
REVIEWS

Methods of Closed-Loop Adaptive Neurostimulation: Features, Achievements, Prospects

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Abstract—The review addresses an innovative and intensively developing approach to organizing stimulation procedures, closed-loop adaptive neurostimulation, in which sensory stimulation parameters are automatically controlled by feedback signals from the patient's own physiological characteristics. The effects of applying invasive and non-invasive magnetic and electrical brain stimulation techniques, as well as closed-loop acoustic and audiovisual stimulation with a feedback control from human rhythmic processes, are considered. The features and achievements of a new approach to the treatment of various psychosomatic disorders and cognitive rehabilitation therapy are demonstrated on numerous examples. The prospects for the development of these technologies are outlined. The results of the author's own studies in this research trend are presented.

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INTRODUCTION

The development and clinical validation of new brain stimulation technologies is an exciting and rapidly expanding field of neurophysiology. To date, a variety of neurostimulation methods have been widely employed in psychiatry and neurology as a therapeutic tool for the restoration of impaired functions [1, 2] and cognitive rehabilitation therapy of patients in neurological clinics [3–5], to treat patients with varied central nervous system (CNS) diseases non-responsive to conservative management [6, 7], activate neuroplasticity processes through reorganization of cortical networks by afferent stimulation [8–10], eliminate cognitive and stress-induced disorders [11–14], as well as to optimize cognitive functions in healthy people [15–17]. Meanwhile, many authors note such drawbacks of the existing methods as low

effectiveness, high variability and poor reproducibility of the obtained results [18–20]. The reason behind these drawbacks lies in the fact that the organization of these therapeutic stimulations, as a rule, employs empirical setting of parameters that remain constant throughout stimulation and do not depend on changes in the patient's condition. In doing this, the dynamic nature of physiological functions is disregarded, while stimuli are presented irrespective of different physiological microstates of the brain, leading to a high variability of the effect of individual stimuli and to a weak total effect of stimulation [21, 22]. As a result, untimely applied neurostimulation may be ineffective [23] or even cause undesirable side effects [24].

To overcome these shortcomings, some authors proposed using the feedback from patient's current physiological parameters that modulate or

adapt therapy in response to physiological changes, ensuring thereby a more effective and robust therapy [25, 26]. Thus, an innovative approach to orchestrating stimulation procedures, called adaptive neurostimulation or closed-loop adaptive neurostimulation, has begun to form [27, 28].

Recently, the number of publications devoted to the effects of closed-loop adaptive neurostimulation has been rapidly increasing. The goal of this review is to summarize the data on up-to-date approaches to the clinical application of different types of adaptive neurostimulation. At the same time, the main objectives of the review are to analyze the features, achievements and limitations of the methods developed by now, as well as the prospects for further development of this trend in brain stimulation. The effects of invasive and non-invasive magnetic and electrical brain stimulation techniques, as well as acoustic and audiovisual stimulation, are considered. The possibilities and prospects for the use of these technologies in clinical medicine are analyzed, and the results of the author's own studies in this research trend are presented.

DISTINCTIVE FEATURES OF ADAPTIVE NEUROSTIMULATION TECHNOLOGIES

The methods of adaptive neurostimulation employ sensory stimuli that adapt to patient-specific current parameters of dynamic processes via feedback control signals from various physiological parameters of the body [29, 30].

It is worth noting that a closure of the feedback loop from patient's individual characteristics is also envisaged in modern adaptive neurofeedback methods. In these methods, a patient is presented with sensory stimuli (visual, acoustic, tactile, electrical) that reflect the current activity of certain neural structures underlying his/her behavior or pathology [31]. Allowing detection of the causal relationships between brain activity and behavior, such a feedback provides a patient with the possibility to learn the conscious self-regulation of his/her own functions, in which sensory stimuli carry not a therapeutic but only an informational load [32, 33]. However, a considerable drawback of neurofeedback technologies is that a

significant number (up to 30%) of patients are unable to learn the skill of modifying their own functions consciously to achieve desirable therapeutic effects, while the rest require very long training [34]. This "learning disability problem" is due to the dependence of learning success on a patient's motivation and mood [35], as well as the difficulty of decoding mental commands correctly and the use of ineffective learning strategies [36].

