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Review

Plasticity induced by non-invasive transcranial brain stimulation: A position paper

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HIGHLIGHTS

- Non-invasive brain stimulation protocols induce variable plasticity-like after-effects in the human brain.
- Many factors produce variability; some are unavoidable; some can be controlled.
- EEG feedback, pulse shape modification and spaced protocols may enhance reliability.

ABSTRACT

Several techniques and protocols of non-invasive transcranial brain stimulation (NIBS), including transcranial magnetic and electrical stimuli, have been developed in the past decades. Non-invasive transcranial brain stimulation may modulate cortical excitability outlasting the period of non-invasive transcranial brain stimulation itself from several minutes to more than one hour. Quite a few lines of evidence, including pharmacological, physiological and behavioral studies in humans and animals, suggest that the effects of non-invasive transcranial brain stimulation are produced through effects on synaptic plasticity. However, there is still a need for more direct and conclusive evidence. The fragility and variability of the effects are the major challenges that non-invasive transcranial brain stimulation currently faces. A variety of factors, including biological variation, measurement reproducibility and the neuronal state of the stimulated area, which can be affected by factors such as past and present physical activity, may influence the response to non-invasive transcranial brain stimulation. Work is ongoing to test whether the reliability and consistency of non-invasive transcranial brain stimulation can be improved by controlling or monitoring neuronal state and by optimizing the protocol and timing of stimulation.

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Contents

1. Introduction

Transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS) are the most commonly used methods of non-invasive transcranial brain stimulation that has been abbreviated by previous authors as either as NIBS or NTBS. Here we use NIBS since it seems to be the most common term at the present time. When it was first introduced in 1985, TMS was employed primarily as a tool to investigate the integrity and function of the human corticospinal system (Barker et al., 1985). Single pulse stimulation was used to elicit motor evoked potentials (MEPs) that were easily evoked and measured in contralateral muscles (Rothwell et al., 1999). The robustness and repeatability of measures of conduction time, stimulation threshold and "hot spot" location allowed TMS to be developed into a standard tool in clinical neurophysiology.

As we review below, a number of NIBS protocols can lead to effects on brain excitability that outlast the period of stimulation. These may reflect basic synaptic mechanisms involving long-term potentiation (LTP)- or long-term depression (LTD)-like plasticity, and because of this there has been great interest in using the methods as therapeutic interventions in neurological and psychiatric diseases. Furthermore, recently they are more frequently applied to modify memory processes and to enhance cognitive function in healthy individuals. However, apart from success in treating some patients with depression (Lefaucheur et al., 2014; Padberg et al., 2002, 1999), there is little consensus that they have improved outcomes in a clinically meaningful fashion in any other conditions. The reason for this is probably linked to the reason why many other protocols failed to reach routine clinical neurophysiology: they are too variable both within and between individuals to make them practically useful in a health service setting (Goldsworthy et al., 2014; Hamada et al., 2013; Lopez-Alonso et al., 2014, 2015).

Below we review the evidence for the mechanisms underlying the "neuroplastic" effects of NIBS, and then consider the problems in reproducibility and offer some potential ways forward in research.

2. Effects of non-invasive brain stimulation

2.1. Repetitive transcranial magnetic stimulation (rTMS)

Traditionally, rTMS is given at a regular frequency. In general, low-frequency (1 Hz or less) rTMS decreases cortical excitability (Chen et al., 1997), whereas high-frequency (5 Hz or greater) rTMS increases cortical excitability (Berardelli et al., 1998; Fitzgerald et al., 2006; Maeda et al., 2000; Pascual-Leone et al., 1994). But this simplistic view has been challenged by findings that continuous 5 Hz rTMS, without the usual inter-train intervals that are often employed with this protocol, decreases rather than increases corticospinal excitability (Rothkegel et al., 2010).

More recently, patterned rTMS, e.g. theta burst stimulation (TBS) and quadripulse TMS (QPS) have been developed with the aim of achieving a more reliable effect than conventional rTMS (Hamada et al., 2008; Huang et al., 2005; Suppa et al., 2016). Continuous TBS (cTBS), which takes only 20 or 40 s to apply, decreases cortical excitability, while intermittent TBS (iTBS; total duration 3 min) facilitates cortical excitability. QPS with a short interstimulus interval (e.g. 5 ms) between the pulses in the 4-pulse burst facilitates MEPs, while longer interstimulus intervals (e.g. 50 ms) suppress MEPs (Hamada et al., 2008). Finally, repetitive paired-pulse TMS with an ISI of 1.5 ms may enhance excitability (Thickbroom et al., 2006).

Paired associative stimulation (PAS) was frist developed by employing low frequency repeated pairing of electrical stimulation of the median nerve and TMS over contralateral M1 in order to change the excitability of M1 (Stefan et al., 2000; Wolters et al., 2003). Corticospinal excitability is increased when the interval between the peripheral stimulus and TMS is equal or a few milliseconds longer than the individual latency of the N20 component of the median nerve somatosensory-evoked potential. In contrast, PAS suppresses excitability when the interval is shorter than the N20 latency (for a review see Muller-Dahlhaus et al., 2010; Ziemann et al., 2004). Later on, this conventional PAS protocol has been supplemented by similar protocols in which the primary motor cortex (M1) TMS pulse is preceded by another type of input, another TMS applied over a remote but interconnected cortical area or even stimulation of subcortical structures from deep brain stimulation (Arai et al., 2011; Buch et al., 2011; Chao et al., 2015; Koganemaru et al., 2009; Lu et al., 2012; Rizzo et al., 2009; Suppa et al., 2013, 2015; Udupa et al., 2016).

