DOI 10.1007/s11055-021-01178-z
Neuroscience and Behavioral Physiology, Vol. 51, No. 8, October, 2021

High-Definition Transcranial Direct Current Electrical Stimulation

A. G. Poydasheva,[1] I. S. Bakulin,[1] D. Yu. Lagoda,[1] E. L. Pavlova,[2] N. A. Suponeva,[1] and M. A. Piradov[1]

UDC 612.825.1

Translated from Uspekhi Fiziologicheskikh Nauk, Vol. 52, No. 1, pp. 3–15, January–March, 2021. Original article submitted July 27, 2020. Revised version received September 28, 2020. Accepted October 3, 2020.

Transcranial direct current electrical stimulation (tDCS) is an intensely developing area in noninvasive neuromodulation. Despite large numbers of published studies, data on the possible clinical applications of the method are contradictory. One limitation of tDCS is the relatively non-local nature of stimulation using the standard montage. High-definition tDCS (HD-tDCS) is a modification of the method in which small ring electrodes are used and has greater stimulation focality. In the most commonly used montage, 4 × 1 HD-tDCS, a ring electrode (anode or cathode) is positioned over the target area and is surrounded by reference electrodes of the opposite polarity. This article addresses current data on the methodology, physiological aspects, clinical efficacy, safety, and tolerance of HD-tDCS.

Keywords: transcranial electrical stimulation, tDCS, micropolarization, HD-tDCS, high-definition tDCS.

1. Introduction. Transcranial electrical stimulation (tES) of the brain with weak currents has a long history of use in research and clinical practice [38, 85, 28]. Methods such as "brain micropolarization" [3–5] and "pulsed transcranial electrostimulation" [2] have been used in Russia for a long time. A significant increase in interest in the use of tES throughout the world has been seen since the beginning of the 21st century, after publication of a series of studies demonstrating the potential of using this method to modulate the arousability of the motor cortex [68, 69, 74]. tES is now an intensely developing area of noninvasive neuromodulation [35, 53, 55, 92, 94].

The most widely used tES method consists of transcranial direct current stimulation (tDCS). tDCS generally used two electrodes, one an anode and the other a cathode. Electrodes of size 5 × 5 or 5 × 7 cm are generally used. Stimulation intensity is usually 1–2.5 mA and session duration is 10–40 min [9].

[1] Neurology Research Center, Moscow, Russia; e-mail: alexandra.poydasheva@gmail.com.
[2] Department of Rehabilitation Medicine, Karolinska Institute, Danderyd University Hospital, Stockholm, Sweden.

Contradictory data have been obtained in relation to the potential clinical application of tDCS in various nervous system diseases [53]. An important limitation in using standard tDCS with large electrodes is the low focality of the stimulation, leading to modulation of activity not only in the target area, but also other brain areas [38, 87]. One solution to this problem consists of using high-definition tDCS (HD-tDCS),first proposed in 2007 [20, 21]. The world has since accumulated experience in the use of this method both in research and in clinical practice. After considering the general questions of the application of tDCS, this article addresses current data on the methodology, physiological aspects, clinical efficacy, safety, and tolerance of tDCS.

2. Transcranial Direct Current Electrical Stimulation (tDCS) – General Data, Clinical Use, and Limitations. The primary effect of tDCS is presumptively linked with a subthreshold shift in the membrane potential towards hyper- or depolarization depending on the polarity of the electrodes. Anodic stimulation is accompanied by a shift in membrane potential towards depolarization, which facilitates spike formation, while cathodic stimulation, conversely, shifts membrane potential towards hyperpolarization and decreases the probability of spike formation [10, 11,

53, 35]. Thus, the physiological effects of tDCS are due to modulation of the excitability and changes in spike formation frequency on activation of neurons by other factors not accompanied by action potential generation [9, 55, 75].

The main confirmation of the neuromodulatory effect of tDCS on cerebral cortical arousability in humans is obtained from results of studies using transcranial magnetic stimulation (TMS) and recording of motor evoked potentials (MEP). Anodic stimulation has been shown to lead to increased and cathodic to decreased MEP amplitude [67–69]. The modulatory action of tDCS on arousability has also been shown to have polarity dependence in the somatosensory and visual cortex [7, 57]. tDCS has effects not only on the brain area beneath the electrodes, but also on a multitude of other cortical and subcortical structures, influencing and modeling neural network activity [56, 62, 94].

It is important to note that the modulatory effect of tDCS can persist for some period of time (from a few minutes to several hours, depending on the protocol used) after stimulation ends [53, 67, 69, 73]. The neuromodulatory effect of tDCS is connected primarily with influences on NMDA receptor-mediated neuroplasticity processes resembling long-term potentiation and depression [53, 94]. In particular, administration of dextromethorphan – an NMDA receptor blocker – eliminates the neuromodulatory effect of anodic and cathodic tDCS [54, 66]. Persistence of the physiological effects of tDCS after cessation of stimulation is of significant interest in relation to the therapeutic application of this method [53].

Many clinical studies addressing the efficacy of using tDCS in a variety of nervous system diseases, including depression, addictive disorders, fibromyalgia, pain syndromes, stroke, Parkinson's disease, epilepsy, multiple sclerosis, tinnitus, and others have been conducted [44, 53, 71, 83, 95]. However, the results of these studies have not led to unambiguous conclusion, because of factors including the use of different stimulation protocols. in addition, most studies have been carried out on small cohorts of patients.

According to the recommendations of an international expert group, there are as yet no recommendations with evidence level A (strong recommendation, definitely effective) for the use of tDCS in clinical practice. Evidence at level B (recommendation, probably effective) has been obtained for 1) anodic tDCS of the primary motor cortex of the left hemisphere in fibromyalgia (cathode over the right orbitofrontal area); 2) anodic tDCS of the left dorsolateral prefrontal cortex in depressive episode without drug resistance (cathode over the right orbitofrontal cortex); and 3) anodic tDCS of the right dorsolateral prefrontal cortex in addictive disorders (addiction/craving, with the cathode over the left orbitofrontal cortex). In addition, evidence of level C (option, possibly effective) has been obtained for anodic tDCS of the left (or side contralateral to pain) of the primary motor cortex in chronic neuropathic leg pain in patients with spinal cord injury (with the cathode over the right orbitofrontal areas). Some cases have led to the conclusion that tDCS is ineffective, with evidence level B. There are insufficient data for all other diseases and stimulation protocols to allow recommendations to be formulated [53].

A major problem for the use of tDCS is high within- and between-individual variability in the physiological effects of stimulation [17, 26, 36, 46, 47, 91]. The classic dichotomous approach, which regards anodic stimulation as activatory and cathodic as inhibitory, has been shown to be quite arbitrary. The physiological effect of stimulation is determined by a large number of factors, including not only the electrode montage, but also the duration of stimulation, its intensity, and other characteristics of the protocol [53, 94]. Ongoing and preceding neuronal activity is of great significance in determining stimulation effects, as are a number of individual characteristics [37, 47]. Various approaches to personalization and increased precision and controllability of the effects of tDCS and other noninvasive brain stimulation methods have now been developed [37, 47, 86, 94].

