Review

Noninvasive Brain Stimulation: Multiple Effects on Cognition

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Abstract

Noninvasive brain stimulation (NIBS) techniques are widely used tools for the study and rehabilitation of cognitive functions. Different NIBS approaches aim to enhance or impair different cognitive processes. The methodological focus for achieving this has been on stimulation protocols that are considered either inhibitory or facilitatory. However, despite more than three decades of use, their application is based on incomplete and overly simplistic conceptualizations of mechanisms of action. Such misconception limits the usefulness of these approaches in the basic science and clinical domains. In this review, we challenge this view by arguing that stimulation protocols themselves are neither inhibitory nor facilitatory. Instead, we suggest that all induced effects reflect complex interactions of internal and external factors. Given these considerations, we present a novel model in which we conceptualize NIBS effects as an interaction between brain activity and the characteristics of the external stimulus. This interactive model can explain various phenomena in the brain stimulation literature that have been considered unexpected or paradoxical. We argue that these effects no longer seem paradoxical when considered from the viewpoint of state dependency.

Keywords

transcranial magnetic stimulation, transcranial electrical stimulation, brain state, virtual lesion, inhibition, facilitation

Introduction

Across the last decades, noninvasive brain stimulation (NIBS) has become an increasingly popular tool to modulate motor and behavioral function in basic and clinical research. NIBS protocols can be used to disrupt or facilitate processing and enable the researcher to probe the causal relevance of specific brain regions for a given task. When applied in a plasticity-inducing fashion, stimulation effects may outlast the stimulation duration, which is particularly interesting for learning and training interventions. Common NIBS approaches include transcranial magnetic stimulation (TMS) and transcranial electrical stimulation, with the latter summarizing transcranial direct current stimulation (tDCS), transcranial alternating current stimulation (tACS), and transcranial random noise stimulation. Box 1 summarizes the basic principles of common NIBS approaches. Crucial for the present review, NIBS protocols can be applied concurrently with a task ("online") or separated in time ("offline"). Online protocols are particularly suited to provide causal structure-function relationships (Walsh and Cowey 2000) because such protocols directly modulate ongoing task processing. Unlike studies in patients with brain lesions, the acute transient effect of online stimulation leaves the brain no time for functional reorganization and is thus not confounded by chronic processes of functional recovery. In contrast to such direct interference, offline protocols are usually given before a task to modulate activity in the targeted area for a longer time, outlasting the stimulation duration for up to 1 h (Chung and others 2016). In some cases, offline stimulation may also be given after a task—for example, to modulate consolidation processes in learning paradigms.

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Box 1. Basic Principles of Different Noninvasive Brain Stimulation Approaches.

Transcranial magnetic stimulation (TMS) is based on the principle of electromagnetic induction. A brief electric current produces a strong time-varying magnetic field in the TMS coil, which penetrates the scalp without attenuation and induces a flow of electric current in the stimulated tissue (Hallett 2000). TMS pulses thereby cause electro-magneto-electric stimulation of neuronal axons, particularly in superficial regions of the cortex that can temporarily excite or inhibit the stimulated area. When applied over the primary motor cortex, TMS can depolarize corticospinal tract neurons and evoke contralateral hand muscle movements. The size of such motor-evoked potentials reflects the excitability of the corticospinal system. TMS protocols range from the application of single or double pulses to short or long bursts of repetitive TMS with different frequencies. Importantly, the induced electric field of a TMS pulse has a short duration in the range of hundreds of microseconds (see Salvador and others 2015) and decreases rapidly with increasing distance from the coil. Hence, only a few regions on the cortical surface can be directly stimulated with TMS while deep brain structures might only be indirectly targeted. The induced electric field dose mediates the physiologic effects of all noninvasive brain stimulation protocols. Yet, no direct in vivo measurements of the induced electrical field in the human brain are possible. Therefore, biophysical modeling and simulation studies are used to estimate the spatial stimulation patterns induced by different noninvasive brain stimulation protocols (e.g., Neggers and others 2015; Saturnino, Thielscher, and others 2019). During TMS, induced electric fields around 100 V/m are thought to induce suprathreshold polarizations at bends and terminations of neurons in the cortex, provided that they are correctly aligned with the applied electric field (see Opitz and others 2015; Salvador and others 2015).