2.2. Transcranial electrical stimulation (TES)

The most frequently used transcranial electric stimulation (TES) methods in research and clinical practice are tDCS, transcranial alternating current (tACS) and random noise stimulation (tRNS) (Paulus, 2011). The after-effect of tDCS is thought to modulate cor-

tical excitability in a polarity-specific manner (Nitsche et al., 2008). Stimulation of M1 with an anode positioned over M1 hand area is usually reported to increase MEP size, while cathodal tDCS has the opposite effect (Nitsche and Paulus, 2000). The duration, strength and direction of the effects also depend on the duration, polarity and intensity of tDCS. tDCS application of durations between 5 and 20 min using 1 mA (electrode size 35 cm^2) anodal stimulation increases MEP size while cathodal tDCS with these stimulation parameters reduces MEP amplitude (Nitsche et al., 2003b; Nitsche and Paulus, 2001). Further prolongation of duration or increasing intensity can reverse the after-effects (Batsikadze et al., 2013; Monte-Silva et al., 2013). Effects of tDCS have not only been documented for the motor cortex, but also for other areas such as visual and somatosensory cortices, although the timing and duration of the effects might vary (Antal et al., 2004a, 2004b; Matsunaga et al., 2004).

The effect of tACS, which applies alternating current at a predetermined certain frequency, is generally considered due to brain wave entrainment. Indeed, if tACS is applied in brain slice models at a frequency very close to the frequency of the intrinsic oscillation, even very low-intensity currents can influence the phase and frequency of discharges in the brain slice models (Frohlich, 2015; Frohlich and McCormick, 2010). In humans it may be that tACS entrainment could also lead to a frequency-specific power enhancement as well as to frequency-specific phase realignment of endogenous brain oscillations (Alekseichuk et al., 2016; Merlet et al., 2013; Vosskuhl et al., 2015). Furthermore, certain frequencies can interact with each other during cognitive processes (cross-frequency coupling) (Jensen and Colgin, 2007).

During tRNS a low intensity biphasic AC is applied where intensity and frequency of the current vary in a randomized manner. Studies are usually divided into those that use a frequency spectrum between 0.1 Hz and 640 Hz (full spectrum) or 101–640 Hz (high frequency stimulation) (Fertonani et al., 2011; Terney et al., 2008). tRNS over M1 had an effect comparable to anodal tDCS, enhancing MEP size (Chaieb et al., 2011; Moliadze et al., 2012, 2014; Terney et al., 2008). With regard to stimulation of other cortical areas in perceptual, learning and memory tasks, mixed results have been reported (Antal and Herrmann, 2016).

2.3. The direction of effects of NIBS

It should be reminded that most of the effects of NIBS were measured using the change in MEPs as a readout when NIBS was applied to M1. MEPs are variable and affected by inhibitory and facilitatory circuits within and outside the motor cortex. Intramotor cortical circuits that affect MEPs can be tested with paired pulse techniques that give two pulses of TMS to the same M1 at a certain interval. The first conditioning pulse activates the intracortical inhibitory or facilitatory circuits to inhibit or faciltate the MEP evoked by the second pulse through short- (SICI) or long-interval intracortical inhibition (LICI) or intracortical facilitation (ICF) (Chen et al., 1998; Udupa et al., 2009; Ziemann, 1999). These intracortical circuits may not always respond to NIBS in the same direction as the size of MEPs. For instance, SICI was reduced by a 5 Hz rTMS protocol that enhanced MEPs (Di Lazzaro et al., 2002, 2010; Peinemann et al., 2000; Quartarone et al., 2005; Wu et al., 2000), while cTBS modified SICI and ICF in parallel with the changes in MEPs (Huang et al., 2005). Furthermore, a recent study showed that different cortical interneuronal populations are differentially modulated by the phase and frequency of tACS-imposed oscillations and spontaneous brain beta activity (Guerra et al., 2016). Even when only one circuit is targeted, a NIBS protocol may also produce a mixture of inhibitory and faciliatory effects, and the measured effect is the net-effect of both (Huang et al., 2011a). Hence, it should be noted that the direction of the effect of a NIBS protocol may not always be predictable. When a NIBS protocol is applied to different areas for different purposes, the effect of the protocol may be different and depend on which neuronal subpopulation is preferentially targeted and measured.

Moreover, MEPs are influenced not only by intracortical circuits, but also intercortical connections. It has been demonstrated that the size of MEP can be modified through the connections from areas outside M1 (Huang et al., 2009; Koch et al., 2007). NIBS to the premotor cortex may modulate plasticity in M1 (Boros et al., 2008; Huang et al., 2012), and, in contrast, QPS over M1 or the premotor cortex modulates the central component of sensory evoked potentials (Nakatani-Enomoto et al., 2012). Functional imaging studies further conform the intercortical effects. NIBS over M1 may remotely affect other brain areas (Groiss et al., 2013; Siebner et al., 2000). Furthermore, stronger connectivity between motor areas in the active state indicated a better iTBS-induced facilitation on MEPs (Cardenas-Morales et al., 2014), while stronger baseline resting-state functional connectivity between the stimulated M1 and premotor areas was found in non-responders to iTBS as compared to responders (Nettekoven et al., 2015). However, resting-state connectivity did not predict the response in MEPs in both studies. Therefore, the influences of inter-cortical connections on NIBS should also be considered. However, the inter-cortical influence has never been systemically studied. In the present review, only intracortical effects will be discussed.

3. Plasticity and NIBS

3.1. Evidence of plasticity after rTMS

Physiological phenomena induced by NIBS have generated interest because they have been mapped onto cellular physiological mechanisms such as synaptic long-term potentiation or long-term depression. It is clear that this similarity has its limitations, but more direct verification of physiological mechanisms by animal studies is still lacking.

Pharmacological properties of MEP amplitude changes are similar to those established for LTP or LTD of glutamatergic synapses in animal work. The magnitude, and perhaps the speed, of postsynaptic Ca2+ surge may decide whether a glutamatergic synapse is potentiated, depressed, or left unchanged by neuronal activity (Lisman, 1989). Experimentally, participation of N-methyl-D-aspartate (NMDA)-receptor activation and Ca2+-channels have been shown in TBS-induced plasticity (Huang et al., 2007) and PAS-induced plasticity (Stefan et al., 2002; Wolters et al., 2003). However, plasticity induced by PAS and cTBS300 are modulated differently by different voltage-gated Ca2+-channels perhaps pointing to an important role of backpropagating action potentials involving spike-timing dependent plasticity (STDP) in PAS and to a requirement of dendritic Ca2+-dependent spikes required for tetanic stimulation-induced plasticity in TBS (Weise et al., 2016). Zonisamide, a blocker of T-type calcium channels enabled QPS-induced plasticity in subjects previously not responding to the protocol (Tanaka et al., 2015). Since Zonisamide also has a multitude of other pharmacological effects, the significance of this finding is not clear.

