INVITED REVIEW

Non-invasive electrical brain stimulation: from acute to late-stage treatment of central nervous system damage

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Abstract

Non-invasive brain current stimulation (NIBS) is a promising and versatile tool for inducing neuroplasticity, protection and functional rehabilitation of damaged neuronal systems. It is technically simple, requires no surgery, and has significant beneficial effects. However, there are various technical approaches for NIBS which influence neuronal networks in significantly different ways. Transcranial direct current stimulation (tDCS), alternating current stimulation (ACS) and repetitive transcranial magnetic stimulation (rTMS) all have been applied to modulate brain activity in animal experiments under normal and pathological conditions. Also clinical trials have shown that tDCS, rTMS and ACS induce significant behavioural effects and can — depending on the parameters chosen — enhance or decrease brain excitability and influence performance and learning as well as rehabilitation and protective mechanisms. The diverse phenomena and partially opposing effects of NIBS are not yet fully understood and mechanisms of action need to be explored further in order to select appropriate parameters for a given task, such as current type and strength, timing, distribution of current densities and electrode position. In this review, we will discuss the various parameters which need to be considered when designing a NIBS protocol and will put them into context with the envisaged applications in experimental neurobiology and medicine such as vision restoration, motor rehabilitation and cognitive enhancement.

Key Words: non-invasive brain stimulation; transcranial direct current stimulation; transcranial magnetic stimulation; transorbital alternating current stimulation; stroke; trauma; neuroprotection; restoration of function

Introduction

Non-invasive electrical brain stimulation (NIBS) has increasingly been used during the last decade to modulate excitability with many beneficial effects ranging from enhanced performance to neuroprotection and rehabilitation “after-effects” (Wagner et al., 2007; Sehic et al., 2016; Thut et al., 2017). For example, application of transcranial direct current stimulation (tDCS) over the dorsolateral prefrontal cortex in humans may reduce depression; however, enhancement of fear memory has been described as well. In stroke patients, tDCS was applied to influence maladaptive post-lesional plasticity with a significant amelioration of hand motor function. Delayed treatment with transcorneal alternating current stimulation (ACS) after optic nerve damage significantly improved the visual field of the patients and an acute ACS of rats with corneal electrodes after optic nerve crush increased the number of surviving neurons (Morimoto et al., 2005; Henrich-Noack et al., 2013; Abd Hamid et al., 2015; Woods et al., 2016) and induced vision recovery in patients with optic nerve damage (Gall et al., 2016). However, although such significant NIBS effects have been demonstrated many times (Yavari et al., 2017), the literature of thousands of reports by now resembles a confusing patchwork when it comes to the details of the stimulation paradigms and experimental treatment designs. There is no unifying hypothesis about the underlying mechanisms and a wide variety of protocols with different timing, locations and parameters of stimulation have been published. Therefore, this perspective suggests a categorization of NIBS techniques and their respective mechanisms with the goal to develop a system which will allow better predictions as to which kind of stimulation may be suitable for acute versus chronic pathophysiological conditions.

Electrical Brain Stimulation – Effects and Mechanisms

Developmental biology has established that sensory stimulation and neuronal activity are necessary for cellular survival and growth. Electro-chemical currents are long known to be the underlying processes of such brain activity. It can be therefore assumed that excitation or inhibition of neuronal networks with extrinsic/induced electrical stimulation may modify mechanisms of plasticity. One way that both mechanisms of development and induced electrical activation may promote and support neuronal plasticity is achieved by stimulating cellular pathways that mediate the synthesis and release of neuronal growth factors. For example, it has been established that during development, growth factors are essential to prevent programmed cell death and they play an important role in developmental plasticity of neurons. These mechanisms have been a long-studied subject across
the whole life span. Not surprisingly, therefore, experiments investigating NIBS’s mode of action demonstrated an increase in growth factors, like, for example, insulin-like growth factor (IGF), vascular endothelial growth factor (VEGF) and activity-dependent neurotrophic factor peptide (ADNF). In case of optic nerve damage, for example, the results indicate that the induction of growth factors by extrinsic electrical stimulation is causal for neuronal survival (Morimoto et al., 2005).