With respect to the strength of the induced stimulation effects, electric field simulations show that numerous factors influence the current flow in the brain, including individual tissue resistivity and cerebrospinal fluid, gyral shapes and gray matter boundaries, as well as electric field direction and magnitude (e.g., Bungert and others 2017). Aside from the strong interindividual variability in the induced electric field strength, there is variability among different cortical sites, which is usually ignored if the stimulation intensity is calibrated to the individual resting motor threshold. For example, stimulation at 100% resting motor threshold has been demonstrated to induce considerably higher electrical field strengths in the primary motor cortex when compared with the dorsolateral prefrontal cortex in the same set of participants (Caulfield and others 2021b), arguing for the need to adjust and personalize electric field dosing depending on the targeted area.

Transcranial direct current stimulation (tDCS) relies on the continuous application of weak direct electrical currents of 1 to 2 mA to the scalp via two or more surface electrodes for usually up to 20 to 30 min (Kuo and Nitsche 2012). The induced electric field of transcranial electrical stimulation in the cortex is typically <1 V/m in strength (e.g., Laakso and others 2015; Opitz and others 2016) and thus considerably lower than for TMS. Electric field simulation studies show strong variability for individualized tDCS doses, with a range of 3.75 to 9.70 mA being necessary to produce 1 V/m (Caulfield and others 2021a). Unlike TMS, the long-lasting low-intensity currents applied during tDCS bring about subthreshold membrane polarizations of the cellular body of pyramidal neurons in the cortex, which cause synaptic plasticity changes (Nitsche and others 2003; Salvador and others 2015). Specifically, surface-anodal polarization of the cortex with the anode near the dendritic poles of radially oriented neurons is thought to increase the firing rates of spontaneously active cells, while cathodal polarization should have the opposite effect. A common assumption is that anodal tDCS increases the overall activity in a brain region while cathodal tDCS decreases it, which should map onto the respective behavioral consequences (improvement vs. disruption) (Krause and others 2013). tDCS does not cause spontaneous firing but is thought to primarily work via passive changes in the resting membrane potential. Modeling studies indicate that a large area under the electrode is polarized (Miranda and others 2006) and functional effects engage distant neural networks (Nitsche and others 2005).

In contrast to tDCS, transcranial alternating current stimulation (tACS) and transcranial random noise stimulation (tRNS) are presumed to modulate oscillations of cortical networks in a frequency-specific (tACS) or random (tRNS) manner (Vosskuhl and others 2018). The ability to modulate cortical oscillations may provide a causal link between oscillatory activity and specific cognitive processes. tACS is usually applied with sinusoidal currents, but the waveforms can be customized. Depending on the applied frequency, tACS can synchronize or desynchronize cortical oscillations and induce plastic effects in the stimulated areas. Most studies apply tACS at fixed frequencies. Intermittent closed-loop applications have recently been introduced, which continuously match the stimulation frequency to the prevalent individual peak frequency of a specific frequency band (e.g., individual alpha) obtained from electroencephalography recordings (Stecher and others 2021). However, first results from these authors suggest that fixed intensities may be more effective to produce persistent synaptic changes, and the efficacy of such individualized closed-loop approaches remains to be determined. Other promising approaches include the combination of multiple frequencies via cross-frequency tACS (e.g., Alekseichuk and others 2016; Riddle and others 2021), which can be used to mimic endogenous phase-amplitude coupling activity patterns (see Riddle and others 2021). Such protocols allow us to probe the causal relevance of cross-frequency coupling, which has been linked to various cognitive processes, such as cognitive control and working memory.