An important property of plasticity of several glutamatergic synapses is the dependency on the timing of the pre-and postsynaptic events, which has been called STDP principle. PAS also follows the STDP principle. When the interval between median nerve stimulation (MNS) and TMS is 25 ms (PAS25) or 21.5 ms (PAS21.5) the afferent signal evoked by MNS may arrive in M1 shortly before transsynaptic excitation of corticospinal neurons by the TMS pulse whereas a reverse sequence is implied with shorter intervals (Weise et al., 2013). Different physiological mechanisms underlie both excitability-enhancing PAS-variants. If

tDCS over the cerebellum is applied concurrently with PAS, then the effect of PAS25 is blocked, but not PAS21.5; PAS25 can be elicited more easily by low intensity anterior-posterior oriented TMS pulses than with posterior-anterior pulses, and vice versa for PAS21.5; and randomly intermixing PAS with 21.5 ms and 25 ms intervals abolishes any effect, even if each interval alone produces facilitation (Hamada et al., 2014, 2012; Kujirai et al., 2006). Temporal pattern also matters with QPS, but unlike PAS, QPS is capable of inducing a bidirectional response pattern independent of the timing of an afferent signal, the direction of changes being solely dependent on the interval between successive QPS bursts, or by the frequency with which QPS bursts are applied (Hamada et al., 2008; Nakamura et al., 2016). The non-linear stimulus–response function appears very similar to those obtained in animal studies (Dudek and Bear, 1992) in which a net LTD generation is changed to a net LTP generation as the stimulation frequency is increased. This behavior conforms to the non-linear function proposed by Bienenstock et al. for changing the threshold of synaptic plasticity as a function of the mean level of postsynaptic activity (Bienenstock et al., 1982).

Based on the finding of epidural recordings, the effects of rTMS are thought to be generated at different synaptic levels (Di Lazzaro et al., 2010). Epidural recordings of descending corticospinal activity evoked by TMS demonstrate PAS-induced changes of later descending volleys (Di Lazzaro et al., 2009a, 2009b), which reflect the activity of intracortical elements located in superficial cortical layers and presynaptic to the corticospinal output neuron (Di Lazzaro et al., 2004; Ziemann and Rothwell, 2000). Indeed, the effects of either excitatory or inhibitory PAS are abolished if the later I-waves of the TMS pulse are suppressed by applying a subthreshold conditioning pulse (i.e. as in SICI) during the protocol (Elahi et al., 2012; Weise et al., 2013). The conclusion is that the excitatory synapses undergoing LTD-like changes are not located on the corticospinal projection neuron, but on the dendritic tree of an excitatory interneuron involving I3 wave generation.

While NIBS-induced plasticity shares certain properties with plasticity of glutamatergic synapses, similarity must not be taken as identity and caution must be applied when comparing system-level findings with cellular mechanisms (Carson and Kennedy, 2013; Muller-Dahlhaus et al., 2010). In vitro studies in organotypic preparations revealed that repetitive magnetic stimulation (rMS) indeed induced a long-lasting increase in glutamatergic synaptic strength, which was accompanied by structural remodeling of dendritic spines (Lenz et al., 2016; Vlachos et al., 2012). Importantly, however, rMS also induced reduction in GABAergic strength at dendritic synapses, which was Ca2+-dependent and accompanied by the remodeling of postsynaptic gephyrin scaffolds (Lenz and Vlachos, 2016).

The interaction between the effect of NIBS protocols and learning is compatible with the common rules regulating synaptic plasticity, including metaplasticity, a term that describes how synaptic plasticity can be modulated by prior synaptic activity (Abraham and Bear, 1996) and plasticity reversal which describes the reversal of previously induced synaptic plasticity (for review, see Zhou and Poo, 2004). Experiments using priming stimulation by non-invasive brain stimulation had suggested that PAS-induced plasticity followed Bienenstock-Cooper-Munro (BCM) homeostatic metaplasticity rules (Bienenstock et al., 1982), i.e. reductions of corticospinal excitability by 1 protocol led to stronger effects of facilitatory PAS applied subsequently, and vice versa (Muller et al., 2007). Similar effects, resembling metaplasticity, were also found in QPS (Hamada et al., 2009, 2008), TBS (Murakami et al., 2012) and between different protocols (Ni et al., 2014; Siebner et al., 2004). Anodal tDCS-induced LTP-like plasticity effects could no longer be induced when applied after motor learning (Rosenkranz et al., 2007; Stefan et al., 2006; Ziemann et al., 2004). In addition, reversal of plasticity, i.e. depotentiation and de-depression, was confirmed in the human motor cortex using TBS (Huang et al., 2010). The depotentiation protocol applied right after motor learning reversed the aforementioned blockage of LTP-like plasticity and restored the ability of anodal tDCS to induce faciliatory effects, but disrupted retention of motor learning (Cantarero et al., 2013). Such interactions are in agreement with the notion that NIBS induces synaptic plasticity.

3.2. Evidence of plasticity after TES

Respective evidence summarized here comes mainly from tDCS studies. Similar to the aftereffects of other brain stimulation protocols, results of animal experiments suggest that aftereffects of tDCS are Ca2+- and NMDA receptor-dependent (Islam et al., 1995), (Monai et al., 2016), require brain-derived neurotrophic factor (Fritsch et al., 2010), and thus resemble to a certain extent mechanisms of LTP and LTD at glutamatergic synapses (Malenka and Bear, 2004).

These physiological mechanisms are also consistent with the aftereffects of tDCS in human experiments. Here blockage of NMDA receptors abolishes, while NMDA receptor agonists enhance tDCS aftereffects (Nitsche et al., 2003a, 2004). Since calcium flux through NMDARs is considered critical in synaptic plasticity, and calcium channel blockage abolishes LTP-like plasticity induced by anodal tDCS (Nitsche et al., 2003a), it can be assumed that tDCS-induced plasticity in humans is determined by intracellular calcium dynamics. Stimulation downregulation of GABA activity (Kim et al., 2014; Stagg et al., 2009) might furthermore have a gating effect on tDCS-induced plasticity.