3. HD-tDCS: Methodology, Distribution of Electric Current, and Physiological Effects. ***Methodology.*** HD-tDCS was proposed to increase the focality of stimulation by using special small electrodes and modifying their distribution [20, 21]. HD-tDCS uses silver chloride ring electrodes (so-called high-definition electrodes) with a contact area of less than 5 cm^2 [9]. The most widely employed version of HD-tDCS uses a 4 × 1 montage in which a central ring electrode (anode or cathode) is positioned over the stimulation target area and is surrounded by four reference electrodes [20, 22, 87]. The central electrode determines stimulation polarity (anode or cathode) and the corresponding neurophysiological effects, while the reference electrodes delimit the stimulation area [89]. The technical and methodological aspects of HD-tDCS have been described in detail by Vilamar et al. [2013a].

Electrode current distribution. Many studies modeling the electric field distribution have shown that HD-tDCS produces greater stimulation focality than standard tDCS [6, 12, 14, 19, 22, 27, 87]. Thus, one study [19] showed that use of the standard montage and standard-size electrodes (anode at C3, cathode at Fp2; electrode size 5 × 7 cm) produced a wide electric current distribution in different parts of the brain, including the prefrontal cortex on both sides, the premotor cortex, the left precentral gyrus, the insular cortex, and the thalamus on both sides, as well as brainstem structures (here and henceforth montage will be described in terms of electrode positions of the standard 10–20% electrode distribution). The strongest current was seen in the prefrontal cortex. Using HD-tDCS (anode at C3), the current distribution was essentially limited to the area in which the reference electrodes were located, the maximum current occurring in the depth of the central sulcus and adjacent cortical areas, including the primary motor and somatosensory cortex. Electrical field tension in other areas of the brain

(insula, cingulate gyrus, thalamus, brainstem structures, and other areas) in HD-tDCS was small as compared with the standard electrode montage [19].

It needs to be emphasized that the most intense current observed on use of the standard electrode montage is between the electrodes, while in HD-tDCS it is in the area containing the central electrode [20, 22]. A decrease in the distance between the central and reference electrodes in HD-tDCS leads to increases in stimulation focality [19]. Increases in this distance can lead to increases in the intensity, as well as the width and depth of the distribution of the electric current [22].

The greater stimulation focality in HD-tDCS provides more targeted and controllable modulation of the activity of defined cortical areas. Modeling of the electric field distribution is extremely important, as it allows use of montages influencing only the target area of the brain. Furthermore, use of HD-tDCS has been seen to produce greater interindividual variability in electric field distribution [60], which makes it necessary to use modeling taking account of individual anatomical characteristics for personalization of the various parameters of stimulation protocols [22].

When four reference electrodes are used, the direction of modulation of arousal of the target area in HD-tDCS is determined largely by the polarity of the central electrode, whereas use of the standard electrode montage requires consideration of the physiological effects of both electrodes [87]. At the same time, it is important to note that use of HD-tDCS does not address the question of the arbitrariness of the conventional dichotomous assessment of the effects of anodic and cathodic stimulation as activatory and inhibitory, respectively [33].

Apart from the 4 × 1 montage, research practice also makes use of a 2 × 2 montage, in which four electrodes are positioned at the corners of a square (size 4 × 4 cm) centered with respect to the stimulation target area. The two anodes are placed rearmost and the two anodes foremost in relation to the target area, such that it is stimulated in the back-to-front direction. Data obtained from modeling the electric field distribution indicate that this montage allows even greater stimulation focality than the 4 × 1 montage because of the smaller distance between electrodes with different polarities [19].

Physiological effects. A number of studies have addressed the physiological effects of HD-tDCS in healthy volunteers. HD-tDCS, like standard protocols, has been found to be able to modulate arousal of the motor cortex [14, 52]. HD-tDCS of the motor cortex was shown to be able to decrease the thresholds of cold and heat sensitivity [12]. In addition, studies in healthy volunteers demonstrated differences in the neuropsychological effects of HD-tDCS (see for example [18, 34, 41, 45, 51]). Detailed analysis of these studies is beyond the remit of this article.

Results obtained from studies reported by Kuo et al. [2013] are of great interest – the effects of anodic and cathodic tDCS using a standard 4 × 1 electrode montage were compared. tDCS with the standard electrode montage was performed using large electrodes: the stimulation electrode (7 × 5 cm) was positioned over the cortical representation of the target muscle and the reference electrode (10 × 10 cm) over the right orbital area. HD-tDCS was run using small (external radius 12 mm, internal radius 6 mm) ring electrodes; the central electrode was also located over the cortical representation of the target muscle and the four reference electrodes were located 3.5 cm from it. Thus, the effects of stimulation electrode polarity (anodic/cathodic) and electrode type (standard-size electrodes/HD electrodes) were compared. In both cases, tDCS used an intensity of 2 mA and a stimulation duration of 10 min. Recording of MEP showed that anodic stimulation with both electrode montages led to increases, while cathodic stimulation led to decreases in the level of motor cortex excitability. At the same time, when HD-tDCS was used, the most marked modulation of motor cortex excitability was seen later (30 min after the end of stimulation) and lasted longer (more than 2 h) than with the standard electrode montage. Data showing the longer-lasting modulatory effect of HD-tDCS may be very important for the therapeutic applications of this method [52].

The principles underlying HD-tDCS can be used for further development of the tES method. Thus, small ring electrodes can be used for multifocal stimulation of the brain, in which large numbers of stimulation electrodes are positioned quite close together [9, 23]. Use of this approach allows simultaneous stimulation of multiple brain areas forming a network, with collection of data on the optimum electrode positioning and current intensity on the basis of individual neuroimaging data, particularly resting functional MRI scans (fMRI) with assessment of functional connectivity [80]. This provides for simultaneous stimulation of brain areas characterized by synchronous oscillations in spontaneous activity. Use of multifocal stimulation of parts of neural networks produces increases in the extent and duration of the neurophysiological effect as compared with stimulation electrodes of the same sizes but distributed in the standard way [30]. These preliminary data open up wide potentials for further studies of the neurophysiological effects and clinical efficacy of multifocal stimulation of neural networks.

Another example of a modification of the HD-tDCS method consists of stimulation with an alternating rather than direct current (HD-tACS) with a 4 × 1 montage [42, 77], though this protocol has received significantly less study.

4. Clinical application of HD-tDCS. Despite the relatively short period since introduction of the HD-tDCS method into research practice, several reports have been published addressing the effects of stimulation in a variety of nervous system diseases.

Tinnitus. One of the best studied indications for use of HD-tDCS is tinnitus [15, 43, 48, 49, 81, 82]. The commonest targets are the parietal-temporal area and the prefrontal

cortex. Stimulation of the temporal area is with the anode positioned midway between C3 and P5 and the cathodes over C5, TP7, CP3, and P5, while stimulation of the prefrontal cortex uses the anode over F4 and the cathodes over F3, FC4, F6, and AF4. A study reported by Jacquemin et al. compared two tDCS protocols (in one the electrodes were located over the dorsolateral prefrontal cortex (dlPFC) on both sides and in the other the electrodes were positioned over the right supraorbital and left temporal areas) using standard-size electrodes and HD-tDCS of the right dlPFC. Statistically significant improvements were seen in all groups, though there were no statistically significant differences in the magnitude of the effect between groups [48].

