Iran J Psychiatry 2023; 18: 1: 72-82

Review Article

Mechanisms of Action of Noninvasive Brain Stimulation with Weak Non-Constant Current Stimulation Approaches

Samaneh Nazarpoy Shirehjini[1], Mahsa Shahrabi Farahani[2], Mazin Khaleel Ibrahim[3], Hayder Mahmood Salman[4], Saeid Motevalli[5], Mohammad Hossein Mohammadi[6*]

Abstract

Objective: Non-constant current stimulation (NCCS) is a neuromodulatory method in which weak alternating, pulsed or random currents are delivered to the human head via scalp or earlobe electrodes. This approach is widely used in basic and translational studies. However, the underlying mechanisms of NCCS, which lead to biological and behavioral effects in the brain, remain largely unknown. In this review, we characterize NCCS techniques currently being utilized in neuroscience investigations, including transcranial alternating current stimulation (tACS), transcranial pulsed current stimulation (tPCS), transcranial random noise stimulation (tRNS), and cranial electrotherapy stimulation (CES).
Method: We unsystematically searched all relevant conference papers, journal articles, chapters, and textbooks on the biological mechanisms of NCCS techniques.
Results: The fundamental idea of NCCS is that these low-level currents can interact with neuronal activity, modulate neuroplasticity and entrain cortical networks, thus, modifying cognition and behavior. We elucidate the mechanisms of action for each NCCS technique. These techniques may cause microscopic effects (such as affecting ion channels and neurotransmission systems) and macroscopic effects (such as affecting brain oscillations and functional connectivity) on the brain through different mechanisms of action (such as neural entrainment and stochastic resonance).
Conclusion: The appeal of NCCS is its potential to modulate neuroplasticity noninvasively, along with the ease of use and good tolerability. Promising and interesting evidence has been reported for the capacity of NCCS to affect neural circuits and the behaviors under their control. Today, the challenge is to utilize this advancement optimally. Continuing methodological advancements with NCCS approaches will enable researchers to better understand how NCCS can be utilized for the modulation of nervous system activity and subsequent behaviors, with possible applications to non-clinical and clinical practices.

Key words: *Neuroplasticity; Review Literature; Transcranial Electrical Stimulation; Transcranial Alternating Current Stimulation; Transcranial Random Noise Stimulation*

1. Department of Clinical Psychology, Faculty of Psychology, Khomeyni Shahr Branch, Islamic Azad University, Isfahan, Iran.
2. Department of Psychology, Imam Khomeini International University of Qazvin, Qazvin, Iran.
3. Department of Accounting, College of Administration and Economics, Al-Farahidi University, Baghdad, Iraq.
4. Department of Computer Science, Al-Turath University College, Al Mansour, Baghdad, Iraq.
5. Department of Psychology, Faculty of Social Sciences & Liberal Arts, UCSI University, Kuala Lumpur, Malaysia.
6. Department of Neurosurgery, Shahid Sadoughi University of Medical Sciences, Yazd, Iran.

***Corresponding Author:**
Address: Department of Neurosurgery, Shahid Sadoughi University of Medical Sciences, Yazd, Iran, Postal Code: 8916978477.
Tel: 98-3533312200, Fax: 98-3533312202, Email: bitanazemi.id@gmail.com

Article Information:
Received Date: 2022/09/06, Revised Date: 2022/10/11, Accepted Date: 2022/10/12

In recent decades, neurophysiologists and neuroscientists exhibited great interest in understanding the effects of low level electrical stimulation applying to the human scalp. Although some of the mechanisms and neurobiological consequences of noninvasive transcranial electrical stimulation remain obscure, the techniques are becoming progressively studied for their advantages in assessing the effects of cortical modulation on different neuronal populations, and interest in this topic remains intriguing (1). Nowadays, we can identify two major types of low intensity, noninvasive transcranial electrical stimulation: (1) transcranial direct current stimulation (tDCS), which applies a weak constant current to the head, and (2) transcranial non-constant current stimulation (NCCS), which applies a weak alternating, pulsed or random current to the head. tDCS provides a noninvasive, safe, inexpensive and easy to use technique of cortical stimulation. It has been demonstrated to be practical and effective in modulating cortical excitability and neuroplasticity and also in guiding human perception and behavior (2, 3). In recent years, many tDCS papers have been published, revealing and confirming effective clinical outcomes (4, 5). Although many researchers have explained the neurophysiological and clinical mechanisms and effects of tDCS through modern methods of brain research, less effort has been dedicated to the review of the mechanisms of action of cranial stimulation with non-constant currents. In this paper, we review various methods of low intensity non-constant transcranial electrical stimulation and their potential mechanisms of action according to neurophysiological and behavioral studies, presenting new insights in the context of noninvasive brain stimulation. Given the considerable effects of the tDCS technique as a direct current approach, the use of a weak non-constant current can also be an interesting alternative. Non-constant electrical current may be delivered with sinusoidal waves at a given frequency, sinusoidal waves at a random noise frequency pattern, or unidirectional current pulses in rectangular waves. Of the variety of approaches of weak non-constant current that have been investigated, here we will review some stimulation techniques that have been suggested to have clinical effects: transcranial alternating current stimulation (tACS), transcranial pulsed current stimulation (tPCS), transcranial random noise stimulation (tRNS), and cranial electrotherapy stimulation (CES).

Transcranial alternating current stimulation

tACS is an electrical stimulation whose current is not constant. Instead, it alternates between the cathode and the anode with a sinusoidal function (switching polarity). It does not have the polarity limitation of tDCS, because the alternating current rhythmically reverses the electron flow. The tACS approach may be utilized clinically through various stimulation intensities and frequencies, including a DC offset. The benefit of tACS, unlike tDCS and other kinds of noninvasive brain stimulation, is that it leads to entrain the intrinsic neural oscillations by applying the sinusoidal currents. Indeed, endogenous activity is modulated through hyperpolarization (cathode) or depolarization (anode) in a global flow of currents (6, 7). Although it has been demonstrated that tACS could modulate electroencephalogram (EEG) oscillations and cortical excitability as well as cognitive processes, there is evidence for an inability to reproduce such effects under some conditions. In fact, tACS effects are contingent upon the applied intensity and frequency (8, 9). For example, although low frequency AC fields are able to regulate neural firing rates, high frequency fields diminish the induced effects (10, 11). The central hypothesis for the tACS mechanism is that applied alternating fields can enhance or diminish the strength of neural oscillations through synchronizing or desynchronizing neuronal networks in a frequency-dependent manner (12).