Given the effects of tDCS, it seems possible that it interacts with cognitive processes which require LTP or LTD, e.g. learning and memory formation. Consistent with this idea, anodal tDCS which induces LTP-like plasticity in motor cortex, has been reported to improve motor learning (Antal et al., 2004a, 2004b; Nitsche et al., 2003c), although this has not been reproduced in all available studies (Ambrus et al., 2016; Ehsani et al., 2016). Importantly, repeated pairing over 5 days of tDCS and motor practice on a skill task improved offline consolidation of learning in the intervals between each trial day (Reis et al., 2009), and resulted in effects stable for at least three months after intervention. This type of effect has been shown to depend critically on intervention protocol characteristics, such as electrode position, and timing of stimulation. tDCS of primary motor cortex, but not premotor or prefrontal cortex improved performance during learning of the serial reaction time task, but premotor stimulation improved performance when applied during reconsolidation during REM sleep (Nitsche et al., 2003a, 2010). These studies thus suggest that stimulation of the critical area during the time it is involved in physiological processes relevant for learning and memory formation is critical. Learning-modulating effects of tDCS are not limited to the motor network, but extend also to other domains (for an overview see Shin et al., 2015).

With regard to plastic changes during or after tACS, there is only little evidence for the effects of tACS on brain plasticity. It is likely that tACS depolarizes and hyperpolarizes the neurons at its frequency and such neurons fire in response to other neurons when they are depolarized through a mechanism called stochastic resonance (McDonnell and Abbott, 2009). Such synergies with inputs close to the stimulation frequency might lead to lasting effects through spike-timing-dependent plasticity (Zaehle et al., 2010).

3.3. Does synaptic plasticity in the form of LTP/LTD underlie long-term NIBS effects?

As reviewed above, there is considerable evidence supporting the idea that the various NIBS protocols induce LTP/D-like

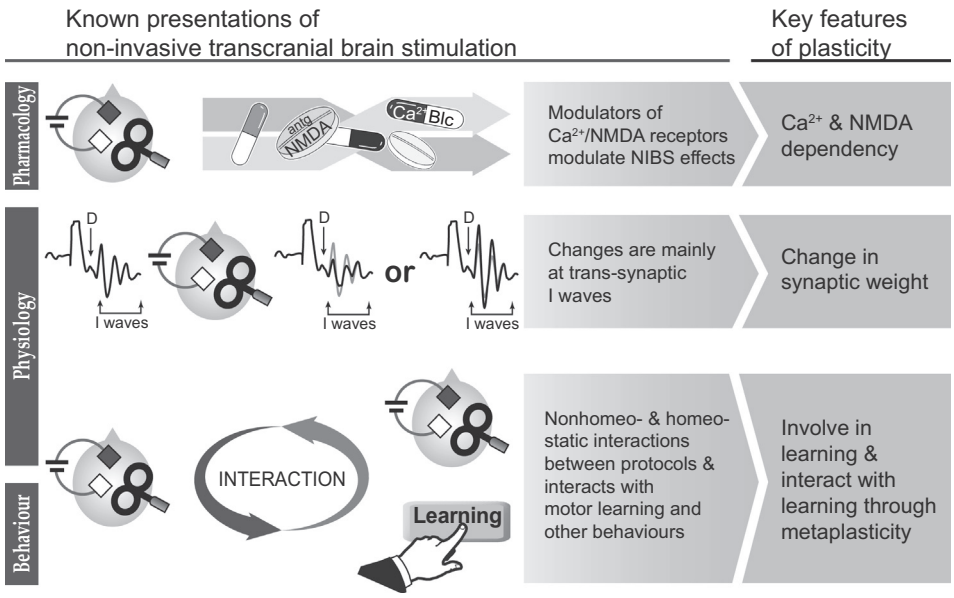

Fig. 1. There are three major lines of evidence supporting NIBS produces effects through mechanisms of synaptic plasticity: (1) Drugs that modulate the function of critical receptors/channels for plasticity, e.g. Ca2+ channels and NMDA receptors, alter the effect of NIBS; (2) NIBS mainly changes I-waves rather than the D-wave in the epidural recording of descending volleys evoked by TMS, suggesting the effect of NIBS occurs trans-synaptically; and (3) NIBS interacts between protocols and with motor practice and cognitive learning processes, suggesting the effect of NIBS is involves in plasticity-related motor and psychological processes.

plasticity in the human brain (Fig. 1), a position that has even been accepted by cellular physiologists (Cooke and Bliss, 2006). Of course, it is important to keep in mind that all of this evidence is indirect since it has been obtained at the systems level and, therefore, it remains to some extent uncertain whether the underlying mechanisms of NIBS effects in human studies are truly LTP/LTD. Thus, the question arises if there is any opportunity of getting more direct evidence. Obviously, the only way would be to record more directly from the brain, ideally from single cells, while applying TMS. One first important step towards this direction was the development of EEG amplifiers that allowed the recording of TMS-evoked EEG potentials (TEPs), i.e., responses directly from the brain (Ilmoniemi et al., 1997; Virtanen et al., 1999). Esser et al. (2006) demonstrated that 5 Hz rTMS of left motor cortex resulted in an amplitude increase in all TEP components within 15–55 ms peak latency, with a topographic source of this effect in bilateral premotor cortex. They argued that the use of EEG to assess brain responses to TMS rather than muscle output allows the direct demonstration of LTP induced by rTMS in the human cortex (Esser et al., 2006). A more appropriate conclusion might be that the TMS-EEG technique has great potential for a less indirect demonstration of LTP/LTD-like plasticity induced by NIBS in humans. The reliability of TEPs has been systematically assessed and is not inferior to MEP amplitude recordings (Casarotto et al., 2010). However, one important general limitation of the EEG is that it does not discriminate between excitatory and inhibitory activity. Another current limitation of TEPs is that the underlying physiology has only started to be explored, largely through pharmacological characterization (Darmani et al., 2016; Premoli et al., 2014; Ziemann et al., 2015). Therefore, the meaning of NIBS-induced changes in TEP amplitudes remains to be further uncovered. Despite this gap of knowledge, several other preliminary studies have demonstrated various NIBS effects on TEP amplitudes, including NIBS of non-motor brain areas (Pellicciari et al., 2013; Romero Lauro et al., 2014; Veniero et al., 2013; Vernet et al., 2013). A further step ahead is the recent demonstration of successful recording of single cell responses to TMS in the motor cortex of an awake monkey (Mueller et al., 2014). Due to the invasiveness of intracortical microelectrodes, this tool will be largely restricted to investigation of TMS effects in non-human primates or other animal models. Nevertheless, this technique may reveal in the near future, whether or not synaptic plasticity in the form of LTP/LTD is the underlying mechanism of the long-term NIBS effects on MEP or TEP amplitude. Finally, it has been demonstrated, using whole-cell patch-clamp recordings, immunohistochemistry, and time-lapse imaging that high-frequency 10 Hz repetitive magnetic stimulation of organotypic entorhino-hippocampal slice cultures induces a long-lasting increase in glutamatergic synaptic strength, accompanied by structural remodeling of dendritic spines (Lenz et al., 2015; Vlachos et al., 2012), and a long-lasting decrease in dendritic GABAergic synaptic strength, associated with remodeling of the GABAergic post-synapses (Lenz et al., 2016). Although these data have been obtained in an *in vitro* preparation, the authors argued that entorhino-hippocampal slice cultures represent a suitable complementary approach to NIBS studies in humans. While this might be true, further evidence is needed from neocortex rather than hippocampus, and from *in vivo* rather than *in vitro* preparations.