Stimulation duration and intensity may be of great importance when HD-tDCS is used in tinnitus patients. Shekhawat et al. showed that the greatest effect of HD-tDCS was obtained with exposure for 20 min and a current of 2 mA (the study compared stimulation intensities of 1 and 2 mA and durations of 10 and 20 min). In another small controlled study, this same group of authors showed that statistically significant reductions in the loudness of subjective noise were obtained only after 15 and 20 min of anodic stimulation of dlPFC of the right hemisphere (anode at F4, cathodes at F2, FC4, F6, and AF4) but not after 5 and 10 min [82].

One approach to increasing the efficacy of HD-tDCS in tinnitus consists of combining this method with other therapeutic interventions. Thus, Henin et al. ran a randomized, controlled study seeking to determine the efficacy of the combined of HD-tDCS with compensatory auditory stimulation (CAS). HD-tDCS used a 2 × 2 montage in which the cathodes were located over the lateral prefrontal cortex and the anodes over the primary auditory areas on both sides. Electrode positioning was refined using special software to find the ideal anode position for stimulation of the superior temporal gyrus and the adjacent nucleus. In this study, neither the combination of HD-tDCS with CAS nor HD-tDCS alone had any statistically significant effect as compared with sham stimulation, which the authors felt was due to lack of power in the study [43].

One of the main limitations of all these studies is that effects were assessed subjectively, and particularly the use of self-assessment questionnaires. The study reported by Jacquemin et al. objectively assessed HD-tDCS effects using brainstem auditory evoked potentials. The study included 22 patients with tinnitus and showed that HD-tDCS was followed by decreases in the latencies of the N1, P2, N2, and P3 peaks, along with an increase in the amplitude of the N2 peak, which the authors felt might reflect more effective processing of sound signals and involvement of synchronized neuron ensembles in the auditory cortex [49]. At the same time, the observed neurophysiological changes did not correlate with scores on the Tinnitus Functional Index (TFI). Furthermore, the study lacked a control group, which makes it difficult to identify a cause-effect relationship between the results obtained and the interventions performed.

Thus, further studies are needed before any conclusions can be drawn regarding the efficacy of HD-tDCS in tinnitus. The protocol of a planned controlled trial including 100 patients with tinnitus was published in 2019; this will assess the effects of six sequential HD-tDCS sessions. Another feature of this study will be the use of a montage with two targets - the right dlPFC and the left temporal area [15].

Chronic pain. A controlled study including 24 patients with temporomandibular joint dysfunction showed that delivery of five sessions of motor cortex stimulation contralateral to the painful side produced statistically significant reductions in pain intensity as compared with sham stimulation; the effect lasted at least four weeks [25]. This study used a 2 × 2 montage in which small ring electrodes were located in pairs (two anodes at C3 and C5 and two cathodes at FC3 and FC5) at the corners of a square of side 4 cm and its center over the caudal part of M1 (the presumptive location of the representation of the masticatory musculature and tongue). Stimulation duration was 20 min and current strength was 2 mA. Another study with a crossover design evaluated the effect of single sessions of anodic or cathodic HD-tDCS of the primary motor cortex (M1) of the left hemisphere in patients with fibromyalgia [90]. Both active protocols were found to produce statistically significant reductions in the perception of pain as compared with controls, though effects immediately after stimulation were seen only in the cathodic stimulation group, with effects demonstrated in both groups 30 min after stimulation.

Castillo-Saavedra et al. ran an open phase II study and found that clinically significant decreases in pain severity (decreases in pain intensity by more than 50% from initial on a visual analog scale) in patients with fibromyalgia on average required 15 sessions of anodic stimulation of M1 in the left hemisphere (anode at C3, cathodes at Cz, T7, P3, and F3) [16]. The responder rate was 50%. Larger and randomized, comparative trials are required to refine the pain-controlling effects of various HD-tDCS protocols.

Stroke. Occasional reports have been published of studies of the effects of HD-tDCS in poststroke patients to improve motor and speech functions.

Poststroke hemiparesis. Utilization of noninvasive modulation methods in poststroke hemiparesis is currently based mainly on interhemisphere competition theory. According to this theory, a lack of physiological inhibition by the stroke-affected hemisphere leads to the development of hyperexcitability of the motor cortex of the unlesioned hemisphere. This leads to an excess pathological inhibition of the motor cortex of the lesioned hemisphere by the unlesioned. Thus, poststroke hemiparesis mostly uses noninvasive stimulation protocols increasing the excitability of the motor cortex of the lesioned hemisphere and/or decreasing that of the unlesioned hemisphere [1, 24].

A controlled study reported by Bao et al. compared the effects of anodic and cathodic HD-tDCS combined with isometric voluntary contraction of the wrist extensors immediate-

ly before stimulation and 10, 30, and 50 min after completing a single 10-min session. The central electrode (the anode) was positioned over the motor cortex of the lesioned hemisphere (electrode C3/C4 depending on stroke lateralization), and four cathodes were placed around the central electrode (F1, F5, P1, and P5 or F2, F6, P2, and P6, respectively). The influences of various protocols on corticomuscular coherence and the spectral power of cortical rhythms were evaluated. These studies showed that only anodic and not cathodic stimulation or sham stimulation affected corticomuscular coherence, with the maximum effect being seen 10 min after stimulation [8].

Another study assessed the effects of single sessions of anodic and cathodic HD-tDCS of the motor cortex of the lesioned hemisphere combined with training on an exercise bicycle on gait kinematics. In addition, influences on motor cortex excitability were evaluated by analysis of MEP amplitude in TMS [50]. Both anodic and cathodic HD-tDCS were found to have no effect on kinematic gait parameters, walking speed, or MEP amplitude in the tibialis anterior muscle. Despite obtaining negative results, studies of the effects of multiple stimulation sessions and use of individual modeling of electric field tension depending on the location and size of foci is a potential direction for further research.

Aphasia. A small study reported by Richardson et al. included eight patients and compared the efficacies of HD-tDCS and tDCS with standard-size electrodes. Both standard and HD electrodes were positioned on the basis of individual structural and functional (using an object-naming paradigm) MRI data. In studies using standard electrodes, the anode was positioned over the area of maximal fMRI activation in the left hemisphere and the cathode in the supraorbital area on the right. Statistically significant improvements in object-naming accuracy and speed were seen in both groups, without any statistically significant between-group differences in effect magnitudes [78]. It is important to note that this study lacked a control group. Studies run by Fiori et al. showed that five sequential sessions of cathodic HD-tDCS of Broca's area in parallel with speech therapy (verb naming) led to a statistically significant improvement in verb naming as compared with sham stimulation, the effect lasting one week. An effect was seen only at a current strength of 2 mA, while use of a 1-mA current was ineffective [29]. The small number of studies means that no clear assessment can be made of the effects found or the benefits of HD-tDCS in aphasia.