From a cellular perspective, AC electric fields delivered to pyramidal neurons could change the transmembrane potential sinusoidally (13). As mentioned, induced AC fields change the membrane potentials of cortical neurons towards hyperpolarization or depolarization in an oscillatory manner by affecting their cell bodies and dendrites. These oscillatory changes in the membrane potential seem to be enough for changing the probability of action potentials generated by a neuron. However, they are not sufficient to alter the rate of neuronal action potentials, and they govern only the timing of action potentials in a location- and frequency-specific fashion. That is why this stimulation is thought to be a kind of sub-threshold one, which does not drive neuron spikes directly (14). Neural entrainment is obtained through the delivered current that changes the transmembrane potential of neurons. We can consider this neural entrainment as acute effects of tACS. The polarization of neurons is proportional to the induced field by AC stimulation. Then, weak polarization of the neuronal membrane can result in modulating the firing pattern of active neurons (15). However, cell susceptibility to polarization of hippocampal pyramidal neurons implicates a decrease in the response of membrane to raising the frequency of the stimulation. In other words, stimulation with lower frequencies induces larger polarization than stimulation with higher frequencies (16). However, it should be noted that the tACS effects depend not only on the frequency and intensity, but also on the 3D direction and orientation of both the penetrating current and the neurons. Indeed, its outcomes come from changing the neuronal membrane potential, aligning with the induced AC field, of mainly pyramidal neurons in layer V that are largely sensitive to current alterations because of their lengthened soma-dendritic axis (17). In general, entraining cells in a certain brain area to follow a firing pattern at a predefined frequency allows scientists to recognize main frequencies associated with various behaviors and to determine causal relationships between them.

Previous researches have indicated the tACS capability to entrain neural oscillations selectively, even with a stimulation of short duration. Moreover, this entrainment is at most effective if the stimulation frequency is the same as the endogenous oscillations (18). This implicates that the tACS effects are contingent upon the state of the brain (19). For example, tACS modulates alpha activity when cognitive demands are high (20). AC stimulation applied to non-active cells and neurons causes simple sinusoidal modulations of transmembrane potential that represent low-pass filtering features. Thus, high frequency tACS may be ineffective to modulate brain activity (21). However, it has been shown that network state and also the consistent AC stimulation of numerous neurons could strengthen and enhance the tACS-induced effects of polarizations. tACS can modulate the timing and rate of spiking neurons as well as the recurrent interaction between them (22, 23). Therefore, neurons modulated through AC fields will regulate the activities of other neurons, creating a feedback process that amplifies the stimulation impacts on single neurons. On the other hand, active networks in the brain often exhibit a continuous balance between inhibition and excitation that controls the timing and firing rates of inhibitory and excitatory neurons. Changing the timing or firing rate by tACS in some cells leads the network to compensate or amplify induced effects in a non-trivial manner (24). Therefore, as with tDCS, tACS priming may elicit metaplastic outcomes through a long-term potentiation (LTP; a cellular correlate of high order cognitive processes) mechanism that is a result of spike-timing-dependent plasticity. Indeed, tACS-induced plasticity differs whether AC fields are applied in relaxed, passive subjects or in subjects performing cognitive tasks. This can lead to clinical protocols combining tACS with other routine rehabilitation or pharmacological strategies for priming the state of the brain to be more responsive to tACS. However, this should be carefully studied in future researches.

tACS, like tDCS, has been shown to change the N-methyl-D-aspartate receptor (NMDAR)-mediated plasticity and local γ-Aminobutyric acid (GABA) levels, particularly GABA-A, implicating that it may modulate connectivity among different brain networks (25). However, an MRI experiment demonstrated the opposite effects of tDCS and tACS on connectivity within the default-mode network at resting-state (26). tACS has been shown to alter functional connectivity within different brain networks in a frequency- and intensity-dependent fashion. For example, applying alpha-tACS over the primary somatosensory cortex could affect whole-brain network level activity through decoupling primary sensory regions from other hubs involved in somatosensory processing (27). Furthermore, application of alpha-tACS over the human motion area elevated functional connectivity between the motion area and other areas of the brain in proportion to the strength of the AC field (28). In addition, beta-tACS altered the connectivity pattern of the primary motor cortex, without changing overall network connectivity (29).

Beside acute-effects (happening throughout the stimulation), several researches have demonstrated neurophysiological after-effects of tACS, outlasting the stimulation period. The exact mechanisms underlying these after-effects are still unclear, and it has been demonstrated that they are not presumably a reflection of neural entrainment. Instead, evidence suggests that these after-effects result from spike time dependent plasticity, causing long-term depression (LTD) or LTP (30). Robust tACS after-effects of power enhancement have been reported in alpha activity. These effects last for about 70 minutes following the alpha-tACS application in a duration-dependent fashion. However, dependency on duration is suggested when the after-effect results from synaptic strengthening between the relevant neuronal networks owing to LTP/LTD (31).

Growing evidence implies that there is a relationship between gamma oscillatory activity and the balance of inhibition and excitation within reciprocally linked networks of excitatory glutamatergic pyramidal neurons within the primary motor cortex and inhibitory GABAergic interneurons that determines the level of corticospinal excitability (32). Multiple researches on tACS at gamma range revealed no after-effects on corticospinal excitability. Rather, they showed decreased inhibition only during the stimulation which is caused by a half-harmonic phenomenon. This phenomenon results from enhanced synchrony of firing rates of excitatory neurons during stimulation with the endogenous frequency. This enhanced synchrony induces a more powerful excitatory valley to inhibitory neurons, for which they are more intensely activated, imposing the neural network to block the following valley (33).

In summary, tACS applied alternating current within the standard EEG frequency ranges and this results in subthreshold modulation of the neural membrane potential. However, it should be noted that the state-of-the-art tACS methods utilize stimulation frequencies on the order of kHz (34). Although the direct tACS effects are probably subthreshold, the coherent stimulation of whole-brain areas and ongoing network activity amplify this effect, resulting in alterations in ongoing neuronal firing rate and spike timing. The effects of AC stimulation are not necessarily a simple scaling of power in the stimulation frequency applied, but can be described by complex nonlinear dynamics. tACS can also induce cross-frequency coupling between exogenous and endogenous activity, and these effects and mechanisms of action may be utilized for targeted stimulation in patients with abnormal brain oscillatory activity. Figure 1 shows an example of waveforms and mechanisms of action of different NCCS methods.