In the area of learning and memory, the concept of Hebbian plasticity is widely discussed. Thus, in the studies of synaptic plasticity, an intensive high frequency stimulation (about 200 Hz), i.e., “tetanization” is applied to induce long-term potentiation (LTP), whereas low frequencies (around 1 Hz) induce long-term depression (LTD). Studies investigating the NIBS’ mode of action after brain damage and diseases indicate that also here processes of Hebbian plasticity may apply. Although most NIBS protocols use frequencies typically corresponding to alpha and beta bands of the human EEG, i.e., 7.5–30 Hz, frequency range to induce Hebbian plasticity are much higher, i.e., most typically 100–200 Hz for LTP. Yet stimulation with 7–13 Hz causes LTP-like “after-effects” that outlast the time of stimulation (Sergeeva et al., 2012) and those after-effects can be associated with increased intracellular free calcium in the retinal cells (Prilloff et al., 2007; Henrich-Noack et al., 2013, 2017). Calcium can regulate many different cellular processes like signal transduction, gene transcription and cell proliferation. This depends on the temporal/spatial pattern of calcium transients in neurons, which can activate various intracellular components, like, for example, Ca\(^{2+}\)/calmodulin (CaM)-dependent kinase II, neuronal nitric oxide synthase, scaffolding proteins (like postsynaptic protein-95 (PSD95)) and syntaxin for exocytotic release of synaptic vesicles (Berridge et al., 2003).

In addition to Hebbian plasticity NIBS protocols, specifically direct current may also be tailored to manipulate homeostatic plasticity, i.e., adjust neuronal excitability through mechanisms of synaptic scaling in order to counteract excessive excitation or inhibition (Siebner et al., 2004; Karabanov et al., 2015).

Electric stimulation-induced mechanisms of neuroplasticity may also take place on a more global, brain network level, where oscillation entrainment and altered connectivity may represent system-wide modulation effects (Bola et al., 2014). Moreover, there are many other effects of NIBS on the molecular and cellular level including anti-inflammatory effects, blood-brain barrier recovery, and/or increase in blood flow (Kurimoto et al., 2011; Yang et al., 2012; Bonaz et al., 2016), to name a few. Glial cells are affected by NIBS as well. Glia can align their processes in an electric field and a special kind of glia in the retina – Mueller glia cells – may be one source of electrical stimulation-induced increase in growth factors (Borgens et al., 1994; Sato et al., 2008a; Gellner et al., 2016). Astrocytes are also indirectly affected by NIBS via the neuronal activity, for example reacting to changes in extracellular transmitter concentrations. Regarding microglia cells, it has been demonstrated that morphological changes and activation are induced with current intensities below the threshold of neurodegeneration (Gellner et al., 2016). However, under pathological conditions, NIBS may also reduce microglia activation (Yin et al., 2016).

All these effects may be an indirect consequence of the above-mentioned widely discussed mechanisms of (post-lesional) neuronal plasticity but they may also well be independent mechanisms associated with protection and/or with regeneration (Figure 1). From these considerations, we can conclude that various mechanisms based on concepts of neuroplasticity, protection and/or regeneration may be induced by NIBS. It can be hypothesized that the individual stimulation protocols determine which mechanisms prevail. Therefore, considering which kind of NIBS protocol to apply is essential for the outcome and the understanding of the treatment mode.

**Different Techniques of NIBS**

Three different approaches are used to stimulate the brain non-invasively: the widely used (i) tDCS and (ii) transcranial magnetic stimulation (TMS) as well as (iii) alternating current stimulation which can be sub-divided into a transcranial and a transorbital application technique (i.e., via the eyes). In tDCS, direct currents applied through surface electrodes on the scalp modulate neuronal membrane potentials in the cortical layers beneath the electrodes. The effects are defined by the current polarity; while anodal stimulation depolarizes neurons and increases neuronal excitability, cathodal currents induce hyperpolarization. Accordingly, tDCS can be used as a “two-in-one” treatment, i.e., anodal stimulation re-activating brain areas which suffer from low excitability or de-synchronization after an incident and cathodal stimulation inhibiting over-activated areas. However, since tDCS currents are direct, i.e., do not have a frequency variable, tDCS can only polarize resting membrane potential to either facilitate or attenuate induction of action potentials and cannot induce spike activity or entrain brain oscillations. This is in contrast with protocols that induce LTD/LTP (Nitsche and Paulus, 2011; Stagg and Nitsche, 2011; Brunoni et al., 2012).

Unlike tDCS, TMS is based on alternating magnetic fields and in addition to the parameters of intensity and polarity, the frequency of alterations can be manipulated. Therefore, in addition to polarization effects, TMS also can be used to induce neuronal firing and to interfere with neuronal activity and brain oscillations. Though precise mechanisms still have to be elucidated, TMS is widely known to change synaptic efficacy by inducing LTP-like or LTD-like effects. In reports about therapeutic TMS applications usually the aim is to increase excitability, and this has been used, for example, for the treatment of depression (Fregni and Pascual-Leone, 2007; Bashir et al., 2010; Oberman et al., 2011; Perera et al., 2016).