Thus, the key feature of closed-loop adaptive neurostimulation technologies is that parameter adjustment of the therapeutic stimulation, controlled by feedback signals from the patient's current physiological indices, is carried out automatically, unconsciously [37]. Neurostimulation adaptability is achieved due to the fact that the therapeutic stimulation, formed at each given moment and based on the recorded physiological parameters, leads under the influence of stimulation to their adaptive changes which, in turn, modulate the parameters of the next stimulation cycle. Due to the principle of automatic feedback loop closure, the methods of adaptive neurostimulation can achieve high effectiveness and therapy personalization [38]. Moreover, they adopt the character of brain state-dependent brain stimulation [39] which allows for the current dynamics of the CNS microstates. Compared to the canonical neurostimulation methods, closed-loop adaptive neurostimulation can improve the effectiveness of therapy, exclude a long initial period of stimulator programming and adjustment, provide personalized therapy, and automatically maintain adaptive stimulation parameters [40, 41].

ACHIEVEMENTS OF CLOSED-LOOP NEUROSTIMULATION TECHNOLOGIES

Analysis of the literature shows that the adaptive methods of closed-loop deep brain stimulation are most widely spread and recognized [42–44]. In these methods, parameters of therapeutic electrostimulation are dynamically controlled by feedback from biomarkers of pathological brain activity [45]. The fact that pathological neural activity can be recorded directly from the target brain region via stimulating electrodes and used to adapt stimulation parameters in accordance with a personalized therapeutic needs gave impetus to

the development of this research trend [46]. Currently, adaptive methods of closed-loop deep electrical stimulation of the brain are successfully used to treat chronic pain [47, 48]. Tourette syndrome [49], tremor [50], parkinsonism [51–53], and other movement disorders, while the search for biomarkers and stimulation algorithms are in progress [54, 55]. Methods of adaptive optogenetic stimulation that provide automatic adjustment of optical stimulation parameters based on neuronal response data are also gaining recognition [56, 57].

The above methods are invasive, as they require the implantation of stimulating electrodes into certain brain structures. At the same time, the literature data attest to the special relevance and prospectivity of adaptive neurostimulation methods allowing noninvasive monitoring of physiological microstates [58] and personalized therapy of diagnosed disorders [59].

Modern technologies enable a non-invasive recording of functional parameters of almost any system of the organism and using them as signals to control stimulation. For example, there has been demonstrated a successful application of closed-loop deep brain stimulation controlled by feedback signals from skin resistance [60]. It has also been shown that the effectiveness of functional electrical stimulation can be improved by using control signals from an electromyogram (EMG) [61].

Therapeutic sensory stimulation automatically modulated by patient's current rhythmic processes—cardiovascular, respiratory and electroencephalogram (EEG) rhythms—is of prime interest in this respect. Indeed, these rhythmic processes are a source of vitally important interoceptive signals, which provide the perception of internal bodily sensations [62–64]. Interoceptive disorders are currently considered as a pathogenetic mechanism of psychosomatic diseases and a potential target for therapeutic intervention [65–67].

The idea of using human endogenous rhythmic processes as a modulation factor for stimulation parameters was formulated yet in 1996 [68]. In this work, it has been shown that even a single electrical neurostimulation, automatically controlled by the patient's breathing rhythm, provides

rapid relief of pain syndromes and long-term persistence of anesthesia effects. Subsequently, breath-controlled electrical stimulation was successfully applied by a number of authors in the treatment of chronic neuropathic pain [69–71]. Complex acoustic effects, automatically controlled by the current values of the patient's heart rate variability, also turned out to be successful in attaining a state of relaxation [72].

The methods of adaptive neurostimulation, using feedback from the patient's EEG, have been developed most actively due to such EEG advantages as non-invasiveness, high temporal resolution, ease of use, and the ability to extract data in a real-time mode [73, 74].

The topicality and relevance of this research trend is accentuated by a host of studies showing the possibility of improving sleep quality, cognitive functions, and memory consolidation processes via a non-invasive sensory stimulation synchronized with certain current EEG parameters. Similar effects have recently been demonstrated in experiments using transcranial electrical stimulation controlled by slow-wave (0.5–1.2 Hz) components of the frontal EEG [75], or a theta rhythm (4–8 Hz) in frontal EEG leads [76]. The authors of this work point out that the proposed method can lead to an increase in the effectiveness of home treatment, but solely after improving the power and temporal parameters of stimulation.

