.*, 2023). Thirdly, therapeutic stimulation procedures achieve high personalization of effects, corresponding to the most promising directions in the development of methods of non-invasive brain stimulation - brain state-dependent closed-loop stimulation (Bergmann, 2018; Bradley *et al.*, 2022; Farkhondeh *et al.*, 2022) and physiologically informed adaptive neuromodulation (Wendt *et al.*, 2022; Nasr *et al.*, 2022; Weiss *et al.*, 2023).

One of the progressive trends in the development of adaptive neurostimulation methods is the use of feedback signals from the patient's rhythmic processes - rhythms of the cardiovascular and respiratory systems, as well as electroencephalogram (EEG) rhythms. These rhythmic processes are closely interrelated and form the basis of the natural homeostatic regulation of functions; they demonstrate the phenomena of synchronization and resonance and are characterized by high sensitivity to the action of external factors (Fedotchev *et al.*, 2021a). In addition, these rhythmic processes are a source of interoceptive signals, which provide the perception of internal bodily sensations (Quadt *et al.*, 2018; Gentsch *et al.*, 2019; Gibson, 2019). Interoception disorders are currently considered as a potential target for therapeutic intervention in psychosomatic diseases (Khalsa *et al.*, 2018; Dobrushina *et al.*, 2020). An important conceptual basis for this line of non-invasive brain stimulation is also the recently intensively developed ideas about "oscillopathies" and the possibilities of "oscillotherapy" (Takeuchi, Berenyi, 2020), according to which external rhythmic influences can directionally modulate endogenous oscillations through resonance mechanisms or rhythm aquisition mechanisms. Therefore, oscillations of the neural network can be effectively used as therapeutic targets when organizing "oscillotherapy" procedures through the use of actively developing methods of adaptive neurostimulation with feedback (Foldi *et al.*, 2021; Takeuchi *et al.*, 2022).

For example, back in 1996 it was shown that rapid relief of pain syndromes and preservation of pain relief effects for a long time is achieved even with a single application of electrical neurostimulation, automatically controlled by the patient's breathing rhythm (Fedotchev, 1996). Subsequently, electrical stimulation controlled by the patient's breathing was successfully used by a number of authors in the treatment of chronic neuropathic pain (Li *et al.*, 2016; Karri *et al.*, 2018, 2021). Complex acoustic interventions automatically controlled by the patient's current heart rate variability have been successfully used to achieve a state of relaxation (Yu *et al.*, 2018).

Adaptive neurostimulation methods that use feedback from the patient's EEG have gained the most popularity and active development. This is due to the advantages of EEG such as ease of use, non-invasiveness, high temporal resolution and the ability to extract data in real time (Koenig *et al.*, 2020; Jangwan *et al.*, 2022). Numerous studies have shown that non-invasive sensory influences, synchronized with certain current EEG parameters, can improve sleep quality, enhance cognitive functions and memory consolidation processes.

For example, increased efficiency has been demonstrated for transcranial magnetic stimulation synchronized with certain phases of EEG oscillations (Stefanou *et al.*, 2019; Ding *et al.*, 2022). In the treatment of pharmacotherapy-resistant depressive disorders, even single magnetic influences controlled in real time by the power of the occipital alpha rhythm of the EEG were effective (Zrenner *et al.*, 2020). When using acoustic influences controlled by feedback signals from slow-wave EEG components (Schneider *et al.*, 2020; Ruch *et al.*, 2022) or sleep EEG spindles (Ngo *et al.*, 2022), the possibility of significant improvements in sleep quality and memory consolidation processes was demonstrated. With audiovisual stimulation, automatically controlled by feedback signals from narrow-frequency spectral components of the EEG, successful elimination of anxiety and depression was observed (Pino, 2021).

Another trend in the development of methods of adaptive neurostimulation with feedback is the use of computer transformations of the current parameters of bioelectrical activity of the brain into acoustic signals. Thus, the presentation of acoustic stimuli generated in real time by software-controlled transformation of the subject's dominant EEG rhythms into sound stimuli causes a clinically significant reduction in symptoms of post-traumatic stress (Tegeler *et al.*, 2017; Tegeler *et al.*, 2020), and also leads to optimization of autonomic functions and improved sleep quality (Shaltout *et al.*, 2018; Tegeler *et al.*, 2023). The authors argue that real-time updating of one's own EEG patterns and resonance between audible acoustic signals and oscillatory brain networks provide the body with the ability to auto-calibrate, relax, and overcome persistent pathological conditions (Tegeler *et al.*, 2020).