Unlike tACS, tRNS is applied with a broad-frequency spectrum (0.1–640 Hz) and a random noise distribution to cover physiologic brain oscillations. At the physiologic level, it is assumed that tRNS may induce cortical plasticity by augmenting the activity of neuronal sodium channels in the stimulated parts of the brain (Kuo and Nitsche 2012).

For an illustration of each approach, see Figure 1.

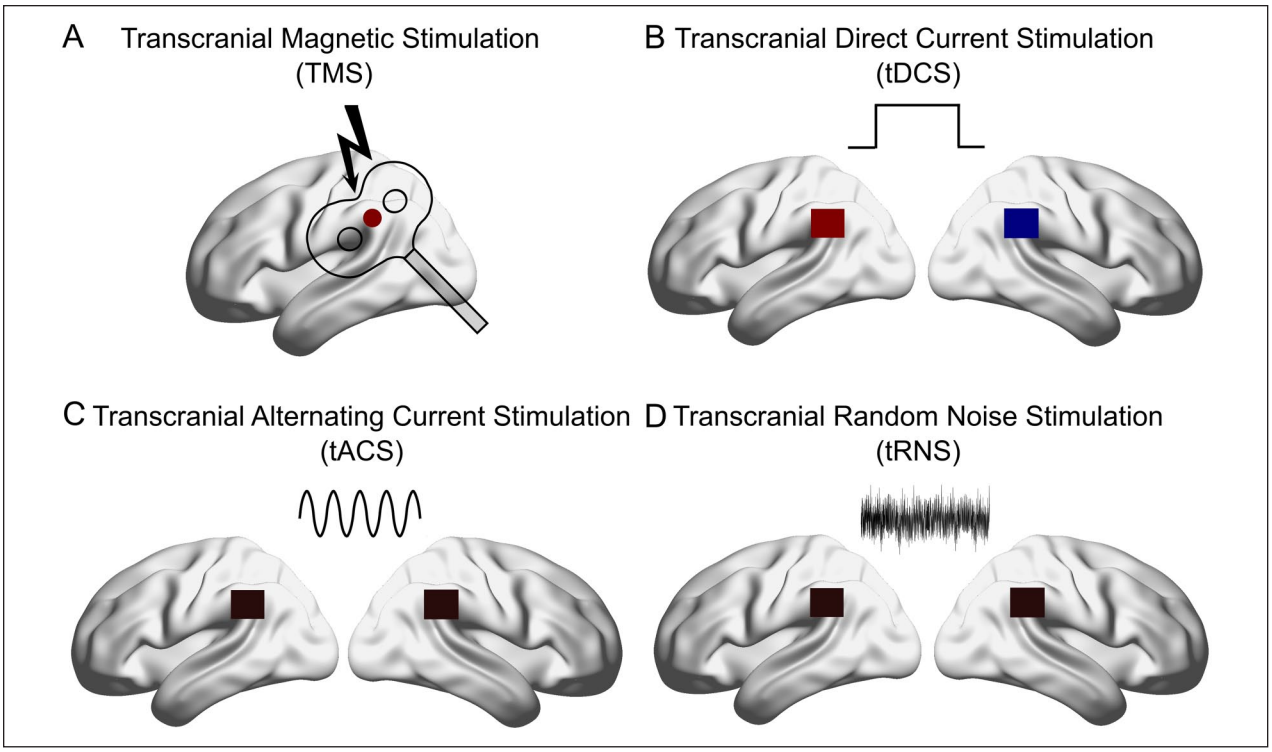

Figure 1. Illustration of different noninvasive brain stimulation approaches. (A) Transcranial magnetic stimulation. (B–D) Different transcranial electrical stimulation techniques illustrated as bilateral montages. (B) Anode = red, cathode = blue.

The present review mainly focuses on online applications of TMS to illustrate brain state–dependent stimulation effects for different cognitive domains. However, we argue that such effects are important to consider for offline protocols. Consequently, our framework introduces some general mechanisms of action for the application of any NIBS protocol.