The possibility of a considerable improvement in sleep quality and memory consolidation has also been shown when using acoustic stimulation (pink noise and pure tones of different frequencies) controlled by closed-loop feedback signals from various EEG parameters, such as sleep spindles [77] and slow-wave (0.25–4.0 Hz) oscillations in the frontal EEG [78], as well as the averaged power of the low-frequency (< 2 Hz) multichannel EEG components, calculated in real time via a special algorithm [79].

When treating depressive disorders, the procedures of transcranial magnetic stimulation, controlled in real time by alpha rhythm components in prefrontal EEG leads, have proved to be very successful [80, 81]. The authors emphasize that therapeutic effects accumulate over days/weeks due to progressive involvement of the neuroplasti-

city mechanisms. A successful elimination of anxiety and depression was achieved via audiovisual stimulation automatically controlled by closed-loop feedback signals from narrow-band frequency spectral components in the central frontal EEG lead [82].

In a number of works, EEG feedback is used through computer conversions of the brain bioelectrical activity's current parameters into acoustic signals. For example, a method of bioacoustic correction has been developed [83, 84], allowing brain functioning to be "heard" in a real time due to the conversion of EEG parameters into a music-like sound scale. Such a conversion employs the operation of matching the values of EEG oscillation periods with a plurality of sound samples, in which each EEG oscillation period in the range from 1 to 30 Hz corresponds to a sound sample with a certain fundamental tone frequency. The method has been successfully used to correct unfavorable functional states in impairments of the cognitive and emotional-volitional spheres [85, 86].

Acoustic stimulation, automatically generated via conversion of dominant EEG rhythms into musical tones, have demonstrated a high effectiveness in the treatment of post-traumatic stress disorders [87, 88], as well as in optimizing autonomic functions and improving sleep quality [89, 90]. The authors of the above-cited works believe that real-time updating of the human own EEG patterns and the resonance between audible acoustic signals and oscillatory brain networks provide the organism with the possibility of auto-calibration, relaxation, and overcoming persistent pathological conditions [88].

In our studies, we proceeded from the fact that musical therapeutic stimulation can be more effective provided being modulated by patient's own EEG parameters [91]. We developed an EEG-guided musical neurointerface in which the current values of the patient's dominant spectral EEG components (EEG oscillators) were converted into music-like signals that resembled flute sounds in timbre, smoothly varying in tone pitch and intensity. This neurointerface has been successfully used to correct stress-induced disorders [92]. Subsequently, the method of EEG-guided single-feedback musical stimulation was

improved by the addition of a second feedback loop, in which rhythmic light stimuli, generated based on the patient's native EEG, were presented simultaneously with music-like stimulation [93, 94]. Such a method of combined, musical and light, stimulation with a double feedback from the patient's EEG has been successfully applied for cognitive rehabilitation of patients with stroke [95], to treat post-traumatic stress and professional burnout [96], correct negative functional states [35], manage post-covid syndrome [97], as well as in cognitive rehabilitation of high-tech specialists [98]. Arranging the above-cited publications in a chronological order, we can trace the developmental dynamics of non-invasive methods of closed-loop adaptive neurostimulation with a feedback from human rhythmic processes (Table 1).

The table data show that the number of publications using non-invasive methods of closed-loop adaptive neurostimulation with a feedback from the body's endogenous rhythmic processes has been growing rapidly, especially in the last 5 years. At the same time, both the assortment of stimulation types and the range of biomedical applications of the certain type of stimulation are significantly expanding.

PROSPECTS FOR DEVELOPMENT OF CLOSED-LOOP ADAPTIVE NEUROSTIMULATION TECHNIQUES

Analysis of the literature shows that the prospects for the development of such an invasive method of closed-loop adaptive neurostimulation as deep brain stimulation are attracting much attention of researchers. This method involves the use of implantable intracranial electrodes, DC batteries, and pulse generators with feedback control, which allows targeted neuromodulation based on neural networks. Therefore, such advances in engineering as the development of reliable electrodes and improved battery designs, the elaboration of effective closed-loop stimulation and remote programming techniques, are seen as immediate prospects [99, 100]. Sophisticated implantable neuromodulation systems, capable of feedback stimulation and the application of new, more effective types of stimulation,

Table 1. Development of non-invasive methods of closed-loop adaptive neurostimulation