Chronic impairments of consciousness (CIC). Two studies have been published addressing the possible behavioral and neurophysiological effects of HD-tDCS in patients with chronic impairments of consciousness [13, 39]. Guo et al. reported a study including 11 patients receiving 20-min stimulation twice daily for 14 sequential days using a current of 2 mA. The centrally positioned anode was placed over the precuneus. Behavioral effects were evaluated using the Coma Recovery Scale Revised (CRS-R), while neurophysiological effects were assessed by analysis of coherence between the frontal and parietal areas, the frontal and parietal areas, the frontal areas on each side, and the central areas on each side. Statistically significant increases in CRS-R scores were seen on stimulation days 7 and 14, while no significant effect was found after single sessions. It is important to note that five patients in a vegetative state (VS) showed no change in status, while four of six patients in a minimally conscious state (MCS) showed a qualitative transition from MCS– to MCS+. A statistically significant reduction in central-parietal coherence was seen only after 14 days of stimulation, but not at other time points. Statistically significant reductions in frontal and parietal interhemisphere coherence were seen at both seven and 14 days of stimulation but not after single sessions [39]. Thus, prolonged application of HD-tDCS may provide for improvements in the recovery of patients with chronic impairments of consciousness. Cai et al. studied 28 patients with CIC who received anodic stimulation of the parietal area (anode at Pz, cathodes at Cz, C3, C4, and POz) once daily for two weeks. Statistically significant increases in total scores on the CRS-R were seen in patients with MCS but not those with VS. Qualitative changes in the level of consciousness were seen in seven patients: six with MCS– transitioned to MCS+ and one with VS started to show signs of consciousness (MCS–). Clinical improvements were linked with reductions in activity power in the δ range and increases in power in the α range. The most important limitation of both studies was the lack of a control group [13].

Epileptic encephalopathy. The influences of tDCS on cortical excitability and the mechanisms of synaptic plasticity, as well as the ability to produce local actions, create the conditions required for use of this method in the treatment of epilepsy. Meiron et al. published a clinical case of the use of ten sessions of HD-tDCS in a 30-month-old patient with early-onset epileptic encephalopathy [58]. Despite the absence of any reduction in attack frequency, there was a reduction in sharp-wave amplitude in the interictal period, which is evidence that the method can influence epileptiform activity. The same group published a clinical case of use of 20 sessions of HD-tDCS in a 40-month-old patient with Otahara syndrome [59]. These observations demonstrated that HD-tDCS had both clinical (decreases in the frequency of myoclonic seizures) and neurophysiological (decreases in the frequency of interictal epileptiform discharges) effects. The published studies may provide the basis for future controlled investigations to assess the efficacy of HD-tDCS in patients with epilepsy.

Nonpsychotic disorders. Parlikar et al. reported successful application of 20 sessions of anodic HD-tDCS (anode at FCz, cathodes at Fz, FC4, FC3, and CPz) in three patients with obsessive-compulsive disorder (OCD) [70]. Hampstead et al. published HD-tDCS results from six patients with post-traumatic stress disorder. Five of the six patients received at least eight sessions of anodic HD-tDCS to the lateral temporal cortex of the right hemisphere (anode at T8). Four patients showed positive clinical effects. In addition, differ-

ently directed changes in the connectivity of the stimulation area were demonstrated [40]. However, both of these studies lacked control groups. there are plans to run a pilot controlled study addressing the efficacy of HD-tDCS in patients with anorexia [72]. All patients will receive 10 sessions of anodic stimulation of the inferior parietal lobe (anode at P3, cathodes at CP3, P1, P5, and PO3). Results will be assessed immediately after the end of stimulation and at four and 12 weeks.

Psychotic disorders. Among the large spectrum of psychotic disorders in which the effects of tDCS have been investigated using standard electrodes, HD-tDCS has been used only in patients with auditory hallucinations in schizophrenia and dementias of various origins. Mukku et al. reported two cases in which HD-tDCS was used in patients with dementia. In the first case, a patient with Lewy body dementia received cathodic stimulation of the left parietal-temporal area (cathode at Cp5, anodes at FT7, FC3, P1, and PO7). After 10 stimulation sessions (twice daily for five days), there was a reduction in the score on the Auditory Hallucinations Rating Scale (AHRD), along with reductions in the frequency and duration of auditory hallucinations [64]. In the second case, this protocol was used in a patient with Alzheimer's disease. A minor effect was seen after 10 sessions, such that the patient received a further 10 sessions, which was followed by a significant reduction in the AHRS score and subjective decreases in the frequency and duration of hallucinations [64]. It should be emphasized that this study used subjective assessment methods and lacked controls. Finally, an open study reported by Sreeraj et al. showed that 10 stimulation sessions (twice daily for five sequential days) to the parietal-temporal junction of the left hemisphere (the montage described above was used) significantly decreased auditory hallucinations in schizophrenia patients [84]. However, despite the efficacy data obtained, determination of the place of HD-tDCS in the treatment of auditory hallucinations in various neurological and psychiatric disorders requires further research,.

Cognitive impairments. Occasional studies have been published assessing the influence of HD-tDCS on various cognitive functions. A controlled study conducted by Motes et al. demonstrated a statistically significant effect using 10 sessions of anodic stimulation of the preSMA/dACC area (anode at FZ, cathodes at FP1, FP2, F7, and F8) in the treatment of impaired verbal reproduction persisting for eight weeks in patients with traumatic brain injury [63]. An open trial in elderly patients with depression showed that HD-tDCS to the left dlPFC (anode at F3, cathodes at FC1, AF3, F7, and FC5) affected cognitive functions and the symptoms of depression [93].

5. Safety and Tolerance of HD-tDCS. Safety and tolerance are important for the clinical use of HD-tDCS, including repeated application and use at different stimulation intensities. HD-tDCS can produce more severe skin sensations than the standard montage [32], which may be associated with an increase in current shunting through the scalp and an increase in the current density [87]. In addition, while cutaneous sensations on use of the standard montage (tingling, burning, itching) generally arise only at the beginning of stimulation [31], they can occur throughout the stimulation period in HD-tDCS [79]. There are as yet no data indicating that this fact limits the safety of using HD-tDCS, though it may require a change in approaches to creating sham stimulation for controlled clinical trials [32]. A study run by Minhas et al. using five electrode versions and seven gel types found no cases of skin damage with HD-tDCS, while unpleasant sensations ceased immediately after stimulation ended [61].

In 2018, Reckow et al. published results from studies of safety and tolerance of HD-tDCS in 101 healthy volunteers (mean age 69.7 years) with stimulus intensities of 2 and 3 mA and compared measures with sham stimulation using different electrode montage variants (central electrode over P5, Pz, T8, or T7). Serious adverse events (AE) were not seen. No statistically significant differences in the frequency of AE during the first session between the active stimulation and sham stimulation were seen. There were also no statistically significant differences in the frequency of AE on comparison of HD-tDCS at intensities of 2 and 3 mA. The most frequent AE in HD-tDCS were found in this study to consist of tingling (59% in the active group and 56% in the sham stimulation group) and burning sensations (51% in the active group and 50% in the sham group), mild in most cases. Strong tingling and burning were recorded in fewer than 4% of sessions. Other AE (itch, scalp pain, headache, drowsiness, changes to concentration and mood, and others) were seen in smaller numbers of cases. Thus, the results of this study demonstrated that HD-tDCS has good tolerance and safety in adults at stimulus intensities of 2 and 3 mA [76]. Furthermore, the safety and good tolerance of HD-tDCS have also been shown in several studies in both healthy people [12, 14, 52, 65] and patients with nervous system diseases [40, 78, 82]. Safety and good tolerance have also been demonstrated in healthy people receiving repeated (up to 20 daily sessions) simultaneous stimulation of multiple parts of the brain [88].