NIBS in the Study of Cognition

The era of NIBS in cognitive neuroscience began with the classic work of Amassian and others (1989) on visual perception. In these studies, single-pulse TMS was applied over the occipital cortex during a letter detection task at different time windows after the presentation of the target stimulus. TMS induced a disruption of task performance at a specific time window, with a temporal resolution of 10 to 20 ms. Furthermore, when the coil was moved laterally, impairments were induced in different visual field positions. This seminal study demonstrated that TMS can be used to impair cognitive function with high temporal resolution and relatively good spatial resolution. It became a popular tool among neuroscientists and psychologists as it enabled "virtual" neuropsychology, creating "reversible brain lesions" (e.g., Pascual-Leone and others 2000; Walsh and Cowey 2000).

The 20 y of NIBS research on perception and cognition following this classic work have been referred to as the "point and shoot" era (see Pitcher and others 2021). A typical experiment in this period attempted to draw causal inferences, linking cognitive processes to specific brain regions by using TMS to disrupt performance in behavioral tasks (Fig. 2). Such studies usually follow the logic of asking "Is region A causally involved in task X?" While this approach has made significant contributions to cognitive neuroscience, response modulation by TMS appears to be more complex.

Challenges with TMS as a Disruptive Tool

The conceptualization of online TMS as a tool for disruption of cognitive processes has always been difficult to reconcile with the fact that modulatory effects are sensitive to a range of factors. As discussed later, intensity, stimulation timing, task difficulty, and baseline brain state strongly influence the nature of behavioral effects induced by any NIBS protocol. For example, some studies show that changing the stimulation intensity may turn behavioral impairment into facilitation (see Role of Stimulation Intensity section). In some cases, behavioral effects are observed only when the task is at a certain level of difficulty. A modulatory effect on a given task

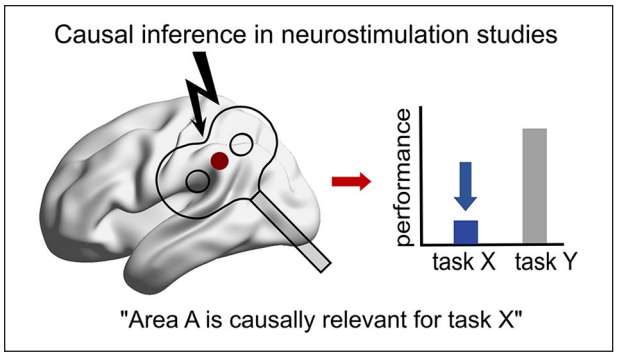

Figure 2. Typical rationale for noninvasive brain stimulation studies. Inhibitory noninvasive brain stimulation applied to area A significantly decreases performance in task X but not in task Y (control task). This leads to the conclusion that area A is causally relevant for task X. Illustrated for transcranial magnetic stimulation.

can disappear by simply asking participants to shift their attention to another stimulus. What is particularly challenging for the interpretation of modulatory NIBS effects is that their impact may not only be nonlinear (with respect to disruption vs. facilitation of task performance) but may also interact with the current brain state. For example, the effect of stimulation intensity on task performance may be different when given directly before or during a task.

Traditionally, unexpected beneficial TMS effects have been referred to as "paradoxical facilitation," reflecting the conceptualization of TMS as a tool for inducing disruption in cognitive tasks (Walsh and Cowey 2000). Facilitatory effects were unexpected and traditionally considered "secondary effects," which may have resulted from disruption of competing or distracting processing ("addition by subtraction"). Yet, facilitation may arise from unspecific stimulation effects or the direct modulation of a cortical area or network that leads to more efficient processing (see Luber and Lisanby 2014). Importantly, these outcomes arise from an interaction between internal and external factors. Ignoring the impact of such factors and their interaction on NIBS-induced modulation contributes to the overall lack of reliability and replicability of the behavioral effects of different NIBS protocols (e.g., Horvath and others 2015).