In contrast to the enduring LTP and LTD that are known to last for hours to days *in vivo* (Abraham and Williams, 2003; Huang et al., 1996), the changes induced by conventional NIBS protocols are relatively short in duration (approximately 30–120 min) and susceptible to disruption by voluntary motor activity (Goldsworthy et al., 2015; Huang et al., 2008; Todd et al., 2009) of the targeted motor cortex. The effect induced with conventional NIBS approaches is likely reminiscent of the labile early phase of LTP/LTD that is easily disrupted by behaviorally related (Xu et al., 1998), or induced (Chen et al., 2001) activity of the stimulated synapses. However, other distinct mechanisms, e.g. post-tetanic potentiation (PSP), short term potentiation (STP), may be also involved (Ugawa, 2012). Furthermore, a recent study found that the after-effects of tRNS seem to be independent from NMDA and dopamine receptors, which are critical for many forms of plasticity, suggesting at least some of the effects of NIBS are not generated through well-known plasticity mechanisms (Chaieb et al., 2015).

In summary, the evidence that plasticity is the underlying mechanism of long-term NIBS effects in humans is consistent with

experimental findings but still not definitely conclusive due to the circumstantial nature of the evidence that has been reported so far.

4. Fragility and variability of the effect of NIBS

4.1. Vulnerability to physical activities

The effects induced in the motor cortex by NIBS are vulnerable to voluntary muscle activity (Huang, 2016), particularly when the activity happens around the time of stimulation. Subtle contraction of the target muscle during TBS abolished the after-effect of TBS, while a 1-min contraction immediately after TBS reversed the depressant effect of cTBS into facilitation and enhanced the facilitatory effect of iTBS (Huang et al., 2008). Moreover, in the absence of prior tonic contraction, 20 s of cTBS failed to produce expected inhibition (Gentner et al., 2008). The nature of the contraction (i.e. tonic versus phasic) can also influence the after-effects of TBS (Iezzi et al., 2008). Similar interactions have been reported for tDCS. Tonic contraction during 10 min of tDCS reversed the facilitation of anodal tDCS to depression and enhanced the depression of cathodal tDCS (Antal et al., 2007), while tonic contraction immediately after tDCS tended to eliminate the aftereffects of both anodal and cathodal tDCS (Thirugnanasambandam et al., 2011). Finally, rhythmic hand opening-closing at 1 Hz for one minute after QPS abolished its effect on corticospinal excitability (Kadowaki et al., 2016). A similar influence of physical activity on TMS-induced effects was also found in areas other than motor cortex (Silvanto et al., 2007).

The vulnerability of NIBS effects by behavior may be explained by metaplasticity, i.e., neural activity at one point in time can change the ability of neurons or synapses to exhibit plasticity at a later time (Abraham, 2008). Indeed, a theoretical model built to explain the pattern-dependent effects of TBS successfully explained the influence of a short period of tonic contraction on the effects of TBS by adjusting the amount of calcium influx that is commonly involved in metaplasticity (Huang et al., 2011a). Reversal of plasticity, including de-potentiation and de-depression, may also interact with the effects of NIBS (Huang et al., 2011b, 2010; Zhou and Poo, 2004). In contrast to metaplasticity that modifies a synapse's response to plasticity induction, de-potentiation/de-depression erases recently produced LTP/LTD. This reversal of plasticity only occurs within a certain time window of a few minutes, after plasticity is induced. Thereafter, plasticity gradually becomes consolidated and difficult to change. Indeed, the effects of NIBS are more resistant to behavioral disturbance beyond this critical time window (Huang et al., 2008; Kadowaki et al., 2016).

This vulnerability of NIBS effects to physical activity indicates significant influence from the ongoing state of neuronal circuits within the stimulated area. Since neuronal activity is not always controllable in the conscious brain, the variable neuronal state may contribute to the known variability of NIBS effects (see below). However, looking in a more positive light, it may be possible to fine tune the amount and direction of the NIBS effects by controlling the neuronal state.

4.2. Variability of NIBS

Although it has been generally assumed that certain NIBS plasticity inducing protocols produce LTP- and LTD-like plasticity (see above; Quartarone et al., 2006) and increasing numbers of studies using NIBS protocols show promising results in fields from cognitive neuroscience to rehabilitation, a major issue is the existence of large inter- and intra-individual variability, with contradictory results often being reported in the literature.