6. Conclusions. HD-tDCS is a relatively new method for noninvasive neuromodulation and has potential. Studies to date have shown that as compared with the standard electrode montage, HD-tDCS has a more local action on the brain, which can be accompanied by increases in the duration and extent of the stimulation effect. It is difficult to draw conclusions regarding the clinical efficacy of this method of transcranial electrical stimulation because many results are contradictory. Most studies have limitations linked with small cohort sizes and lack of controls. Large multicenter, randomized trials are needed, as well as further development of approaches directed to increasing the precision and personalization of the use of HD-tDCS with refinement of the neurophysiological effects, individual stimulation protocols based on models of the electric field distribution, determination of efficacy predictors, etc.

REFERENCES

1. I. S. Bakulin, A. G. Poydasheva, N. A. Pavlov, et al., "Transcranial electrical stimulation in improving hand function in stroke," *Usp. Fiziol. Nauk.*, **50**, No. 1, 90–104 (2019), https://doi.org/10.1134/S030117981901003X.
2. V. P. Lebedev (ed.), *Transcranial Electrical Stimulation. Experimental and Clinical Studies*, St. Petersburg (2009).
3. V. A. Ilyukhina, "Theoretical and applies aspects of transcranial micropolarization in psychophysiology and clinical practice," in: *Therapeutic Electrical Stimulation of the Human Brain and Nerves*, N. P. Bekhtereva (ed.), AST, Moscow, Sova, St. Petersburg, VKT, Vladimir (2008), pp. 378–461.
4. A. M. Shelyakin and G. N. Ponomarenko, *Micropolarization of the Brain*, Kirov VMedA Press, St. Petersburg (2006).
5. A. M. Shelyakin, I. G. Preobrazhenskaya, and O. G. Tyul'kin, "Micropolarization of the brain: a nonainvasive means of correcting morphofunctional impairments in acute focal brain lesions and their sequelae," *Zh. Nevrol. Psikhiat.*, **106**, No. 10, 27–37 (2006);
6. M. Alam, D. Q. Truong, N. Khadka, et al., "Spatial and polarity precision of concentric high-definition transcranial direct current stimulation (HD-tDCS)," *Phys. Med. Biol.*, **61**, No. 12, 4506–4521 (2016), https://doi.org/10.1016/j.brs.2014.01.039.
7. A. Antal, T. Z. Kincses, M. A. Nitsche, et al., "Excitability changes induced in the human primary visual cortex by transcranial direct current stimulation: direct electrophysiological evidence," *Invest. Ophthalmol. Vis. Sci.*, **45**, No. 2, 702–707 (2004), https://doi.org/10.1167/iovs.03-0688.
8. S. C. Bao, W. W. Wong, T. W. H. Leung, et al., "Cortico-muscular coherence modulated by high-definition transcranial direct current stimulation in people with chronic stroke," *IEEE T. Neural Syst. Rehabil. Eng.*, **27**, No. 2, 304–313 (2019), https://doi.org/10.1109/tnsre.2018.2890001.
9. M. Bikson, Z. Esmaeilpour, D. Adair, et al., "Transcranial electrical stimulation nomenclature," *Brain Stimul.*, **12**, No. 6, 1349–1366 (2019), https://doi.org/10.1016/j.brs.2019.07.010.
10. L. J. Bindman, O. C. Lippold, and J. W. Redfearn, "Long-lasting changes in the level of the electrical activity of the cerebral cortex produced by polarizing currents," *Nature*, **196**, 584–585 (1962), https://doi.org/10.1038/196584a0.
11. L. J. Bindman, O. C. Lippold, and J. W. Redfearn, "The action of brief polarizing currents on the cerebral cortex of the rat (1) during current flow and (2) in the production of long-lasting after-effects," *J. Physiol. (London),* **172**, 369–382 (1964), https://doi.org/10.1113/jphysiol.1964.sp007425.
12. J. J. Borckardt, M. Bikson, H. Frohman, et al., "A pilot study of the tolerability and effects of high-definition transcranial direct current stimulation (HD-tDCS) on pain perception," *J. Pain*, **13**, No. 2, 112–120 (2012), https://doi.org/10.1016/j.jpain.2011.07.001.
13. T. Cai, X. Xia, H. Zhang, et al., "High-definition transcranial direct current stimulation modulates neural activities in patients with prolonged disorders of consciousness," *Brain Stimul.*, **12**, No. 6, 1619–1621 (2019), https://doi.org/10.1016/j.brs.2019.08.017.
14. E. M. Caparelli-Daquer, T. J. Zimmermann, E. Mooshagian, et al., "A pilot study on effects of 4×1 high-definition tDCS on motor cortex excitability," *Conf. Proc IEEE Eng. Med. Biol., Soc.*, **2012**, 735–738 (2012), https://doi.org/10.1109/EMBC.2012.6346036.
15. E. Cardon, V. Van Rompaey, L. Jacquemin, et al., "Sequential dual-site High-Definition transcranial Direct Current Stimulation (HD-tDCS) treatment in chronic subjective tinnitus: study protocol of a double-blind, randomized, placebo-controlled trial," *Trials*, **20**, No. 1, 471 (2019), https://doi.org/10.1186/s13063-019-3594-y.