Similar to TMS, transcranial ACS can induce neuronal firing. The effects are spatially limited to the upper layer of the cortex, although influences on network oscillations are also possible (Abd Hamid et al., 2015). However, notably, in the transorbital ACS method, the current can stimulate neurons and axons along the visual pathway. As the eye is highly conductive due to the water-like vitreous, the current is guided to the retina - where the neurons are excited – and travels even into the brain through the optic nerve foramen. With this method the neuro-activating character of the stimulation can be demonstrated in human studies: when adjusting frequency and current intensity, subjects see phosphenes, a clear indication that retinal ganglion cells are firing (Foik et

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**Figure 1**

1591
Post-lesional plasticity

Protection

Plasticity

Glaucoma

Disease/chronic

Reorganization/reactivation

Cathodal

Rehabilitation

ticted cells. This may interrupt the excitotoxic

Learning

1592

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Technical parameters

Biological, medical parameters

Stimulation strength (voltage, field strength, amplitude)

Stimulation duration (one session)

Aim protection/rehabilitation

Behavioral training

NIBS: Before During After Without

Penumbra: Damaged area Remote, healthy areas

Target area of NIBS

Pathophysiological phase

Acute phase Intermediatphase Late phase

Trauma Stroke Glaucoma Vascular dementia M. Alzheimer M. Parkinson Depression

Acute damage Disease/chronic

NIBS for Acute Disease State

Not much is known from human studies about NIBS for acute treatment after brain insults. Patients in acute conditions are highly vulnerable and the risk of unwanted NIBS-side effects cannot be excluded, especially pertaining to the risks of post-lesion epilepsy. However, NIBS applied during the first hours and days post-injury was tested in animal studies (Ni et al., 2009; Morimoto et al., 2010, 2012; Henrich-Noack et al., 2013). Counterintuitively, stimulation protocols which are used for neuronal activation have resulted in neuroprotection. This is surprising as in general over-excitation is one main cause of neuronal death after an insult and adding even more stimulation input does not seem to be the right strategy in this situation. Yet, this kind of stimulation may have a dual beneficial influence: a vascular and a neuronal one. The interaction of NIBS with the vascular system needs to be studied in more detail; however, as underlying mechanism improved blood flow has been suggested (Kurimoto et al., 2010).

On the neuronal level of analysis, NIBS applied during the acute excitotoxic phase can lead to fast and complete dendritic stripping of neurons and result in input isolation from connected cells. This may interrupt the excitotoxic cascade and help cells survive (Henrich-Noack et al., 2017). Obviously, this rescue comes at a cost as the neurons will be

NIBS Treatment for Brain Lesions – Basic Concepts

As discussed above, the stimulation location and the stimulation method determine the effects of NIBS. For example, in studies on healthy volunteers, modifications of motor performance can be induced by applying electrodes or stimulating coils on the scalp over the motor cortex. However, in case of brain injury, the situation is more complex because different plasticity mechanisms can be involved and the location of cell death, the post-injury state and the time of treatment have to be considered.

Therefore a therapeutic approach needs to be defined before deciding on the proper location and parameter of electric stimulation. The three basic concepts to be considered for the treatment of diseases affecting the nervous system (including the retina) are: (i) acute protection; (ii) post-lesional reorganization and regeneration at an intermediate post-injury state; (iii) compensation and activation of residual function at a late, chronic stage (Figure 1).

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Figure 1 Concepts and categories of brain damage and diseases

(A) Temporal phases of brain pathphysiologies. (B) Categories of post-lesional interventions in neurology.

Figure 2 Flow chart for designing non-invasive electrical brain stimulation (NIBS) protocols

tDCS: Transcranial direct current stimulation; TMS: transcranial magnetic stimulation; ACS: alternating current stimulation.