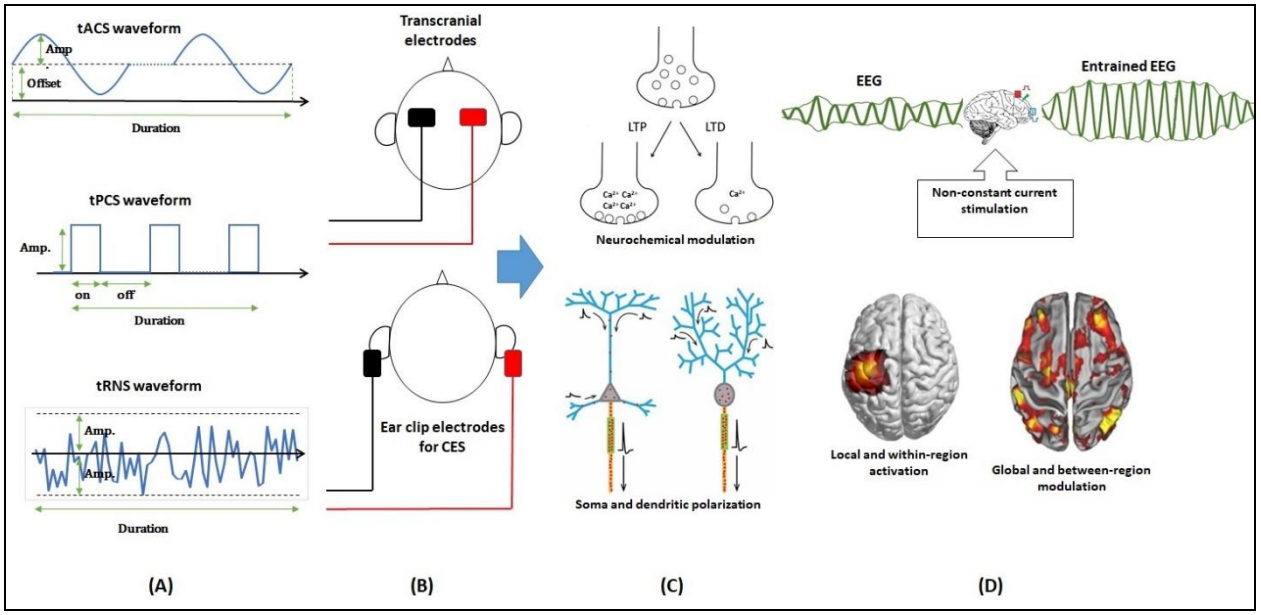

Figure 1. Non-Constant Current Stimulation (NCCS) Approaches and their Mechanisms of Action. (A) NCCS waveforms; note that each of the waveforms shown can be used for cranial electrotherapy stimulation (CES); tACS, transcranial alternating current stimulation; tPCS, transcranial pulsed current stimulation; tRNS, transcranial random noise stimulation. (B) Transcranial electrodes for stimulation through tACS, tPCS and tRNS techniques, and ear clip electrodes for stimulation through the CES protocol. (C) Microscopic effects of NCCS techniques on individual neurons including long term potentiation/depression, and soma and dendritic polarization. (D) Macroscopic effects of NCCS techniques on brain networks and long range interactions including electroencephalogram (EEG) entrainment, activation of local networks and between-regions modulation.

Transcranial pulsed current stimulation

In the tPCS paradigm, non-constant current is delivered through periodical pulses of unidirectional or bidirectional current in square or rectangular waves with a DC offset. In the unidirectional paradigm, intensity is immediately elevated to a given magnitude, held at the peak or maximum value with no change, and brought to zero current; whereas in the bidirectional paradigm, the current pulses alternate with opposite amplitudes. Although the neurobiological mechanisms of action of tPCS are not understood well, it was hypothesized that this paradigm of stimulation applies its influences not only through modulation of the ongoing activity of the brain networks, but also by the on-off pattern of pulses that affects voltage gated carrier proteins in the neuronal membranes (35). The amount of activation in the underlying cortices throughout tPCS may be affected by different factors, including electrode size, the positions of the electrodes over the scalp, the anatomy of the area under stimulation, frequency and intensity of the pulses, pulse duration, inter-pulse interval, and output waveforms (monophasic or biphasic) (36).

tPCS may be delivered through long or short inter-pulse intervals. As compared with tDCS, anodal tPCS with a short inter-pulse interval strengthens its effects for enhancement in corticospinal excitability. In addition, the side effects of stimulation were reduced throughout anodal tPCS and following it. Also, subjects tolerated anodal tPCS better than the tDCS (35). tPCS has been shown to induce alterations in neural actions and networks connectivity via the modulation of endogenous oscillatory activity. It has been found that anodal tPCS changes cortical excitability through both phasic and tonic effects (37). A recent in vivo study showed that the increase in cortical excitability caused by weak anodal tPCS may be associated with increased calcium in astrocytes, while the reduction of cortical excitability because of strong anodal tPCS might be associated with immoderate activity of calcium in neurons within the somatosensory cortex (38). Besides, it has been demonstrated that tPCS modulates interhemispheric coherence of oscillatory activity and, thus, increases functional connectivity in an intensity-dependent manner, particularly in frontal and fronto-temporal areas (39). New evidence demonstrated that tPCS could regulate brain oscillations in a frequency-dependent fashion (40). In these trials, researchers mostly employed EEG signals to explore the neural activity within the brain as well as brain oscillatory activities. The underlying mechanism of action of tPCS may be based on the stochastic resonance phenomenon observed in biological and nonlinear threshold-like systems, in which the capability to recognize and penetrate low-intensity currents is improved in the presence of additive noise. According to this rule, tPCS entrains brain waves as they synchronize with a certain frequency range (41).

The neurobiological effects caused by anodal tPCS on motor performance and clinical symptoms of diseases have been extensively studied. However, the potential impact of cathodal tPCS remains mostly unrevealed.

Cathodal tPCS provides negative pulses to deliver negative DC offset that may result in reduced excitability in the brain area under stimulation through a polarity-dependent manner. A previous research reports that cathodal tPCS could modulate inherent neural fluctuations, causing frequency-dependent alterations in corticospinal excitability. This study showed that low-frequency (0.5 Hz) tPCS induces LTD and decreases corticospinal excitability on the primary motor cortex, irrespective of the current direction (42). However, a new transcranial magnetic stimulation (TMS) research demonstrated that cathodal tPCS at 4 Hz and 75 Hz result in an increase in corticospinal excitability (40).