To explain why this problem arose, it is informative to go back to the parameters used in the original study by Amassian and others (1989). In that study, TMS was applied at a relatively high intensity, at 90% to 100% of stimulator output, during a task in which baseline performance level was high—conditions in which behavioral disruptions are most likely to arise (as discussed later). The key point is that this is just one possible combination of parameters, yet it shaped the way that the technique was generally used. In recent years, the parameter space of modulatory brain stimulation effects has been explored in more detail, challenging the conventional view of TMS as a mere disruption tool in the study of cognition (e.g., Bergmann and Hartwigsen 2021; Luber and Lisanby 2014; Silvanto and Cattaneo 2017 for discussion).

When one is attempting to explain neurostimulation effects, a conceptualization of such effects as interaction between an external stimulus and ongoing brain activity is required, with the outcome depending on the strength of the stimulus and the susceptibility of the brain to be activated by it. Furthermore, if we think about these effects as an interaction between neural excitability and the strength of the external signal, then we explicitly acknowledge that we are studying stimulation effects for one specific combination of conditions.

Here, we attempt to discuss the parameters that modulate NIBS effects and integrate them into a model that considers such effects an interaction between external and internal factors. We provide examples from low-level sensory perception (e.g., color perception) and higher-level cognitive functions (e.g., language) to demonstrate how variables such as timing, task difficulty, stimulation intensity, and brain state determine behavioral effects of brain stimulation.

Interactions between External and Internal Factors Modulate NIBS Effects

There is an ongoing debate regarding the lack of reliability and replicability of behavioral NIBS effects (e.g., Horvath and others 2015). One important but often neglected aspect that may explain some of the inconsistency is the nonlinear nature in which NIBS protocols interact with brain activity. Numerous factors determine NIBS effects, including stimulation intensity, frequency, and prior state of brain activity (e.g., Romei and others 2016). With "brain state," we here refer to the current state of excitability of the brain, which may be different at rest or during different tasks with varying cognitive load. The current brain state may also be influenced by previous tasks, fatigue, and internal factors and may show strong interindividual variability. Particularly noteworthy is the way that these factors interact, which is often unknown or ignored. For example, altering TMS intensity or brain state (e.g., rest vs. task) might turn a disruptive TMS effect into a facilitatory one (see Silvanto and Cattaneo 2017). Such nonlinearities are important because they may fundamentally change the conclusions about "necessity" or "causality" of a given area in a cognitive task. While NIBS studies usually involve control sites or montages and control tasks to demonstrate functional and regional specificity of the induced effects, these tend to control for only a small amount of the parameter space involved in determining NIBS effects.

In the next sections, we discuss different factors that influence the stimulation outcome. To foreshadow the most important take-home message, we argue that rather than focusing on a single factor, the stimulation outcome is always shaped by the interaction of different factors.

External Factors That Modulate NIBS Effects

Role of Stimulation Intensity

Valid models of NIBS effects need to consider nonlinearities of brain stimulation effects that have been observed at the neural level. For example, a first study (Moliadze and others 2003) reported that whereas low-intensity TMS induces a facilitation in neural activity and visually induced neural firing lasting up to 200 ms, high TMS intensities reversed the early facilitation into a suppression of neural activity. Likewise, nonlinear dependencies between intensity and motor cortical excitability were found for gamma tACS (Moliadze and others 2012) and tDCS (Jamil and others 2017). Moliadze and others (2012) found that low-stimulation intensities of gamma tACS resulted in cortical inhibition, while high intensities facilitated cortical excitability and decreased motor thresholds. Notably, no significant effects were observed for intermediate intensities, presumably indicating that inhibitory and excitatory effects canceled each other out at such intensities. In a systematic investigation of different stimulation intensities, Jamil and others (2017) reported equal effects of lower and higher tDCS intensities on motor excitability, independent of the stimulation polarity. Other work in the motor system showed strong interindividual variability in the response direction to plasticity inducing TMS protocols (Sasaki and others 2018). Those subjects who demonstrated the expected inhibition of motor cortical excitability after conventional low-intensity continuous theta burst stimulation (cTBS) showed facilitation with higher intensities. Yet, some subjects who demonstrated facilitation by low-intensity stimulation showed inhibition when stimulation intensities were further decreased, which may reflect intrinsic differences in the recruitment of cortical neurons, pointing to the impact of individual differences in cortical excitability and recruitment.