16. L. Castillo-Saavedra, N. Gebodh, M. Bikson, et al., "clinically effective treatment of fibromyalgia pain with high-definition transcranial direct current stimulation: Phase II open-label dose optimization," *J. Pain*, **17**, No. 1, 14–26 (2016), https://doi.org/10.1016/j.jpain.2015.09.009.
17. T. Chew, K. A. Ho, and C. K. Loo, "Inter- and intra-individual variability in response to transcranial direct current stimulation (tDCS) at varying current intensities," *Brain Stimul.*, **8**, No. 6, 1130–1137 (2015), https://doi.org/10.1016/j.brs.2015.07.031.
18. E. F. Chua, R. Ahmed, and S. M. Garcia, "Effects of HD-tDCS on memory and metamemory for general knowledge questions that vary by difficulty," *Brain Stimul.*, **10**, No. 2, 231–241 (2017), https://doi.org/10.1016/j.brs.2016.10.013.
19. A. F. DaSilva, D. Q. Truong, M. F. DosSantos, et al., "State-of-art neuroanatomical target analysis of high-definition and conventional tDCS montages used for migraine and pain control," *Front. Neuroanat.*, **15**, No. 9, 89 (2015), https://doi.org/10.3389/fnana.2015.00089.
20. A. Datta, V. Bansal, J. Diaz, et al., "Gyri-precise head model of transcranial direct current stimulation: improved spatial focality using a ring electrode versus conventional rectangular pad," *Brain Stimul.*, **2**, No. 4, 201–207 (2009), https://doi.org/10.1016/j.brs.2009.03.005.
21. A. Datta, M. Elwassif, F. Battaglia, et al., "Transcranial current stimulation focality using disc and ring electrode configurations: FEM analysis," *J. Neural Eng.*, **5**, No. 2, 163–74 (2008), https://doi.org/10.1088/1741-2560/5/2/007.
22. A. Datta, D. Truong, P. Minhas, et al., "Inter-individual variation during transcranial direct current stimulation and normalization of dose using MRI-derived computational models," *Front. Psychiatry*, 3, 91 (2012), https://doi.org/10.3389/fpsyt.2012.00091.
23. J. P. Dmochowski, A. Datta, M. Bikson, et al., "Optimized multi-electrode stimulation increases focality and intensity at target," *J. Neural Eng.*, **8**, No. 4, 046011 (2011), https://doi.org/10.1088/1741-2560/8/4/046011.
24. K. C. Dodd, V. A. Nair, and V. Prabhakaran, "Role of the contralesional VS. ipsilesional hemisphere in stroke recovery," *Front. Hum. Neurosci.*, **11**, 469 (2017), https://doi.org/10.3389/fnhum.2017.00469.
25. A. Donnell, D. Nascimento, M. Lawrence, et al., "High-definition and non-invasive brain modulation of pain and motor dysfunction in chronic TMD," *Brain Stimul.*, **8**, No. 6, 1085–1092 (2015), https://doi.org/10.1016/j.brs.2015.06.008.
26. K. Dyke, S. Kim, G. M. Jackson, et al., "Intra-subject consistency and reliability of response following 2 mA transcranial direct current stimulation," *Brain Stimul.*, **9**, No. 6, 819–825 (2016), https://doi.org/10.1016/j.brs.2016.06.052.
27. D. Edwards, M. Cortes, A. Datta, et al., "Physiological and modeling evidence for focal transcranial electrical brain stimulation in humans: a basis for high-definition tDCS," *Neuroimage*, **74**, 266–275 (2013), https://doi.org/10.1016/j.neuroimage.2013.01.042.
28. Z. Esmaeilpour, P. Schestatsky, M. Bikson, et al., "Notes on human trials of transcranial direct current stimulation between 1960 and 1998," *Front. Hum. Neurosci.*, **11**, 71 (2017), https://doi.org/10.3389/fnhum.2017.00071.
29. V. Fiori, M. A. Nitsche, G. Cucuzza, et al., "High-definition transcranial direct current stimulation improves verb recovery in aphasic patients depending on current intensity," *Neuroscience*, **406**, 159–166 (2019), https://doi.org/10.1016/j.neuroscience.2019.03.010.
30. D. B. Fischer, P. J. Fried, G. Ruffini, et al., "Multifocal tDCS targeting the resting state motor network increases cortical excitability beyond traditional tDCS targeting unilateral motor cortex," *Neuroimage*, **157**, 34–44 (2017), https://doi.org/10.1016/j.neuroimage.2017.05.060.
31. P. C. Gandiga, F. C. Hummel, and L. G. Cohen, "Transcranial DC stimulation (tDCS) : a tool for double-blind sham-controlled clinical studies in brain stimulation," *Clin. Neurophysiol.*, **117**, No. 4 845–850 (2006), https://doi.org/10.1016/j.clinph.2005.12.003.
32. E. O. Garnett and D. B. den Ouden, "Validating a sham condition for use in high definition transcranial direct current stimulation," *Brain Stimul.*, **8**, No. 3, 551–4 (2015), https://doi.org/10.1016/j.brs.2015.01.399.
33. E. O. Garnett, S. Malyutina, A. Datta, et al., "On the use of the terms anodal and cathodal in high-definition transcranial direct current stimulation: A technical note," *Neuromodulation*, **18**, No. 8, 705–713 (2015), https://doi.org/10.1111/ner.12320.