Transcranial random noise stimulation

tRNS is a noninvasive electrical brain stimulation approach described as an oscillating current applied at random intensities and frequencies. In fact, the standard tRNS is generated by sampling a Gaussian probability distribution to produce a sequence of random intensities. The sampling rate is usually 1280 Hz which covers a frequency band from near DC to 640 Hz and might be filtered for low-tRNS or high-tRNS. In some commercial products, randomizing the frequency of tACS is being introduced as tRNS which is not acceptable among the scientific community. Early studies have emphasized the importance of random noise in biological systems and it has been demonstrated that tRNS could change cortical activity throughout and after stimulation, with important neural and behavioral effects (43). In particular, 10 minutes of high frequency tRNS, but not low frequencies in the EEG range, over the primary motor cortex enhances cortical excitability, with after-effects persisting at least 60 minutes (6). A recent study showed that only the full range tRNS (100-700 Hz) modulates cortical excitability by increasing motor evoked potentials (44). In addition to modulating cortical excitability, tRNS has been shown to effectively improve motor performance in healthy volunteers (45). Compared to other stimulation techniques, such as tACS or tDCS, tRNS has been shown to be a more comfortable intervention method for human subjects, which is an important advantage for use with cognitive behavioral training as well as for effective blinding in clinical trials. The 50% perception threshold was determined at 0.4 mA for tDCS, but at 1.2 mA for tRNS (46). Moreover, a TMS study showed that tRNS leads to a larger cortical excitability enhancement than tDCS and tACS under similar stimulation conditions (47). In addition, tRNS is less sensitive to gyrification or cortical folding than other neuromodulation techniques, minimizing the impact of structural and anatomical variations between individuals (48).

tRNS was first developed with the aim of desynchronizing pathological cortical oscillations; but later, further accepted mechanisms of action were suggested for it, including stochastic resonance. tRNS is a random stimulation method that may apply random activity and therefore neural noise when delivered to the head. The presence of an optimal level of neural noise could increase the signal to noise ratio at the neural level and thus the sensitivity of the neuron to a low-intensity stimulation (49, 50). There is growing evidence in support for the stochastic resonance mechanism to interpret the influences of high frequency tRNS on the visual cortex. This evidence demonstrated that contrast detection of near threshold stimuli is enhanced during tRNS over the primary visual cortex in an intensity-dependent fashion (51, 52). Furthermore, there is psycho-physical evidence that adding random noise to an auditory or a visual stimulus can enhance discriminability and detectability of a signal (53).

The physiological mechanisms of action of tRNS are not fully understood yet, and it is not clear whether tRNS interferes with ongoing network activity through homeostatic mechanisms or causes plastic changes in the brain (6). As mentioned, enhancement of the ratio of signal to noise in the central nervous system and, thus, the sensitization of sensory processing is a potential effect of tRNS. It has been hypothesized that tRNS may elevate synchronization of neuronal firing by amplifying the subthreshold oscillatory activity, with subsequent reduction in the level of endogenous noise (54). In addition, the tRNS effects may be related to repetitious opening of the calcium channel. In fact, the GABA-A agonist lorazepam and the sodium channel blocker carbamazepine showed a tendency toward reducing and suppressing the tRNS-induced cortical excitability (55). In contrast to tDCS, after-effects of tRNS are likely not NMDAR-dependent. A recent in vivo study showed that multi-session tRNS over the prefrontal cortex induces an excitatory effect associated with reduced GABAergic activity with no significant change in glutamatergic activity. Indeed, tRNS might modulate the excitation/inhibition (E/I) ratio through reduction in the inhibitory GABA neurotransmitter (56). A new EEG research indicated that the impacts of tRNS on human arithmetic learning rely on the E/I level in healthy volunteers. Individuals with lower E/I ratio benefited more from the potential tRNS-induced excitatory effects (57).

Cranial electrotherapy stimulation

CES is a kind of non-constant electrical stimulation that delivers a low-intensity oscillating current (50 μA - 4 mA) through a pair of electrodes located on bilateral anatomical structures around the head, such as earlobes and mastoids, with the aim of regulating the peripheral or central nervous system. While the precise underpinning mechanisms of CES on the human brain and behavior remain ambiguous, suggested possible effects are modulation of CNS and PNS, limbic system activity, brain oscillatory activity, and neurotransmitter and hormonal systems (58). Computational studies showed that a weak current from CES could effectively reach both cortical and subcortical areas, leading to subthreshold modulation of neuron populations (41). Moreover, different EEG studies have examined the

effects of CES on brain oscillations and functional connectivity across the brain networks. These studies have reported a little shift to lower alpha frequencies throughout and after CES, increased high alpha frequency with 0.5 Hz CES and increased beta activity with 100 Hz CES (59, 60). Furthermore, CES has been shown to increase theta and alpha coherence in the frontal and fronto-temporal regions of the brain depending on the stimulation duration (39). Indeed, some evidence reported a nonlinear relationship between the CES duration and its effects, implicating the possibility of the involvement of homeostatic mechanisms in the CES after effects (61).

Two neuroimaging studies have examined CES effects on the hemodynamics of the brain using Xenon-enhanced computed tomography and fMRI. They indicated that CES induces cortical deactivation and changes connectivity in the default-mode network in the resting-state, independent of the stimulation frequency. Furthermore, CES could cause a substantial decrease in the cerebral blood flow locally, at both thalamus and brainstem, but not globally, suggesting the ability of CES in local modulation of cerebral blood flow in the structures associated with anxiety and pain responses (62, 63). In addition, previous studies have examined the effects of CES on neurotransmitter and hormonal systems as well. Although early in vivo studies have reported some CES-induced variations in neurotransmitters and hormones, including increased dopaminergic activity in the basal ganglia and elevated beta-endorphin levels in the cerebrospinal fluid, the results reported in human studies are highly inconsistent and lack sufficient evidence to support CES-induced variations in human neurotransmitters and hormones (58).

A recent study showed that the influences of CES on human arithmetic performance are associated with sympathetic-vagal balance during stressful situations through modulating the central autonomic network (64). This finding is relatively consistent with a proposed model of CES effect on the human brain and behavior that reflects the broad neuromodulatory effects on the limbic, thalamic, and hypothalamic systems. This model anticipates variations in arousal or mood states and sensory processing, possibly by making active the parasympathetic part of the autonomic nervous system (65). Table 1 summarizes the microscopic effects, macroscopic effects and possible mechanisms of action of NCCS methods.