Taken together, NIBS therapy and physiological studies of tDCS, TMS and ACS employ neuro-activating and de-activating protocols. Regarding the affected brain regions, usually specific cortical areas are influenced by NIBS, with the exception of transcorneal ACS which allows stimulation of the retina and even different other brain regions. It is also of importance that local changes induced by NIBS can affect global network oscillations. This applies mainly to NIBS methods where alternating current pulses of different frequencies play a role, i.e., in TMS and ACS. In addition to this modulation of local and global network excitability also other, long-term effects like induction of stem cells and growth factors may take place after NIBS (Corredor and Goldberg, 2009; Rueger et al., 2015; Gall et al., 2015, 2016).
disconnected and not functional. They seem to change into a mode of functional “silence”. However, survival of such stripped neurons might allow them to later reconnect or regenerate, opening the door for their re-activation. Only through future research may we find ways how such transiently silent survivors might be integrated back again into the brain’s functional connectivity network.

**Intermediate Disease State: Post-Lesional Plasticity and Cellular Regeneration by NIBS**

Spontaneous recovery by reorganization and neural regeneration, e.g., formation of new synapses, is possible to a limited extent only in a certain time-window after an incidence, i.e., within weeks after an insult (Caleo, 2015). Cells at risk which are typically located in the penumbra zone, i.e., the area surrounding an ischemic core, are endangered to either progress slowly towards delayed cell death or be inactivated. There are different means to help them survive, for example, by electric current stimulation protocols that lead to increased blood flow, induction of growth factors and growth associated proteins, induction of anti-apoptotic mechanisms or anti-inflammatory effects (Corredor and Goldberg, 2009). Besides neurons located inside or in the immediate vicinity of the damaged zone, neurons located in areas far remote from the damage may appear morphologically normal but can still become functionally inactive (“silent”). Here re-activation by LTP-inducing electrical stimulation (tetanization) is possible (Henrich-Noack et al., 2005). Therefore, it seems that for the treatment during an intermediate disease state, an activating NIBS protocol should be applied. Indeed, the work of Alber et al. (2017) demonstrated that anodal tDCS over visual cortex in early post-stroke when rehabilitation training is taking place improved the outcome to a greater extent than training alone.

**Facilitating Compensation at a Late, Chronic Stage**

Another concept of NIBS involves the restoration of function mainly by compensation and activation of residual structures. It can be applied even when the initial damage occurred long ago. At this stage the pathophysiological processes of degeneration and re-organization in lesioned areas are complete. Scars or cavitations have been formed where the damage occurred (Henrich-Noack et al., 2008) and cellular regeneration is not possible anymore. Therefore, any therapeutic effort should focus on activating remaining brain structures in other, remote areas or in the damaged area itself (“within-system-compensation”). Regarding the latter, NIBS can improve function of residual structures through synchronization of neuronal firing patterns and modulation of cortical excitability. The protocols to entrain cortical oscillations with a frequency range known to be associated with a certain function were suggested to treat functional loss. For example, it was demonstrated that stimulation in the alpha range (7.5–12.5 Hz) is beneficial for visual restoration (Sabel et al., 2011; Bola et al., 2014). Reduced inhibition of affected local networks can be achieved, for example, by cathodal tDCS stimulation in areas distant from the impaired brain structure (Brunoni et al., 2012; Gall et al., 2015). Moreover, NIBS can improve cell metabolism, oxygenation and glucose supply through increased blood flow in the affected areas (Kurimoto et al., 2010).

In addition, sensory functions other than those lost can be trained to facilitate cross-modal plasticity and compensate for lost abilities (“extra-system-compensation”; e.g., enhanced hearing after vision loss). This requires mechanisms of normal learning, like training to write with the left hand for right-handed people or learning to read Braille after vision loss (Bedny et al., 2015; Siuda-Krzywicka et al., 2016). In such cases it can be assumed that activating the compensating neuronal network area with electrical stimulation may be beneficial. In addition, anti-depressant effects or mood-improvements induced by NIBS may be an indirect mechanism whereby learning of compensatory skills is facilitated based on increased motivation during training (Dundon et al., 2015).

**Summary**

Different stages of brain damage and degeneration require adaptation of NIBS protocols depending on whether the aim is compensation, regeneration or protection (for a detailed overview of the relevant parameters see Figure 2). While significant knowledge has accumulated for intermediate and late diseases stages (Otal et al., 2016), the possible benefits and risks of NIBS for an acute treatment are not yet investigated much and await further research endeavors. In any event, we need to better understand the interaction of electric current in the human eye and brain and their interaction on the molecular, cellular and network level.

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**Comments to authors:** The article undergone to revision has demonstrated the intention to formulate a review of all scientific literature concerning the therapeutic possibilities to be implemented in different stages of brain damage and degeneration requires adaptation of NIBS protocols depending on whether the aim is compensation, regeneration or protection.

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