Inter-individual variability had been already recognized in initial studies in small numbers of subjects (Maeda et al., 2000; Muller-Dahlhaus et al., 2008; Nitsche and Paulus, 2001). Nevertheless, such variability did not emerge as an important problem until subsequent studies using larger cohorts of healthy subjects confirmed that there is a considerable inter- and intra-individual variability in response to all NIBS protocols. Hamada et al. (2013) reported in 52 non-selected healthy participants that neither iTBS nor cTBS induced the expected LTP- or LTD-like plasticity, respectively, at the group level, and that "expected" effects were found in only about 50% of the individuals. Consistent with this, Wiethoff et al. (2014) (in 53 healthy participants) also reported that approximately 50% of the individuals had only a minor, or no response to anodal or cathodal tDCS, while the remainder had a facilitatory effect to both forms of stimulation. Lopez-Alonso et al. (2014) showed in 56 healthy volunteers that the expected increase of MEPs after anodal tDCS, iTBS, and PAS25 was only present in 45%, 43%, and 39% of subjects, respectively. Another study reported that the response rate of anodal tDCS was 42% in 54 healthy older adults (Puri et al., 2015). The combined dataset of 190 healthy subjects of nine PAS25 studies from 3 centers in Germany showed that the response rate (i.e. expected increase of MEP) was 53% (Lahr et al., 2016). Hinder et al. (2014), on the other hand, reported a "better" response rate of iTBS (about 73%) in 30 healthy subjects having been stimulated twice. Another study showed that 67% and 80% of subjects responded expectedly to anodal tDCS and PAS25 in 30 healthy participants (Strube et al., 2015). Thus, the probability of producing the "expected" response may be lower than 50%, at least as measured by effects on MEPs, in most NIBS plasticity-inducing protocols. Recent studies, using the newer QPS form of rTMS, classified subjects into three groups, i.e. expected responder, non-responder and opposite responder, based on the baseline variability in a sham condition may provide a better description of real variability (Nakamura et al., 2016; Simeoni et al., 2016). In these studies, the expected responder rate was 60% (Simeoni et al., 2016) or 80% (Nakamura et al., 2016) for QPS5. When the subjects were simply divided into responder and non-responder as that did in other protocols, the responder rate was higher (78% Simeoni et al., 2016 and 86% Nakamura et al., 2016) in QPS than in other protocols. However, head-to-head comparisons between QPS and other protocols are needed to confirm this result.

As regard to session-to-session, intra-individual variability, Lopez-Alonso et al. (2015) found that 69% of the tested 45 healthy subjects maintained their response pattern of anodal tDCS between sessions, and concluded that intra-individual variability is lower than inter-individual variability. Vallence et al. (2015) also reported a similar percentage of intra-individual variability in 18 subjects. Such inter- and intra-individual variability will severely hamper attempts to use NIBS for treatment of neurological or psychiatric disorders and, thus, the underlying reasons for these variability need urgently to be explored (Ziemann and Siebner, 2015).

4.3. Possible reasons of fragility and variability

Several determinants, including biological and methodological factors, have been identified to explain the variable effect of NIBS protocols (Fig. 2). Biological factors, such as age, gender, time of day, prior history of muscle activity (for M1 studies), lifestyle influences (e.g. physical activity patterns), genetics (Huang, 2016; Ridding and Ziemann, 2010), and variability in the response of neuronal circuits to TMS (Hamada et al., 2014, 2013; McCambridge et al., 2015; Wiethoff et al., 2014), may fundamentally contribute to the variation in response to NIBS (Nakamura et al., 2016). Age, gender, genetics and subjects' neurocircuits responding to TMS are in-born factors determining the response to a NIBS protocol and causing inter-individual variability, while time of day, lifestyle physical activity patterns, and prior history of muscle activity, may

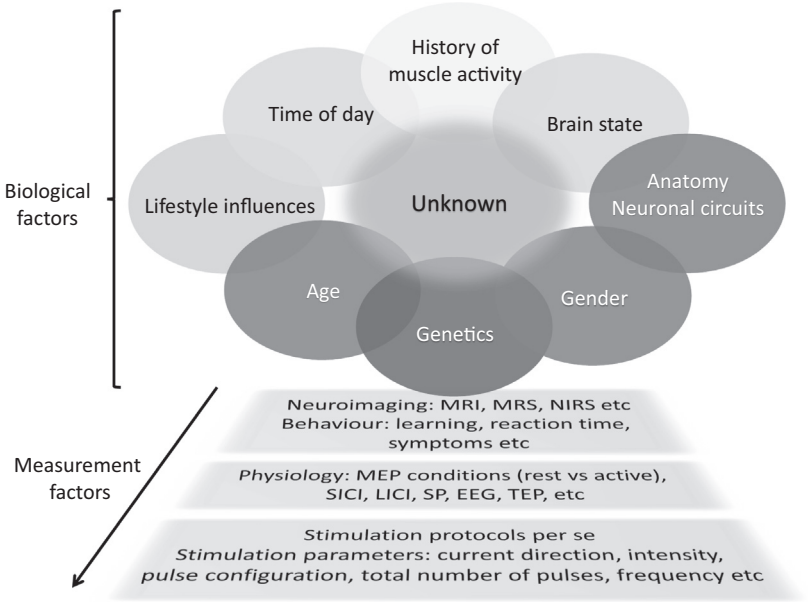

Fig. 2. Several biological and methodological factors may cause fragility and intra- and inter-individual variability of NIBS effects. Biological factors include age, gender, genetics, anatomy (neuronal circuits and/or gyrification), brain state, prior history of muscle activity, lifestyle influences, and time of day (circadian rhythm). The light gray circles indicate state factors which are modifiable, whereas the dark gray circles indicate trait factors, which may be controlled via an appropriate experimental design. Methodological factors include stimulation protocols and the methods for outcome measurements in physiology, neuroimaging and behavior.

influence subjects' response from session to session and contribute to both inter- and intra-individual variability.

Regarding methodological factors, the stimulation protocol per se and stimulation parameters, e.g. direction of induced current, pulse configuration, total number of pulses and stimulation frequency of rTMS, polarity and electrode location of TES, stimulus intensity, may not yet have been optimized. The measures for the effect induced by NIBS could also cause variability. For example, MEP is frequently used to measure the change in the motor cortical excitability induced by NIBS, since the MEP is a clear objective immediate readout evoked by TMS. However, the MEP itself is variable and affected by the physical condition, e.g. rest vs. active state of the muscle, and other inhibitory and excitatory circuits (Pascual-Leone et al., 2002).