Table 1. Comparison of Possible Mechanisms of Action of Four Non-Constant Current Stimulation (NCCS) Methods at both Microscopic and Macroscopic Levels

Stimulation technique	Microscopic effects	Macroscopic effects
tACS	- Subthreshold modulation of neuronal membrane potential. - Modulation of timing and rate of spiking neurons. - Modulation of NMDAR-mediated plasticity and local GABA levels. - LTP/LTD through spike-timing-dependent plasticity.	- Entrain EEG oscillations. - Modulation functional connectivity within brain networks.
tPCS	- Affecting voltage gated carrier proteins in the neuronal membranes. - Affecting calcium activity in astrocytes and neurons. - LTP/LTD.	- Modulation of brain oscillations. - Affecting functional connectivity between brain networks.
tRNS	- Affecting the opening rate of the calcium channel. - Modulating synchronization of neuronal firing. - Modulation of the excitation/inhibition ratio by affecting the GABA neurotransmitter. - LTP.	- Enhance the signal to noise ratio in the CNS.
CES	- Local modulation of cerebral blood flow. - Possible alterations in neurotransmitters and hormones.	- Modulation of brain oscillations. - Affecting connectivity in the default-mode network.
Possible mechanisms of action of NCCS methods	1. Temporal bias of neural spikes 2. Rhythm resonance 3. Stochastic resonance 4. Half-harmonic 5. Neural entrainment 6. Imposed patterns	

tACS: transcranial alternating current stimulation. tPCS: transcranial pulsed current stimulation. tRNS: transcranial random noise stimulation. CES: cranial electrotherapy stimulation. LTP: long-term potentiation. LTD: long-term depression. CNS: central nervous system.

Cognitive and behavioral effects of non-constant current stimulation

Several human researches have studied the effects and impacts of NCCS modalities on cognitive and behavioral aspects. Most of these studies have been performed on healthy adult volunteers with the aim of improving cognitive and executive capacities. These studies showed that NCCS techniques may be an effective tool to modify cognition and behavior. Enhancements have been found in attention, memory, perception, visual detection, mathematical learning, creativity, priming, morality, risk-taking behaviors, eating behaviors, addictive behaviors and multiple other cognitive functions. For example, gamma tACS has been shown to facilitate endogenous attention, but not exogenous attention (66). Alpha tACS could successfully modulate mental rotation in healthy participants (67). tRNS has been shown to enhance non-verbal working memory in older adults (68). Both tPCS and tRNS have been shown to enhance sensory perception through regulating neural function in the primary somatosensory cortex (69). Furthermore, CES could improve reaction time in an attention switching task in healthy volunteers (70).

On the other hand, several studies have also been performed on different clinical populations with the aim of improving the symptoms of the disease (71). These studies used NCCS approaches to modulate pathological brain oscillations or pathological patterns of connectivity to manage the diseases. A recent systematic review supported the feasibility of tACS in different clinical psychiatric populations including schizophrenia, depression and ADHD without important side effects (31). tRNS has shown beneficial and positive modulatory effects on the distress network and different hubs involved in the tinnitus brain network (72). Moreover, CES has been used successfully in recent years to improve the symptoms of insomnia, depression and anxiety (58).

Methodological limitations of non-constant current stimulation research

We have recognized some serious limitations in the publications exploring the effects of NCCS approaches on both subclinical and clinical populations. Across literature, NCCS is applied through a variety of technical and clinical parameters, including the scheduling and duration of stimulation; the type, montage and location of electrodes; and the frequency, amplitude and dynamics of non-constant waveforms. For example, in the studies reviewed here, the stimulation duration varied between 5 and 40 minutes, and the stimulation intensity varied from 1 to 4 mA. This heterogeneity among the stimulation parameters influences the comparability, reproducibility and generalizability of findings and observations, making it challenging to make definitive statements about the mechanisms of action of NCCS methods.

In addition, we identified several instances of potential risk of bias in reviewed studies. One of these issues is sham reliability and appropriate blinding in human studies. Most experiments and trials used different and mixed methods for sham protocols. There was no control group in some studies. In other studies, the electrodes were placed on the subject's head and the stimulation device was either turned off or turned on, but at a lower intensity as compared to the active condition. However, some low intensity sham methods utilize a larger intensity than the active stimulation applied in other studies. In other words, these high levels of sham intensity can induce effects similar to those of the real stimulations applied in other studies, limiting interpretability and comparability among studies. On the other hand, the use of a turned off device as a sham protocol cannot induce signs and symptoms of active stimulation in the subject (e.g., skin irritation, dizziness or light headedness); thus, limiting proper blinding. Without proper blinding of trials and experiments, the possibility of experimental biases increases and the validity of the findings decreases.

Future research directions

Although the field of NCCS research has well progressed in the last decade, there is still a long way to go to make full use of the potential of these techniques. As mentioned, the precise mechanisms of action of the NCCS techniques are not completely understood in spite of multiple researches attempting to elucidate them. So far, a little is known about tPCS, CES and tRNS, with some proposed mechanistic hypotheses and very few researches on the cortical and subcortical responses to NCCS. Therefore, further experiments and trials are needed to describe the effects and mechanisms of the NCCS methods at the neural and behavioral levels.

Although stimulation effects are contingent upon the dynamics of brain networks during the stimulation, there is a large gap in our insights into the NCCS types in this regard. Particularly, there is the need to carefully examine the NCCS effects on important neurophysiological rhythms including beta and theta waves as well as sharp wave and spindle activity that have been shown to link to various cognitive functions such as motor control, attention and memory. Furthermore, a crucial issue in brain stimulation is the within- and between-subject variability in reaction to stimulation (73, 74). Several tDCS studies have considered this important issue either by defining an individual base for stimulation or by selecting the optimal parameters of stimulation (16). However, very few NCCS studies have attempted to recruit such an individualized method to design their neuromodulatory protocols, and therefore further studies are needed to investigate this issue in the future in order to achieve closed-loop systems to stimulate human subjects in a brain state-dependent manner.