Goal/stimulation effect	Stimulation modality	Feedback parameter	Reference
Elimination of pain syndromes	electrical stimulation	respiratory rhythm	Fedotchev, 1996 [68]
Bioacoustic correction of a functional state	acoustic stimulation	EEG rhythms	Konstantinov et al., 2014 [83]
Treatment of chronic pain	electrical stimulation	respiratory rhythm	Li et al., 2016 [69]
Elimination of stress consequences	music-like stimulation	EEG oscillators	Fedotchev et al., 2017 [92]
Treatment of post-traumatic stress	acoustic stimulation	dominant EEG rhythms	Tegeler et al., 2017 [87]
Treatment of chronic pain	electrical stimulation	respiratory rhythm	Karri et al., 2018 [70]
Improvement of sleep quality and memory consolidation	transcranial electrical stimulation	slow-wave EEG components	Ketz et al., 2018 [75]
Optimization of autonomic functions and sleep	acoustic stimulation	dominant EEG rhythms	Shaltout et al., 2018 [89]
Relaxation state induction	music-like stimulation	heart rate variability	Yu et al., 2018 [72]
Improvement of sleep quality and memory consolidation	acoustic stimulation	sleep EEG spindles	Ngo et al., 2019 [77]
Elimination of stress consequences	musical and light stimulation	EEG oscillators + native EEG	Fedotchev et al., 2019 [93]
Improvement of sleep quality and cognitive control	transcranial electrical stimulation	EEG rhythm phase	Mansouri et al., 2019 [76]
Treatment of post-traumatic stress	acoustic stimulation	dominant EEG rhythms	Tegeler et al., 2020 [88]
Treatment of depressive disorders	transcranial magnetic stimulation	alpha and theta EEG rhythms	Zrenner et al., 2020 [80]
Cognitive post-stroke rehabilitation	musical and light stimulation	EEG oscillators + native EEG	Mukhina et al., 2021 [95]
Treatment of chronic pain	electrical stimulation	respiratory rhythm	Karri et al., 2021 [71]
Treatment of post-traumatic stress and professional burnout	musical and light stimulation	EEG oscillators + native EEG	Fedotchev et al., 2021 [96]
Bioacoustic correction of a functional state	acoustic stimulation	frontal and occipital EEG	Ivanova, Kormushkina, 2021 [85]
Correction of negative functional states	musical and light stimulation	EEG oscillators + native EEG	Fedotchev et al., 2021 [38]
Correction of anxiety and depressive states	audiovisual stimulation	spectral EEG components	Pino, 2021 [82]
Treatment of depressive disorders	transcranial magnetic stimulation	prefrontal alpha EEG rhythm	Faller et al., 2022 [81]
Improvement of sleep quality and memory consolidation	acoustic stimulation	slow-wave EEG components	Debellemanière et al., 2022 [78]
Treatment of post-covid syndrome	musical and light stimulation	EEG oscillators + native EEG	Polevaya et al., 2022 [97]

Table 1. (Contd.)

Goal/stimulation effect	Stimulation modality	Feedback parameter	Reference
Bioacoustic correction of a functional state	acoustic stimulation	frontal and occipital EEG	Shchegolkov et al., 2022 [86]
Correction of stress-induced disorders	musical and light stimulation	EEG oscillators + native EEG	Fedotchev et al., 2022 [94]
Improvement of sleep quality	acoustic stimulation	slow-wave EEG components	Ruch et al., 2022 [79]
Cognitive rehabilitation of high-tech specialists	musical and light stimulation	EEG oscillators + native EEG	Fedotchev, 2022 [98]
Optimization of autonomic functions and sleep	acoustic stimulation	dominant EEG rhythms	Tegeler et al., 2023 [90]

are expected to enter the market within the coming five years, while immediately after that, the integration of adaptive network neuromodulation with a predictive artificial intelligence is expected to provide automatic brain- and external sensor-controlled tuning and will be monitored via cloud applications [101].

While considering the prospects for the development of adaptive deep brain electrical stimulation, an important role is given to bidirectional implantable brain–computer interfaces that can detect and selectively modulate the activity of pathophysiological brain circuits. Therapeutic success is predicted to be achieved through the integrated development of strategies for feedback signal identification, artifact suppression, signal processing, and control modes for precise localization of stimulation in a patient-specific manner [102]. To optimize deep brain stimulation devices, machine learning models, able to predict/identify the presence of disease symptoms based on neural activity and adaptively modulate stimulation, are suggested to be used in the future [103].