NIBS effects are usually measured by recording changes in the MEP amplitude in a relaxed muscle. Several descending volleys contribute to MEP generation in relaxed muscles (Day et al., 1987; Nakamura et al., 2016). A variety factors, e.g. the excitability of cortical synapses, corticospinal axons, spinal synapses, motoneurons, neuromuscular junctions and muscles, may affect MEP size. NIBS may work differently on different circuits for MEP generation. Hence the effects on MEPs may be difficult to predict and become fragile and variable. Moreover, it is important to bear in mind that NIBS has been applied to modulate a number of physiological and behavioral readouts. The direction of change in these readouts does not need to correspond to the direction of change in MEP size.

Factors that might contribute to fragility and variability of NIBS are particularly important when applying NIBS in patients with neurological disorders. Over the last two decades, a growing number of authors have investigated M1 plasticity induced by NIBS protocols in patients with various neurological diseases including movement disorders and stroke. Such an experimental approach followed the hypothesis that possible changes in the amount of LTP/LTD in M1 contribute to the pathophysiology of specific neurologic symptoms. Although a detailed discussion of these TMS findings is beyond the scope of the present review, it should be considered that the investigation of plasticity processes in patients with neurological diseases offers a rather complex scenario. Non-specific pathological brain changes (i.e. brain atrophy) or specific neurodegenerative processes (i.e. dopaminergic denervation in Parkinson's disease – PD) may act as additional factors leading to increased inter-individual and intra-individual variability compared to healthy subjects. A possible example comes from studies investigating responses to various NIBS protocols in patients with PD in whom the specific response to NIBS is now known to reflect also the stage of the disease and the specific pharmacological treatment of the patients studied (i.e. total L-Dopa daily dose) (for a review see Suppa et al., 2017).

4.4. Available solutions for fragility and variability

It would be ideal if the biological factors which influence the response to NIBS were known and even could be measured before a NIBS experiment, and then, it would be useful to control these factors as closely as possible. Although it is not always easy to control the neuronal state, one simple thing that could be done to reduce variability would be monitoring physical activity. At least for effects of motor area stimulation, voluntary motor activity around the period of stimulation may critically influence the after-effects of NIBS. It has been argued that activation of neurons may render both magnetic and electric transcranial stimulation less effective by opening ion channels with a concomitant leaky membrane (Paulus and Rothwell, 2016). In general, keeping the subject alert but relaxed is likely to reduce variation in outcome. Similarly, if physical activity is required after NIBS, it is recommended to allow time for the induced effect to be consolidated, while bearing in mind the fact that the time required for consolidation may itself vary between protocols. However, there are occasions when movement can be used to refine or adjust the effect of NIBS for specific purposes. For instance, subtle voluntary contraction of the muscle antagonist to the target muscle during cTBS can be used to enhance the inhibitory effect on the target muscle (Fang et al., 2014), while a short subtle voluntary contraction of the target muscle immediately after cTBS may reverse the effect to facilitation (Huang et al., 2008). In order to avoid possible metaplastic effects, activity before the stimulation should be controlled. Thus, the consistency of response to cTBS is increased significantly by controlling motor activity prior to the NIBS intervention (Goldsworthy et al., 2014). Sometimes, activity prior

stimulation is beneficial for a demanded effect. For example, prior contraction for a certain period of time is critical for a shorter version of cTBS to produce reliable inhibition (Gentner et al., 2008). Moreover, a recent study showed that a cognitive task modulating frontal theta wave activity augmented the antidepressant effect of rTMS (Li et al., 2016), whereas anodal and cathodal tDCS aftereffects may collapse when tDCS is applied during mental challenge (Antal et al., 2007). Many factors that contribute to the variability of plasticity-inducing NIBS effects, such as age, gender and genetic polymorphisms, cannot be changed and it would be helpful to control for them through the experimental design (Hanajima et al., 2017).

Another strategy is to monitor the rapidly changing states of neuronal activity within the stimulated neuronal network, for instance by monitoring these states in real-time using EEG, and then triggering TMS pulses only at pre-defined states of, e.g., high or low network excitability (Zrenner et al., 2016). However, while this closed-loop approach is founded on convincing evidence in rat hippocampal slice preparations (Huerta and Lisman, 1993, 1995), there is only one published study on NIBS induced plasticity that suggests that similar effects may occur in humans (Goldsworthy et al., 2016).

Another strategy is to try to increase the specificity of stimulation. It would be ideal if a NIBS protocol could specifically target the neural circuits that participate in a given behavior or readout. In this instance, a test TMS pulse in the same direction as that used in the plasticity induction protocol may be helpful (Nakamura et al., 2016). MEPs, which are commonly used to measure the effect of NIBS, are usually evoked by monophasic TMS pulses. rTMS delivered with monophasic pulses might have a clearer effect on MEPs by matching the activated pathways of intervention and measurement. Moreover, a monophasic TMS pulse, particularly at low intensity, activates descending volleys more selectively (Hanajima et al., 1998). The selective activation could reduce contamination from different circuits and make monophasic TMS pulses superior to biphasic pulses for plasticity induction. This concept of the superiority of monophasic stimulation was recently used to introduce the new QPS protocol (Hamada et al., 2008) and recently developed cTMS (controllable TMS) has made monophasic rTMS possible at higher frequencies (Peterchev et al., 2010).

The importance of achieving greater selectivity by reducing stimulus intensity and using monophasic pulses is illustrated by past work on SICI (Hanajima et al., 2003, 2011, 1998). These authors found that the true time course of SICI was only revealed when they examined SICI in an active, rather than relaxed target muscle. In this case the test MEP was evoked by a small stimulus that preferentially recruited late I-waves. The advantage was that it prevented contamination of SICI by ICF, and thus showed that SICI lasted up to 20 ms instead of the usual 5 ms observed in the usual test protocol. In fact, since later descending volleys are more affected by NIBSs than earlier descending volleys (Di Lazzaro et al., 2010), it may be better to test and induce NIBS effects using TMS pulses that selectively activate these neurons, such as posteriorly directed pulses of low intensity.