34. O. Gbadeyan, K. McMahon, M. Steinhauser, et al., "Stimulation of dorsolateral prefrontal cortex enhances adaptive cognitive control: A high-definition transcranial direct current stimulation study," *J. Neurosci.*, **36**, No. 50, 12530–12536 (2016), https://doi.org/10.1523/JNEUROSCI.2450-16.2016.
35. J. Giordano, M. Bikson, E. S. Kappenman, et al., "Mechanisms and effects of transcranial direct current stimulation, *Dose Response*, **15**, No. 1, 1559325816685467 (2017), https://doi.org/10.1177/1559325816685467.
36. A. Guerra, V. López-Alonso, B. Cheeran, et al., "Variability in non-invasive brain stimulation studies: Reasons and results," *Neurosci. Lett.*, **719**, 133330 (2020a), https://doi.org/10.1016/j.neulet.2017.12.058.
37. A. Guerra, V. López-Alonso, B. Cheeran, et al., "Solutions for managing variability in non-invasive brain stimulation studies," *Neurosci. Lett.*, **719**, 133332 (2020b), https://doi.org/10.1016/j.neulet.2017.12.060.
38. B. Guleyupoglu, P. Schestatsky, D. Edwards, et al., "Classification of methods in transcranial electrical stimulation (tES) and evolving strategy from historical approaches to contemporary innovations," *J. Neurosci. Meth.*, **219**, No. 2, 297–311 (2013), https://doi.org/10.1016/j.jneumeth.2013.07.016.
39. Y. Guo, Y. Bai, X. Xia, et al., "Effects of long-lasting high-definition transcranial direct current stimulation in chronic disorders of consciousness: A pilot study," *Front. Neurosci.*, **13**, 412 (2019), https://doi.org/10.3389/fnins.2019.00412.
40. B. M. Hampstead, N. Mascaro, S. Schlaefflin, et al., "Variable symptomatic and neurophysiologic response to HD-tDCS in a case series with posttraumatic stress disorder," *Int. J. Psychophysiology*, **154**, 93–100, (2019), https://doi.org/10.1016/j.ijpsycho.2019.10.017.
41. M. Hartmann, S. Singer, B. Savic, et al., "Anodal high-definition transcranial direct current stimulation over the posterior parietal cortex modulates approximate mental arithmetic," *J. Cogn. Neurosci.*, **18**, 1–15 (2019), https://doi.org/10.1162/jocn_a_01514.
42. R. F. Helfrich, H. Knepper, G. Nolte, et al., "Selective modulation of interhemispheric functional connectivity by HD-tACS shapes perception," *PLoS Biol*, **12**, No. 12, e1002031 (2014), https://doi.org/10.1371/journal.pbio.1002031.
43. S. Henin, D. Fein, E. Smouha, et al., "The effects of compensatory auditory stimulation and high-definition transcranial direct current stimulation (HD-tDCS) on tinnitus perception – A randomized pilot study," *PLoS One*, **11**, No. 11, e0166208 (2016), https://doi.org/10.1371/journal.pone.0166208.
44. A. L. Herrera-Melendez, M. Bajbouj, and S. Aust, "Application of transcranial direct current stimulation in psychiatry," *Neuropsychobiology*, **24**, 1–12 (2019), https://doi.org/10.1159/000501227.
45. A. T. Hill, N. C. Rogasch, P. B. Fitzgerald, et al., "Effects of prefrontal bipolar and high-definition transcranial direct current stimulation on cortical reactivity and working memory in healthy adults," *Neuroimage*, **152**, 142–157 (2017), https://doi.org/10.1016/j.neuroimage. 2017.03.001.
46. J. C. Horvath, O. Carter, and J. D. Forte, "Transcranial direct current stimulation: five important issues we aren't discussing (but probably should be)," *Front. Syst. Neurosci.*, **8**, 2 (2014), https://doi.org/10.3389/fnsys.2014.00002.
47. Y. Z. Huang, M. K. Lu, A. Antal, et al., "Plasticity induced by non-invasive transcranial brain stimulation: A position paper," *Clin. Neurophysiol.*, **128**, No. 11, 2318–2329 (2017), https://doi.org/10.1016/j.clinph.2017.09.007.
48. L. Jacquemin, G. S. Shekhawat, P. Van de Heyning, et al., "Effects of electrical stimulation in tinnitus patients: conventional versus high-definition tDCS," *Neurorehabil. Neural Repair*, **32**, No. 8, 714–723 (2018), https://doi.org/10.1177/1545968318787916.
49. L. Jacquemin, G. Mertens, P. Van de Heyning, et al., "An exploratory study on the use of event-related potentials as an objective measure of auditory processing and therapy effect in patients with tinnitus," *Otol. Neurotol.*, **40**, No. 9, e868–e875 (2019), https://doi.org/10.1097/MAO.0000000000002380.
50. J. H. Kindred, S. A. Kautz, E. C. Wonsetler, et al., "Single sessions of high-definition transcranial direct current stimulation do not alter lower extremity biomechanical or corticomotor response variables post-stroke," *Front. Neurosci.*, **13**, 286 (2019), https://doi.org/10.3389/fnins.2019.00286.
51. M. Kuehne, K. Schmidt, H. J. Heinze, et al., "Modulation of emotional conflict processing by high-definition transcranial direct current stimulation (HD-TDCS)," *Front. Behav. Neurosci.*, **13**, 224 (2019), https://doi.org/10.3389/fnbeh.2019.00224.
52. H. I. Kuo, M. Bikson, A. Datta, et al., "Comparing cortical plasticity induced by conventional and high-definition 4 × 1 ring tDCS: a neurophysiological study," *Brain Stimul.*, **6**, No. 4, 644–648 (2013), https://doi.org/10.1016/j.brs.2012.09.010.
53. J. P. Lefaucheur, A. Antal, S. S. Ayache, et al., "Evidence-based guidelines on the therapeutic use of transcranial direct current stimulation (tDCS)," *Clin. Neurophysiol.*, **128**, No. 1, 56–92 (2017), https://doi.org/10.1016/j.clinph.2016.10.087.
54. D. Liebetanz, M. A. Nitsche, F. Tergau, et al., "Pharmacological approach to the mechanisms of transcranial DC stimulation-induced after-effects of human motor cortex excitability," *Brain*, **125**, No. 10, 2238–2247 (2002), https://doi.org/10.1093/brain/awf238.
55. A. Liu, M. Vöröslakos, G. Kronberg, et al., "Immediate neurophysiological effects of transcranial electrical stimulation," *Nat. Commun.*, **9**, Article 5092 (2018), https://doi.org/10.1038/s41467-018-07233-7.
56. C. D. Luft, E. Pereda, M. J. Banissy, et al., "Best of both worlds: promise of combining brain stimulation and brain connectome," *Front. Syst. Neurosci.*, **8**, 132 (2014), https://doi.org/10.3389/fnsys.2014.00132.
57. K. Matsunaga, M. A. Nitsche, S. Tsuji, et al., "Effect of transcranial DC sensorimotor cortex stimulation on somatosensory evoked potentials in humans," *Clin. Neurophysiol.*, **115**, No. 2, 456–460 (2004), https://doi.org/10.1016/s1388-2457 (03) 00362-6.
58. O. Meiron, R. Gale, J. Namestnic, et al., "High-definition transcranial direct current stimulation in early onset epileptic encephalopathy: a case study," *Brain Inj.*, **32**, No. 1, 135–143 (2018), https://doi.org/10.1080/02699052.2017.1390254.
59. O. Meiron, R. Gale, J. Namestnic, et al., "Antiepileptic effects of a novel non-invasive neuromodulation treatment in a subject with early-onset epileptic encephalopathy: Case report with 20 sessions of HD-tDCS intervention," *Front. Neurosci.*, **13**, 547 (2019), https://doi.org/10.3389/fnins.2019.00547.
60. M. Mikkonen, I. Laakso, S. Tanaka, et al., "Cost of focality in TDCS: Interindividual variability in electric fields," *Brain Stimul.*, **13**, No. 1, 117–124 (2020), https://doi.org/10.1016/j.brs.2019.09.017.
61. P. Minhas, V. Bansal, J. Patel, et al., "Electrodes for high-definition transcutaneous DC stimulation for applications in drug delivery and electrotherapy, including tDCS," *J. Neurosci. Meth.*, **190**, No. 2, 188–197 (2010), https://doi.org/10.1016/j.jneumeth.2010.05.007.
62. E. Morya, K. Monte-Silva, M. Bikson, et al., "Beyond the target area: an integrative view of tDCS-induced motor cortex modulation in patients and athletes," *J. Neuroeng. Rehabil.*, **16**, No. 1, 141 (2019), https://doi.org/10.1186/s12984-019-0581-1.
63. M. A. Motes, J. S. Spence, K. Yeatman, et al., "High-definition transcranial direct current stimulation to improve verbal retrieval deficits in chronic traumatic brain injury," *J. Neurotrauma*, **37**, No. 1, 170–177 (2020), https://doi.org/10.1089/neu.2018.6331.
64. S. S. R. Mukku, S. Selvaraj, R. Parlikar, J., et al., "High-definition transcranial direct current stimulation (HD-tDCS) for auditory hallucinations in dementia – A case series," *Asian J. Psychiatry*, **37**, 102–105 (2018), https://doi.org/10.1016/j.ajp.2018.08.013.
65. S. Nikolin, C. K. Loo, S. Bai, et al., "Focalised stimulation using high definition transcranial direct current stimulation (HD-tDCS) to investigate declarative verbal learning and memory functioning,"