An interesting version of EEG-controlled acoustic stimulation has been successfully used in the bioacoustic correction method, which consists of presenting a person with acoustic signals obtained by computer conversion of the current EEG (Konstantinov *et al.*, 2014, 2015). The method allows one to "hear" the work of the brain in real time and has been successfully used to correct unfavorable functional states with disorders of the cognitive and emotional-volitional sphere (Ivanova & Kormushkina, 2021; Shchegolkov *et al.*, 2022).

Computer conversion of current EEG parameters into therapeutic sensory influences was also used in our studies. Initially, a musical neurointerface was developed in which the current values of the subject's dominant spectral EEG components (EEG oscillators) are converted into music-like signals, timbre reminiscent of the sounds of a flute, smoothly varying in pitch and intensity. This neurointerface has been successfully used in the correction of stress-induced disorders (Fedotchev *et al.*, 2018). Subsequently, the described method of EEG-controlled musical stimulation was improved by adding a second feedback loop, in which, simultaneously with music-like stimulation, photic rhythmic stimuli are presented, formed on the basis of the patient's native EEG (Fedotchev *et al.*, 2019a; Fedotchev *et al.*, 2022). The created method of light and music

stimulation with double feedback from the EEG was successfully used to eliminate the risks of reliability of high-tech specialists (Fedotchev *et al.*, 2019b, 2021b), in the treatment of post-traumatic stress and professional burnout (Fedotchev *et al.*, 2021c), as well as for cognitive rehabilitation of patients with stroke (Mukhina *et al.*, 2021).

Our research also outlined a promising approach to increasing the effectiveness of EEG-controlled sensory stimulation. This approach consists of using resonance scanning, or LED rhythmic photostimulation with a gradually increasing frequency in the range of basic EEG rhythms (Savchuk *et al.*, 2022). It has been experimentally shown that resonance scanning can serve as a kind of preliminary tuning of the brain, causing activation of potential resonators in the EEG spectrum and increasing brain responses to subsequent EEG-controlled adaptive neurostimulation (Fedotchev *et al.*, 2023). Previously, modeling studies proved the possibility of enhancing cognitive activity and improving overall well-being through the interaction of endogenous and exogenous oscillations (Nuidel *et al.*, 2019). When combining resonance scanning with EEG-controlled adaptive neurostimulation, significant positive effects in the treatment of patients with post-Covid syndrome were registered after only a single combined stimulation (Polevaya *et al.*, 2022).

Conclusion

The presented data allow us to conclude that the creation and improvement of methods of non-invasive brain stimulation is an actively developing and promising area of neurophysiology. Judging by the reviewed publications, the greatest development and effectiveness are demonstrated by methods using multimodal sensory stimulation, taking into account functional brain imaging data. A particularly promising line of research seems to be the automatic modulation of non-invasive sensory influences by feedback signals from a person's own rhythmic processes – breathing rhythm, heartbeat rhythm and EEG rhythms. The complex feedback from these rhythms promotes the involvement of interoceptive signals that are meaningful to humans into the mechanisms of multisensory integration, neuroplasticity and resonance mechanisms of the brain. Thanks to the use of control signals from endogenous rhythms, such non-invasive stimulation, by taking into account the dynamics of brain microstates, achieves high personalization and effectiveness of therapeutic interventions. Automatic control of therapeutic sensory influences makes it possible to use methods of adaptive neurostimulation with feedback in conditions that do not require conscious efforts of the subjects, which is especially important when conducting therapeutic sessions with children and patients who are characterized by altered mental states or drug therapy is contraindicated.

The listed advantages of adaptive neurostimulation methods with feedback open up prospects for their use in a wide range of rehabilitation activities, in educational institutions to enhance human cognitive activity and learning processes, in military and sports medicine, disaster medicine, and scientific research.

The research was funded by the Russian Scientific Foundation, grant No. 22-18-20075.

The authors declare that there is no conflict of interest.

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