Silvanto and Cattaneo (2017) contend that when such nonlinearities in response to NIBS are considered, the strong variability in behavioral NIBS effects can be accounted for in terms of inhibitory and facilitatory effects. These authors argue that the combination of stimulation strength and neural excitability determines whether behavior is facilitated or impaired. Indeed, some studies on visual perception demonstrate selective facilitatory TMS effects on near-threshold stimuli (e.g., Abrahamyan and others 2011), which turn into inhibition when stimulation intensity and visual stimulus intensity are increased (Schwarzkopf and others 2011). In the latter study, the authors found that TMS facilitated the detection of weak motion signals when given at low intensities, whereas higher intensities selectively impaired the detection of stronger motion signals. These findings suggest that TMS adds noise to neuronal processing, which may synchronize with the task-related activity. It should be noted that the exact mechanisms by which TMS and other NIBS protocols modulate cognitive functions are unknown. The idea behind the noise hypothesis is that stimulation-induced excitation of random neural elements causes neuronal noise in the stimulated circuits (e.g., Walsh and Pascual-Leone 2003). Noise pervades all levels of information processing in the nervous system, from receptor signal transduction to behavioral responses (Faisal and others 2008). The artificial induction of noise may impair or delay task-relevant neuronal computations because neural activity needs to be sampled longer to discriminate signal and noise. Alternatively, noise may be synchronized with the ongoing task signal and thereby improve processing. This means that adding noise to a nonlinear system such as the human brain may produce opposite effects (see Bergmann and Hartwigsen 2021). An appropriate amount of noise can add to the weak neuronal signal of a subthreshold stimulus, elevate it above threshold, and result in behavioral facilitation (Schwarzkopf and others 2011). In contrast, exceeding noise levels may rather mask the task-relevant neuronal signal. Importantly, the NIBS-induced activity or neural noise is not totally random (Ruzzoli and others 2010) and not independent of the task-induced neural activity or brain state. Depending on the activated neuron population, the induced activity can even be considered noise and part of the signal (Miniussi and others 2010). Unfortunately, these factors are rarely considered before an experiment and often unknown, implying that they are mainly used as post hoc explanations for unexpected findings in most cognitive studies.

Role of Stimulation Frequency

Frequency-specific repetitive TMS (rTMS) effects are well described in the motor system, with the general assumption that frequencies <1 Hz decrease motor cortical excitability while frequencies >1 Hz cause facilitatory effects (e.g., Hallett 2000; Wassermann and others 1998). Yet, this does not necessarily hold for cognitive functions. Indeed, numerous studies describe inhibitory effects of high-frequency rTMS protocols (≥ 10 Hz), at least when given during a task (e.g., Hartwigsen 2015 for review in the language system). One study addressed potential conditioning effects of rTMS protocols at

different frequencies on a language detection task (Andoh and others 2008). Specifically, these authors explored if 1-Hz rTMS or cTBS applied before the task would modulate the effects of subsequent low-frequency rTMS during word detection. As a main finding, priming with 1-Hz rTMS facilitated the detection of native words, whereas priming with cTBS facilitated the detection of foreign words. Accordingly, it was suggested that the priming frequency of the TMS protocol plays a crucial role in word detection in the auditory stream, with the facilitatory effects of cTBS likely depending on a larger network stimulation effect. However, it remains unclear if these effects depend on the combination of TMS protocols or would also occur without additional online stimulation.