Although we often encounter the fact that NCCS methods may be appropriate tools for treating and improving the symptoms of diseases, there are still many ambiguous aspects in this regard. A usually neglected

fact is that the biological outcomes of NCCS in animals and healthy human subjects, which fundamentally give the rationale and justification for its use in illness, may not directly and completely translate to patients. For instance, using a similar stimulation procedure in two healthy and psychiatric populations with different neural states may not produce similar effects. Moreover, it should be noted that brain lesion in patients may substantially affect the distribution of induced electric fields. How this influences the NCCS effects is not clear, but it is probably an important factor. Therefore, a serious issue is the translation of the effects of NCCS on the healthy brain to the pathologic brain, because patients' brains may respond differently to stimulation. So, moving towards disorder-specific protocols for the application of NCCS in clinical populations is very important.

Limitation

The main limitation of this article is the lack of a systematic literature search to retrieve all possible original studies. However, an attempt was made to minimize this limitation with the authors' experience.

Conclusion

Our purpose was to elucidate the benefits of NCCS on neural researches. Despite many technical and clinical advancements, many questions remain unanswered. However, we have been in such a situation before. Remember that transcranial magnetic stimulation also faced such issues at the beginning, but several years later a lot of research provided more answers to questions and turned it into an approved tool in clinical practice. Similarly, we are now in the early days of the process of refining NCCS. The appeal of NCCS is its potential to modulate neuroplasticity noninvasively, along with the ease of use and good tolerability. Promising and interesting evidence has been reported for the capacity of NCCS to affect neural circuits and the behaviors under their control. Today, the challenge is to utilize this advancement optimally. Continuing methodological advancements with NCCS approaches will enable researchers to better understand how NCCS can be utilized for the modulation of nervous system activity and subsequent behaviors, with possible applications to non-clinical and clinical practices.

Conflict of Interest

None.

References

1. Khaleghi A, Mohammadi MR, Shahi K, Nasrabadi AM. Computational Neuroscience Approach to Psychiatry: A Review on Theory-driven Approaches. Clin Psychopharmacol Neurosci. 2022;20(1):26-36.
2. Khaleghi A, Zarafshan H, Vand SR, Mohammadi MR. Effects of Non-invasive Neurostimulation on Autism Spectrum Disorder: A Systematic Review. Clin Psychopharmacol Neurosci. 2020;18(4):527-52.
3. Khaleghi A, Pirzad Jahromi G, Zarafshan H, Mostafavi SA, Mohammadi MR. Effects of transcranial direct current stimulation of prefrontal cortex on risk-taking behavior. Psychiatry Clin Neurosci. 2020;74(9):455-65.
4. Mostafavi SA, Khaleghi A, Mohammadi MR. Noninvasive brain stimulation in alcohol craving: A systematic review and meta-analysis. Prog Neuropsychopharmacol Biol Psychiatry. 2020;101:109938.
5. Mostafavi SA, Khaleghi A, Mohammadi MR, Akhondzadeh S. Is transcranial direct current stimulation an effective modality in reducing food craving? A systematic review and meta-analysis. Nutr Neurosci. 2020;23(1):55-67.
6. Paulus W, Nitsche MA, Antal A. Application of transcranial electric stimulation (tDCS, tACS, tRNS): From motor-evoked potentials towards modulation of behaviour. Eur Psychol. 2016;21(1):4.
7. Helfrich RF, Schneider TR, Rach S, Trautmann-Lengsfeld SA, Engel AK, Herrmann CS. Entrainment of brain oscillations by transcranial alternating current stimulation. Curr Biol. 2014;24(3):333-9.
8. Vöröslakos M, Takeuchi Y, Brinyiczki K, Zombori T, Oliva A, Fernández-Ruiz A, et al. Direct effects of transcranial electric stimulation on brain circuits in rats and humans. Nat Commun. 2018;9(1):483.
9. Yaghmazadeh O, Vöröslakos M, Alon L, Carluccio G, Collins C, Sodickson DK, et al. Neuronal activity under transcranial radio-frequency stimulation in metal-free rodent brains in-vivo. Communications Engineering. 2022;1(1):1-13.
10. Anastassiou CA, Perin R, Markram H, Koch C. Ephaptic coupling of cortical neurons. Nat Neurosci. 2011;14(2):217-23.
11. Deans JK, Powell AD, Jefferys JG. Sensitivity of coherent oscillations in rat hippocampus to AC electric fields. J Physiol. 2007;583(Pt 2):555-65.
12. Vieira PG, Krause MR, Pack CC. tACS entrains neural activity while somatosensory input is blocked. PLoS Biol. 2020;18(10):e3000834.
13. Reato D, Rahman A, Bikson M, Parra LC. Effects of weak transcranial alternating current stimulation on brain activity-a review of known mechanisms from animal studies. Front Hum Neurosci. 2013;7:687.
14. Tavakoli AV, Yun K. Transcranial Alternating Current Stimulation (tACS) Mechanisms and Protocols. Front Cell Neurosci. 2017;11:214.
15. Pozdniakov I, Vorobiova AN, Galli G, Rossi S, Feurra M. Online and offline effects of transcranial alternating current stimulation of the primary motor cortex. Sci Rep. 2021;11(1):3854.
16. Reed T, Cohen Kadosh R. Transcranial electrical stimulation (tES) mechanisms and its