As for the prospects of non-invasive closed-loop adaptive neurostimulation, the rapidly developing research trend concerned with “oscillopathies” and “oscillotherapy” deserves special attention [104]. This trend is conceptually based on the following key points. Oscillatory brain activity reflects and supports numerous physiologic functions, from motor control to cognition and emotions. Neurological and psychiatric dis-

orders, such as epilepsy, parkinsonism, Alzheimer’s disease, schizophrenia, anxiety, depressive and other disorders, are commonly characterized by disturbances of normal oscillatory brain activity. Such disorders can be thought of as general oscillatory defects, or oscillopathies, which are a biomarker of the symptoms involved. External rhythmic stimulation can directionally modulate endogenous oscillations through the resonance or rhythm entrainment mechanisms. Many authors, therefore, point to the prospect of using neural network oscillations as therapeutic targets when organizing oscillotherapy procedures through application of actively developing methods of closed-loop adaptive neurostimulation [105, 106].

In this regard, a recently proposed method of brain states “transplantation” through sensory or transcranial stimulation generated on the basis of the EEG characteristics of a “donor” appears quite promising [107]. The author assumes that sensory and transcranial stimulations that entrain the brain to certain rhythms can effectively evoke the desired brain states (e.g., of sleep or attention) correlating with these cortical rhythms. Therefore, it appears possible to evoke a desired brain state by reproducing these neural correlates via stimulation. To do this, it is proposed to record the EEG characteristics of a “donor” being at a certain functional state and to use them as feedback control signals during sensory or transcranial stimulation of a “recipient”. The author believes that the proposed method opens up a new effec-

tive neuromodulation approach to non-invasive non-pharmacological treatment of various psychiatric and neurological disorders for which modern therapeutic methods are mainly confined to pharmacotherapeutic interventions [107].

In our experimental work, we also outlined some promising directions for further research. One of them is concerned with the insertion of an additional control loop from the heart rhythm into the EEG-based musical neurointerface [108]. In strictly controlled studies, it has been shown that a complex feedback from brain and heart biopotentials enables to considerably increase the effectiveness of therapeutic procedures in correcting stress-induced states [109] and leads to a maximum increment in the EEG α -rhythm power versus background, accompanied by positive emotional reactions and shifts in the functional state of the organism due to the involvement of interoceptive signals in the mechanisms of multisensory integration and neuroplasticity, as well as in the resonance mechanisms of the brain [110].

Another promising direction of studies relates to the application of resonance scanning, or LED rhythmic photostimulation with a gradually increasing frequency in the range of basic EEG rhythms [111]. In a recent work, it has been shown that resonance scanning can serve as a kind of brain pre-tuning, causing activation of potential resonators in the EEG spectrum and increasing brain responses to subsequent EEG-guided adaptive neurostimulation [112]. Due to such a combination of exogenous and endogenous rhythmic exposures, significant positive effects are recorded already after a single therapeutic procedure and intensify with repeated examinations when correcting human stress-induced states and during cognitive rehabilitation.

CONCLUSION

The data presented here allow concluding that closed-loop adaptive neurostimulation techniques represent an actively developing and promising trend in neurophysiology. As judged from the publications reviewed, the methods using multimodal sensory closed-loop stimulation automatically modulated by feedback signals from

subject's own rhythmic processes—breathing, heartbeat and EEG rhythms—demonstrate the greatest development and effectiveness. Complex feedback from these rhythms promotes the involvement of interoceptive signals, significant for humans, in the mechanisms of multisensory integration and neuroplasticity, as well as in the resonance mechanisms of the brain. Due to the employment of control signals from endogenous rhythms, such a non-invasive stimulation allows for the dynamics of brain microstates and thus achieves high personalization and effectiveness of therapeutic impacts.

Automodulation of sensory stimulation by current human EEG parameters appears to be a particularly promising line of research. Automatic control of therapeutic sensory stimulations provides the opportunity to use EEG-guided adaptive neurostimulation under conditions that do not require a subject's conscious endeavor, which is particularly important when conducting therapeutic sessions with children and patients characterized by altered mental states or whom drug therapy is contraindicated.

The above advantages of closed-loop adaptive neurostimulation techniques open up avenues for their application in wide-profile rehabilitation activities, in educational institutions to activate human cognitive activity and learning processes, in military and sports medicine, disaster medicine, scientific research.

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CONFLICT OF INTEREST

The author declares that he has no conflict of interest related to the publication of this article.

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