Frequency-specific effects are reported for tACS, with theta tACS being associated with performance improvements across several cognitive domains, including working memory, executive functions, and declarative memory (see Klink and others 2020 for review). Individual adjustment of stimulation frequency based on preceding EEG recordings may be advisable to increase stimulation efficiency (Vosskuhl and others 2018). Yet, most existing tACS and rTMS studies did not include a control frequency, questioning the frequency specificity of the observed effects. Moreover, the impact of a given stimulation frequency on task performance likely interacts with the current brain state (e.g., rest or task; Moliadze and others 2021), which may contribute to the strong variability of stimulation effects for different frequencies across studies.

Role of Stimulation Duration

Stimulation duration is particularly important for the after-effects of plasticity-inducing NIBS protocols. Dose-dependent effects have been reported for different NIBS protocols (see Gamboa and others 2010). Early tDCS work proposed a linear relationship between stimulation duration and after-effects on motor cortical excitability for single-session anodal tDCS (e.g., Nitsche and Paulus 2000, 2001). Accordingly, conventional tDCS protocols usually employ stimulation durations of 15 to 20 min. Recent work shows that the facilitatory after-effects of anodal tDCS on motor excitability vanish or reverse after stimulation durations ≥26 min (e.g., Hassanzahraee and others 2020; Monte-Silva and others 2013; Vignaud and others 2018). Similar effects on motor cortical excitability have been demonstrated for theta burst stimulation. Conventional inhibitory cTBS effects reversed into facilitation when the stimulation duration was doubled, while facilitatory intermittent TBS resulted in inhibition after doubling the stimulation duration (Gamboa and others 2010). Such reversal effects may be explained in terms of counterregulatory homeostatic mechanisms, which might prevent excessive brain activation (homeostatic plasticity; see next section). Moreover, stimulation duration was shown to interact with the current brain state. Another study (Gentner and others 2008) found that cTBS-induced inhibition turned into facilitation when only half of the protocol (300 pulses) was applied. Yet, when voluntary muscle contraction was performed before stimulation, both the short and conventional protocol induced inhibition. Stimulation duration further affected the duration of the after-effects, which lasted up to 20 min for the short protocol and up to 1 h for the conventional one.

Less is known about the impact of stimulation duration on cognitive tasks. One study in older adults showed that anodal offline tDCS over the bilateral dorsolateral prefrontal cortex improved attentional control when applied for only 10 min, while the conventional 20-min protocol had no significant effects (Hanley and others 2020). This is surprising given that neural plasticity is thought to decrease with age. As no young control cohort was included, it remains unclear whether these effects reflect age-related changes in homeostatic plasticity or a more general interaction of such effects with the task-induced brain state and the specific bilateral electrode montage employed in that study.

Internal Factors That Modulate NIBS Effects

Role of the Current Brain State

The difference between active and resting motor threshold is a simple yet impressive example for the role of the current brain state for the observed stimulation outcome: a single TMS pulse that is just suprathreshold for evoking a motor response induces a considerably larger motor response in the target muscle if the subject performs a slight voluntary precontraction (see Siebner and others 2009). In other words, lower-stimulation intensities are already sufficient to induce motor-evoked potentials under precontraction, while higher intensities are required to evoke a visible response at rest, demonstrating the interaction between brain state and stimulation intensity.

Moving beyond the motor system, some studies have shown that "classical" inhibitory TMS protocols can result in facilitation if the current brain state changes. For example, Andoh and others (2006) reported a site- and condition-specific facilitation in response speed when 1-Hz rTMS was applied over the left posterior superior temporal gyrus *during* a language-fragment detection task. Likewise, 10-Hz rTMS—a protocol that is often reported to disrupt performance when applied during a language task (Hartwigsen 2015)—resulted in condition-specific facilitation of native words when applied over the left posterior superior temporal gyrus *before* task

Box 2. Combination of Noninvasive Brain Stimulation with Different Readouts.