effects on cortical excitability and connectivity. J Inherit Metab Dis. 2018;41(6):1123-30.
17. Fröhlich F. Endogenous and exogenous electric fields as modifiers of brain activity: rational design of noninvasive brain stimulation with transcranial alternating current stimulation. Dialogues Clin Neurosci. 2014;16(1):93-102.
18. Stonkus R, Braun V, Kerlin JR, Volberg G, Hanslmayr S. Probing the causal role of prestimulus interregional synchrony for perceptual integration via tACS. Sci Rep. 2016;6:32065.
19. Alagapan S, Schmidt SL, Lefebvre J, Hadar E, Shin HW, Fröhlich F. Modulation of Cortical Oscillations by Low-Frequency Direct Cortical Stimulation Is State-Dependent. PLoS Biol. 2016;14(3):e1002424.
20. Violante IR, Li LM, Carmichael DW, Lorenz R, Leech R, Hampshire A, et al. Externally induced frontoparietal synchronization modulates network dynamics and enhances working memory performance. elife. 2017;6.
21. Liu A, Vöröslakos M, Kronberg G, Henin S, Krause MR, Huang Y, et al. Immediate neurophysiological effects of transcranial electrical stimulation. Nat Commun. 2018;9(1):5092.
22. Reato D, Rahman A, Bikson M, Parra LC. Low-intensity electrical stimulation affects network dynamics by modulating population rate and spike timing. J Neurosci. 2010;30(45):15067-79.
23. Fröhlich F, McCormick DA. Endogenous electric fields may guide neocortical network activity. Neuron. 2010;67(1):129-43.
24. Bergmann TO. Brain State-Dependent Brain Stimulation. Front Psychol. 2018;9:2108.
25. Nowak M, Hinson E, van Ede F, Pogosyan A, Guerra A, Quinn A, et al. Driving Human Motor Cortical Oscillations Leads to Behaviorally Relevant Changes in Local GABA(A) Inhibition: A tACS-TMS Study. J Neurosci. 2017;37(17):4481-92.
26. Weinrich CA, Brittain JS, Nowak M, Salimi-Khorshidi R, Brown P, Stagg CJ. Modulation of Long-Range Connectivity Patterns via Frequency-Specific Stimulation of Human Cortex. Curr Biol. 2017;27(19):3061-8.e3.
27. Gundlach C, Müller MM, Hoff M, Ragert P, Nierhaus T, Villringer A, et al. Reduction of somatosensory functional connectivity by transcranial alternating current stimulation at endogenous mu-frequency. Neuroimage. 2020;221:117175.
28. Kar K, Ito T, Cole MW, Krekelberg B. Transcranial alternating current stimulation attenuates BOLD adaptation and increases functional connectivity. J Neurophysiol. 2020;123(1):428-38.
29. Wischnewski M, Engelhardt M, Salehinejad MA, Schutter D, Kuo MF, Nitsche MA. NMDA Receptor-Mediated Motor Cortex Plasticity After 20 Hz Transcranial Alternating Current Stimulation. Cereb Cortex. 2019;29(7):2924-31.
30. Guerra A, Suppa A, Bologna M, D'Onofrio V, Bianchini E, Brown P, et al. Boosting the LTP-like plasticity effect of intermittent theta-burst stimulation using gamma transcranial alternating current stimulation. Brain Stimul. 2018;11(4):734-42.
31. Elyamany O, Leicht G, Herrmann CS, Mulert C. Transcranial alternating current stimulation (tACS): from basic mechanisms towards first applications in psychiatry. Eur Arch Psychiatry Clin Neurosci. 2021;271(1):135-56.
32. Sohal VS, Rubenstein JLR. Excitation-inhibition balance as a framework for investigating mechanisms in neuropsychiatric disorders. Mol Psychiatry. 2019;24(9):1248-57.
33. Aspart F. Investigating the effects of weak extracellular fields on single neurons: a modelling approach: Technische Universitaet Berlin (Germany); 2018.
34. Antal A, Grossman N, Paulus W. Basic Mechanisms of Transcranial Alternating Current and Random Noise Stimulation. Transcranial Direct Current Stimulation in Neuropsychiatric Disorders: Springer; 2021. p. 21-8.
35. Jaberzadeh S, Bastani A, Zoghi M. Anodal transcranial pulsed current stimulation: A novel technique to enhance corticospinal excitability. Clin Neurophysiol. 2014;125(2):344-51.
36. Moreno-Duarte I, Gebodh N, Schestatsky P, Guleyupoglu B, Reato D, Bikson M, et al. Transcranial electrical stimulation: Transcranial direct current stimulation (tDCS), transcranial alternating current stimulation (tACS), transcranial pulsed current stimulation (tPCS), and transcranial random noise stimulation (tRNS). The stimulated brain: Elsevier; 2014. p. 35-59.
37. Thibaut A, Russo C, Morales-Quezada L, Hurtado-Puerto A, Deitos A, Freedman S, et al. Neural signature of tDCS, tPCS and their combination: Comparing the effects on neural plasticity. Neurosci Lett. 2017;637:207-14.
38. Ma Z, Du X, Wang F, Ding R, Li Y, Liu A, et al. Cortical Plasticity Induced by Anodal Transcranial Pulsed Current Stimulation Investigated by Combining Two-Photon Imaging and Electrophysiological Recording. Front Cell Neurosci. 2019;13:400.
39. Castillo Saavedra L, Morales-Quezada L, Doruk D, Rozinsky J, Coutinho L, Faria P, et al. QEEG indexed frontal connectivity effects of transcranial pulsed current stimulation (tPCS): A sham-controlled mechanistic trial. Neurosci Lett. 2014;577:61-5.
40. Dissanayaka T, Zoghi M, Farrell M, Egan G, Jaberzadeh S. The effects of a single-session cathodal transcranial pulsed current stimulation on corticospinal excitability: A randomized sham-controlled double-blinded study. Eur J Neurosci. 2020;52(12):4908-22.
41. Datta A, Dmochowski JP, Guleyupoglu B, Bikson M, Fregni F. Cranial electrotherapy stimulation and transcranial pulsed current stimulation: a computer based high-resolution modeling study. Neuroimage. 2013;65:280-7.
42. Luu P, Essaki Arumugam EM, Anderson E, Gunn A, Rech D, Turovets S, et al. Slow-