NeuroImage, **117**, 11–19 (2015), https://doi.org/10.1016/j.neuroimage. 2015.05.019.

66. M. A. Nitsche, K. Fricke, U. Henschke, et al., "Pharmacological modulation of cortical excitability shifts induced by transcranial direct current stimulation in humans," *J. Physiol.*, **553**, No. 1, 293–301 (2003a), https://doi.org/10.1113/jphysiol.2003.049916.
67. M. A. Nitsche, D. Liebetanz, A. Antal, et al., "Modulation of cortical excitability by weak direct current stimulation–technical, safety and functional aspects," *Suppl. Clin. Neurophysiol.*, **56**, 255–276 (2003b), https://doi.org/10.1016/s1567-424x (09) 70230-2.
68. M. A. Nitsche and W. Paulus, "Excitability changes induced in the human motor cortex by weak transcranial direct current stimulation," *J. Physiol.*, **527**, No. 3, 633–639 (2000), https://doi.org/10.1111/j.1469-7793.2000.t01-1-00633.x.
69. M. A. Nitsche and W. Paulus, "Sustained excitability elevations induced by transcranial DC motor cortex stimulation in humans," *Neurology*, **57**, No. 10, 1899–1901 (2001), https://doi.org/10.1212/wnl.57.10.1899.
70. R. Parlikar, V. S. Sreeraj, H. Chhabra, et al., "Add-on HD-tDCS for obsessive-compulsive disorder with comorbid bipolar affective disorder: A case series," *Asian J. Psychiatry*, **43**, 87–90 (2019), https://doi.org/10.1016/j.ajp.2019.05.015.
71. N. S. Philip, B. G. Nelson, F. Frohlich, et al., "Low-intensity transcranial current stimulation in psychiatry," *Am. J. Psychiatry*, **174**, No. 7, 628–639 (2017), https://doi.org/10.1176/appi.ajp.2017.16090996.
72. A. Phillipou, M. Kirkovski, D. J. Castle, et al., "High-definition transcranial direct current stimulation in anorexia nervosa: A pilot study," *Int. J. Eat. Disord.*, **52**, No. 11, 1274–1280 (2019), https://doi.org/10.1002/eat.23146.
73. A. Priori, "Brain polarization in humans: a reappraisal of an old tool for prolonged non-invasive modulation of brain excitability," *Clin. Neurophysiol.*, **114**, No. 4, 589–595 (2003), https://doi.org/10.1016/s1388-2457 (02) 00437-6.
74. A. Priori, A. Berardelli, S. Rona, et al., "Polarization of the human motor cortex through the scalp," *Neuroreport*, **9**, No. 10, 2257–2260 (1998), https://doi.org/10.1097/00001756-199807130-00020.
75. D. Reato, A. Rahman, M. Bikson, et al., "Effects of weak transcranial alternating current stimulation on brain activity – a review of known mechanisms from animal studies," *Front. Hum. Neurosci.*, **7**, 687 (2013), https://doi.org/10.3389/fnhum.2013.00687.
76. J. Reckow, A. Rahman-Filipiak, S. Garcia, et al., "Tolerability and blinding of 4x1 high-definition transcranial direct current stimulation (HD-tDCS) at two and three milliamps," *Brain Stimul.*, **11**, No. 5, 991–997 (2018), https://doi.org/10.1016/j.brs.2018.04.022.
77. R. M. G. Reinhart and J. A. Nguyen, "Working memory revived in older adults by synchronizing rhythmic brain circuits," *Nat. Neurosci.*, **22**, No. 5, 820–827 (2019), https://doi.org/10.1038/s41593-019-0371-x.
78. J. Richardson, A. Datta, J. Dmochowski, et al., "Feasibility of using high-definition transcranial direct current stimulation (HD-tDCS) to enhance treatment outcomes in persons with aphasia," *Neurorehabilitation*, **36**, No. 1, 115–126 (2015), https://doi.org/10.3233/NRE-141199.
79. J. D. Richardson, P. Fillmore, A. Datta, et al., "Toward development of sham protocols for high-definition transcranial direct current stimulation (HD-tDCS)," *NeuroRegulation*, **1**, No. 1, 62–72 (2014), https://doi.org/10.15540/nr.1.1.62.
80. G. Ruffini, M. D. Fox, O. Ripolles, et al., "Optimization of multifocal transcranial current stimulation for weighted cortical pattern targeting from realistic modeling of electric fields," *Neuroimage*, **89**, 216–225 (2014), https://doi.org/10.1016/j.neuroimage.2013.12.002.
81. G. S. Shekhawat, F. Sundram, M. Bikson, et al., "Intensity, duration, and location of high-definition transcranial direct current stimulation for tinnitus relief," *Neurorehabil. Neural Repair*, **30**, No. 4, 349–359 (2016), https://doi.org/10.1177/1545968315595286.
82. G. S. Shekhawat and S. Vanneste, "High-definition transcranial direct current stimulation of the dorsolateral prefrontal cortex for tinnitus modulation: a preliminary trial," *J. Neural Transm. (Vienna),* **125**, No. 2, 163–171 (2018), https://doi.org/10.1007/s00702-017-1808-6.
83. C. D. Solomons and V. Shanmugasundaram, "A review of transcranial electrical stimulation methods in stroke rehabilitation," *Neurology India*, **67**, No. 2, 417–423 (2019), https://doi.org/10.4103/0028-3886.258057.
84. V. S. Sreeraj, D. Dinakaran, R. Parlikar, et al., "High-definition transcranial direct current simulation (HD-tDCS) for persistent auditory hallucinations in schizophrenia," *Asian J. Psychiatry*, **37**, 46–50 (2018), https://doi.org/10.1016/j.ajp.2018.08.008.
85. H. Steinberg, "Letter to the editor: transcranial direct current stimulation (tDCS) has a history reaching back to the 19th century," *Psychol. Med.*, **43**, No. 3, 669–671 (2013), https://doi.org/10.1017/S0033291712002929.
86. G. Thut, T. O. Bergmann, F. Fröhlich, et al., "Guiding transcranial brain stimulation by EEG/MEG to interact with ongoing brain activity and associated functions: A position paper," *Clin. Neurophysiol.*, **128**, No. 5, 843–857 (2017), https://doi.org/10.1016/j.clinph.2017.01.003.
87. W. T. To, J. Hart, D. De Ridder, et al, "Considering the influence of stimulation parameters on the effect of conventional and high-definition transcranial direct current stimulation," *Expert Rev. Med. Devices*, **13**, No. **4**, 391–404 (2016), https://doi.org/10.1586/17434440.2016.1153968.
88. C. A. Turski, A. Kessler-Jones, C. Chow, et al., "Extended Multiple-Field High-Definition transcranial direct current stimulation (HD-tDCS) is well tolerated and safe in healthy adults," *Restor. Neurol. Neurosci.*, **35**, No. 6, 631–642 (2017), https://doi.org/10.3233/RNN-170757.
89. M. F. Villamar, M. S. Volz, M. Bikson, et al., "Technique and considerations in the use of 4 × 1 ring high-definition transcranial direct current stimulation (HD-tDCS)," *J. Vis. Exp.*, **77**, e50309 (2013a), https://doi.org/10.3791/50309.
90. M. F. Villamar, P. Wivatvongvana, J. Patumanond, et al., "Focal modulation of the primary motor cortex in fibromyalgia using 4×1-ring high-definition transcranial direct current stimulation (HD-Tdcs) : Immediate and delayed analgesic effects of cathodal and anodal stimulation," *J. Pain*, **14**, No. 4, 371–383 (2013b), https://doi.org/10.1016/j.jpain.2012.12.007.
91. S. Wiethoff, M. Hamada, and J. C. Rothwell, "Variability in response to transcranial direct current stimulation of the motor cortex," *Brain Stimul.*, **7**, No. 3, 468–475 (2014), https://doi.org/10.1016/j.brs.2014.02.003.
92. A. J. Woods, A. Antal, M. Bikson, et al., "A technical guide to tDCS, and related non-invasive brain stimulation tools," *Clin. Neurophysiol.*, **127**, No. 2, 1031–1048 (2016), https://doi.org/10.1016/j.clinph.2015.11.012.
93. H. Wong, W. C. Chan, Y. Wong, et al., "High-definition transcranial direct current stimulation-An open-label pilot intervention in alleviating depressive symptoms and cognitive deficits in late-life depression," *CNS Neurosci. Ther.*, **25**, No. 11, 1244–1253 (2019), https://doi.org/10.1111/cns.13253.
94. F. Yavari, A. Jamil, M. Mosayebi Samani, et al., "Basic and functional effects of transcranial Electrical Stimulation (tES) – An introduction," *Neurosci. Biobehav. Rev.*, **85**, 81–92 (2018), https://doi.org/10.1016/j.neubiorev.2017.06.015.
95. T. Yuan, A. Yadollahpour, J. Salgado-Ramírez, et al., "Transcranial direct current stimulation for the treatment of tinnitus: a review of clinical trials and mechanisms of action," *BMC Neurosci.*, **19**, No. 1, 66 (2018), https://doi.org/10.1186/s12868-018-0467-3.