In animal models the induction of enduring, late-phase plasticity requires the application of multiple induction trains in a spaced manner (inter-train intervals of typically 5–15 min). This type of induction contrasts with the approach typically used in NIBS studies where protocols are applied only once, or once per day for a number of consecutive days. Therefore, it may be possible to improve the reproducibility of NIBS effects using spaced application. There is emerging neurophysiological and behavioral evidence that such an approach might be very useful. Nyffeler and colleagues (Nyffeler et al., 2006) were the first to use spaced NIBS protocols in human studies and reported that, when applied to the cortical frontal eye field region, two spaced (10 min interval) cTBS trains increased saccadic eye movement latency for a significantly longer period than a single cTBS protocol. This effect could be extended further by increasing the number of cTBS trains applied, with 4 trains (inter-train intervals of 15, 45, 15 min) increasing saccade latency for approximately 10 h (Nyffeler et al., 2006). Using a similar approach there is convincing evidence that the symptoms of visual neglect following stroke can be improved when spaced stimulation is directed to the parietal cortex contralateral to the stroke (Nyffeler et al., 2009). In the motor system, two cTBS protocols separated by 10 min reduced corticospinal excitability for significantly longer that a single cTBS protocol (Goldsworthy et al., 2012). Additionally, this plastic change was resilient to disruption by both, behaviorally related and TMS-induced activity in the target cortical region (Goldsworthy et al., 2015). iTBS separated by 15 min also showed similar dose-dependent effects on the motor cortical excitability and resting-state connectivity (Nettekoven et al., 2014)

Similar results have been reported with tDCS where the spaced application of both anodal and cathodal tDCS can result in cortical excitability changes that outlast those seen after a single tDCS protocol (Fricke et al., 2011; Monte-Silva et al., 2013; Bastani and Jaberzadeh, 2014). These studies showed that optimal effects on the duration of the aftereffects occurs only if the second tDCS application is given while the effect of the first tDCS application is still present. However, considering metaplasticity and the BCM theory, the parameters of repeated spaced stimulation, e.g. the time interval, require further investigation (Karabanov et al., 2015; Muller-Dahlhaus and Ziemann, 2015). Moreover, it is still unclear if spaced stimulation within time scales of minutes shares similar mechanisms with daily repetitions of stimulation such as are employed regularly in therapeutic studies.

The question of whether extending train duration is beneficial for plasticity induction is complex. However, it has been shown that this approach may have limitations. For example, simply extending the train duration with several forms of NIBS including TBS (Gamboa et al., 2010; Gentner et al., 2008) and tDCS (Monte-Silva et al., 2013) can reverse the direction of the induced plasticity or abolish the effects (Hamada et al., 2008; Nakamura et al., 2016). Similarly, increasing intensity does not necessarily increase the response but may even reverse depression into facilitation (Batsikadze et al., 2013). There is some limited evidence that increasing the number of stimulation sessions might provide some additional gain (Fregni et al., 2006; Huang et al., 2012; Reis et al., 2009). However, other reports suggest that the gains might be minimal (O'Connell et al., 2011). Interestingly, the design and efficacy of "maintenance" stimulation sessions in clinical populations has received little systematic study.

In summary, the spaced application of multiple NIBS protocols within a session might provide significant opportunities to improve the reliability and extend the duration of NIBS effects. However, there are still significant challenges ahead to identify the optimum spacing between stimulation sessions (which may vary among different forms of NIBS). Additionally, for therapeutic utility, how best to extend these changes with multi-session stimulation requires much further study. Such studies are time consuming to conduct but will provide information critical to harness the potential of NIBS in both research and clinical settings.

5. Prospect and conclusion

Several lines of evidence suggest that the after-effects of NIBS are induced through mechanisms of synaptic plasticity, although more direct evidence is still required. A number of factors are known to be responsible for the variability of after-effects of NIBS. By controlling known biological factors, e.g. physical activity, gender, age and genetics, more reliable and predictable effects may be

possible. Several methodological issues have been raised and require further corroboration. Breakthroughs in the technique are needed. Indeed, optimization of desired plasticity inducing protocols will remain not easy. A multidimensional parameter space needs to be mapped onto the individual brain to be targeted. First, physics needs to be addressed by advanced computational modeling of induced electrical fields, taking into account bone thickness with local thinnings, CSF volume, and gyral folding of the individual brain (Laakso et al., 2014; Opitz et al., 2015). Current flow direction in relation to cortex folding plays a crucial role, best investigated for TMS of the motor cortex, much less in other cortical areas and even less for TES. Fortunately, different plasticity inducing NIBS protocols exist that may allow a better targeting of intended aftereffects. However, this comes with a level of complexity in particular when NIBS protocols being combined that still leads to not well understood and sometimes apparently even paradoxical effects. State-dependency may be the most difficult to be controlled factor for obtaining reproducible results. Many seemingly well-established concepts, such as anodal tDCS over the motor cortex equals excitation and cathodal tDCS equals inhibition collapse or even reverse when being investigated during activity or under physical or mental challenge (Antal et al., 2007) or when the stimulation intensity and duration are increased (Batsikadze et al., 2013; Monte-Silva et al., 2013). Hence, controlled physical activity around the period of intervention should be a priority for achieving reproducible effects. Recently developed EEG-based closed loop TMS may be helpful for monitoring the neuronal state for rTMS intervention (Zrenner et al., 2016). Moreover, training tasks for specific brain state enhancement may provide future breakthrough in state-dependent issues (Li et al., 2016). Pharmacological neuromodulation by varying dopamine, noradrenaline, acetylcholine or serotonin neurotransmitters induces similar alterations in NIBS induced plasticity. Another major challenge will be to improve our understanding of the role of spacing in repeatedly applied NIBS protocols and integrate this knowledge in a general concept allowing for optimized outcome of NIBS aftereffects. This will be particularly important for improving the so far limited effect sizes of NIBS protocols for treatment of neurological or psychiatric disorders (Lefaucheur et al., 2014, 2017).

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Conflict of interest statement

Michael Nitsche is in the advisory board of Neuroelectrics.

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