Frequency Pulsed Transcranial Electrical Stimulation for Modulation of Cortical Plasticity Based on Reciprocity Targeting with Precision Electrical Head Modeling. Front Hum Neurosci. 2016;10:377.
43. Abe T, Miyaguchi S, Otsuru N, Onishi H. The effect of transcranial random noise stimulation on corticospinal excitability and motor performance. Neurosci Lett. 2019;705:138-42.
44. Moret B, Donato R, Nucci M, Cona G, Campana G. Transcranial random noise stimulation (tRNS): a wide range of frequencies is needed for increasing cortical excitability. Sci Rep. 2019;9(1):15150.
45. Gao Y, Cavuoto L, Schwaitzberg S, Norfleet JE, Intes X, De S. The Effects of Transcranial Electrical Stimulation on Human Motor Functions: A Comprehensive Review of Functional Neuroimaging Studies. Front Neurosci. 2020;14:744.
46. Ambrus GG, Paulus W, Antal A. Cutaneous perception thresholds of electrical stimulation methods: comparison of tDCS and tRNS. Clin Neurophysiol. 2010;121(11):1908-14.
47. Inukai Y, Saito K, Sasaki R, Tsuiki S, Miyaguchi S, Kojima S, et al. Comparison of Three Non-Invasive Transcranial Electrical Stimulation Methods for Increasing Cortical Excitability. Front Hum Neurosci. 2016;10:668.
48. Terney D, Chaieb L, Moliadze V, Antal A, Paulus W. Increasing human brain excitability by transcranial high-frequency random noise stimulation. J Neurosci. 2008;28(52):14147-55.
49. Harty S, Cohen Kadosh R. Suboptimal Engagement of High-Level Cortical Regions Predicts Random-Noise-Related Gains in Sustained Attention. Psychol Sci. 2019;30(9):1318-32.
50. Fertonani A, Miniussi C. Transcranial Electrical Stimulation: What We Know and Do Not Know About Mechanisms. Neuroscientist. 2017;23(2):109-23.
51. Battaglini L, Contemori G, Fertonani A, Miniussi C, Coccaro A, Casco C. Excitatory and inhibitory lateral interactions effects on contrast detection are modulated by tRNS. Sci Rep. 2019;9(1):19274.
52. Battaglini L, Contemori G, Penzo S, Maniglia M. tRNS effects on visual contrast detection. Neurosci Lett. 2020;717:134696.
53. Pavan A, Ghin F, Contillo A, Milesi C, Campana G, Mather G. Modulatory mechanisms underlying high-frequency transcranial random noise stimulation (hf-tRNS): A combined stochastic resonance and equivalent noise approach. Brain Stimul. 2019;12(4):967-77.
54. Miniussi C, Harris JA, Ruzzoli M. Modelling non-invasive brain stimulation in cognitive neuroscience. Neurosci Biobehav Rev. 2013;37(8):1702-12.
55. Chaieb L, Antal A, Paulus W. Transcranial random noise stimulation-induced plasticity is NMDA-receptor independent but sodium-channel blocker and benzodiazepines sensitive. Front Neurosci. 2015;9:125.
56. Sánchez-León CA, Sánchez-López Á, Gómez-Climent MA, Cordones I, Cohen Kadosh R, Márquez-Ruiz J. Impact of chronic transcranial random noise stimulation (tRNS) on GABAergic and glutamatergic activity markers in the prefrontal cortex of juvenile mice. Prog Brain Res. 2021;264:323-41.
57. Sheffield JG, Raz G, Sella F, Kadosh RC. How can noise alter neurophysiology in order to improve human behaviour? A combined transcranial random noise stimulation and electroencephalography study. bioRxiv. 2020.
58. Brunyé TT, Patterson JE, Wooten T, Hussey EK. A Critical Review of Cranial Electrotherapy Stimulation for Neuromodulation in Clinical and Non-clinical Samples. Front Hum Neurosci. 2021;15:625321.
59. Wagenseil B, Garcia C, Suvorov AV, Fietze I, Penzel T. The effect of cranial electrotherapy stimulation on sleep in healthy women. Physiol Meas. 2018;39(11):114007.
60. Lee J, Lee H, Park W. Effects of cranial electrotherapy stimulation on electrocephalogram. J Int Acad Phys Ther Res. 2019;10(1):1687-94.
61. Vasquez A, Malavera A, Doruk D, Morales-Quezada L, Carvalho S, Leite J, et al. Duration Dependent Effects of Transcranial Pulsed Current Stimulation (tPCS) Indexed by Electroencephalography. Neuromodulation. 2016;19(7):679-88.
62. Feusner JD, Madsen S, Moody TD, Bohon C, Hembacher E, Bookheimer SY, et al. Effects of cranial electrotherapy stimulation on resting state brain activity. Brain Behav. 2012;2(3):211-20.
63. Gense de Beaufort D, Sesay M, Stinus L, Thiebaut R, Auriacombe M, Dousset V. Cerebral blood flow modulation by transcutaneous cranial electrical stimulation with Limoge's current. J Neuroradiol. 2012;39(3):167-75.
64. Morales-Quezada L, Cosmo C, Carvalho S, Leite J, Castillo-Saavedra L, Rozisky JR, et al. Cognitive effects and autonomic responses to transcranial pulsed current stimulation. Exp Brain Res. 2015;233(3):701-9.
65. Asamoah B, Khatoun A, Mc Laughlin M. tACS motor system effects can be caused by transcutaneous stimulation of peripheral nerves. Nat Commun. 2019;10(1):266.
66. Hopfinger JB, Parsons J, Fröhlich F. Differential effects of 10-Hz and 40-Hz transcranial alternating current stimulation (tACS) on endogenous versus exogenous attention. Cogn Neurosci. 2017;8(2):102-11.
67. Kasten FH, Herrmann CS. Transcranial Alternating Current Stimulation (tACS) Enhances Mental Rotation Performance during and after Stimulation. Front Hum Neurosci. 2017;11:2.
68. Brambilla M, Dinkelbach L, Bigler A, Williams J, Zokaei N, Cohen Kadosh R, et al. The Effect of Transcranial Random Noise Stimulation on Cognitive Training Outcome in Healthy Aging. Front Neurol. 2021;12:625359.

69. Saito K, Otsuru N, Inukai Y, Miyaguchi S, Yokota H, Kojima S, et al. Comparison of transcranial electrical stimulation regimens for effects on inhibitory circuit activity in primary somatosensory cortex and tactile spatial discrimination performance. Behav Brain Res. 2019;375:112168.
70. Morales-Quezada L, Leite J, Carvalho S, Castillo-Saavedra L, Cosmo C, Fregni F. Behavioral effects of transcranial pulsed current stimulation (tPCS): Speed-accuracy tradeoff in attention switching task. Neurosci Res. 2016;109:48-53.
71. Feng Y, Zhang J, Zhou Y, Bai Z, Yin Y. Noninvasive brain stimulation for patients with a disorder of consciousness: a systematic review and meta-analysis. Rev Neurosci. 2020.
72. Mohsen S, Mahmoudian S, Talebian S, Pourbakht A. Multisite transcranial Random Noise Stimulation (tRNS) modulates the distress network activity and oscillatory powers in subjects with chronic tinnitus. J Clin Neurosci. 2019;67:178-84.
73. Pellegrini M, Zoghi M, Jaberzadeh S. Cluster analysis and subgrouping to investigate inter-individual variability to non-invasive brain stimulation: a systematic review. Rev Neurosci. 2018;29(6):675-97.
74. Pellegrini M, Zoghi M, Jaberzadeh S. Biological and anatomical factors influencing interindividual variability to noninvasive brain stimulation of the primary motor cortex: a systematic review and meta-analysis. Rev Neurosci. 2018;29(2):199-222.