Complementing the investigation of stimulation effects at the behavioral level, noninvasive brain stimulation (NIBS) can be combined with functional neuroimaging or electrophysiologic techniques to map stimulation-induced changes at the neural network level and identify neural markers of stimulation effects (Fig. 3). Neuroimaging or electrophysiologic techniques may be more sensitive to capture stimulation-induced modulation, even when stimulation effects are not strong enough to induce behavioral changes. Such combinations can be separated in time and space but can also be performed concurrently. For example, functional magnetic resonance imaging (fMRI) before NIBS can be used to localize target areas for subsequent NIBS application (Fig. 3A). This is particularly interesting for most target areas outside the motor system where the stimulation site cannot be determined functionally. Such combinations are often used in "classical" perturbation studies to probe the functional relevance of the observed activity patterns in specific areas for a given task. Targeting accuracy may be highest if individual functional localizers are used (see Bergmann and others 2016). Likewise, localizers with electrophysiologic techniques (magneto- or electroencephalography [M/EEG]) can be used to inform subsequent NIBS applications with respect to task-specific oscillatory frequencies or electrophysiologic markers of interest.

In the second approach, plasticity-inducing NIBS protocols are given prior to fMRI or M/EEG to map lasting neurostimulation effects at the neural network level (Fig. 3B). When separated in time, one needs to bear in mind that the after-effects of a specific NIBS protocol decrease after a certain period. The exact duration of such after-effects outside the motor cortex is unknown and likely depends on the interaction of internal and external factors, as discussed in this review. Nevertheless, strong NIBS-induced changes in task-related activity and connectivity as well as electrophysiologic parameters have been described for different cognitive domains (e.g., Bergmann and others 2016; Hartwigsen 2016 for an overview). Such changes have been associated with task-related modulation induced by different NIBS protocols. Relative to the study of behavioral effects, such combinations provide insight into the underlying modulation at the network level.

Finally, NIBS protocols can also be combined concurrently with fMRI or EEG to map immediate consequences of the stimulation (Fig. 3C). The simultaneous combination of transcranial magnetic stimulation (TMS) and magnetoencephalography is technically not feasible yet. Concurrent combinations of NIBS and fMRI or EEG can be used to map changes in activity, connectivity, and other electrophysiologic responses across the time course of a specific task—for example, during learning paradigms. Subsequent and concurrent combinations of NIBS and neuroimaging have demonstrated that the stimulation effects are not as focal as often assumed, challenging the simplistic notion that changes at the behavioral level are always caused by a modulation in the stimulated area. Indeed, concurrent TMS-fMRI studies in the motor system reported remote effects outside the stimulated area even for single-pulse TMS, including changes in neighboring cortical areas and in distant cortical and subcortical regions (Bestmann and others 2003; see also Bestmann and Feredoes 2013). Offline TMS-fMRI studies point toward the behavioral relevance of stimulation-induced changes in remote connected areas for different cognitive functions (e.g., Hartwigsen and others 2017; Herz and others 2014).

performance (Andoh and Paus 2011). However, it remains an open question how such changes in task performance are reflected at the underlying neural level.

Effects of NIBS on task-related activity and connectivity can be mapped with neuroimaging and electrophysiologic techniques, as summarized in Box 2. Behavioral improvements and impairments induced by different NIBS protocols have been associated with decreased task-related activity in the stimulated area and network during language tasks (e.g., Fiori and others 2018; Hartwigsen and others 2017; Holland and others 2011), although such activity decreases likely reflect different processes. Indeed, decreased task-related activity during facilitatory stimulation is often explained in terms of more efficient task processing (Holland and others 2011). In contrast, decreased activity after inhibitory NIBS protocols likely reflects neural inhibition (see Hartwigsen 2016). As discussed in the Conclusions section, a better understanding of the neural underpinnings of brain state–dependent NIBS effects may give new insight into modulatory stimulation effects at the systems level.

Other examples for the role of the current brain state on the stimulation outcome can be derived from studies on picture naming. For example, when given immediately before or early during a task, TMS was reported to facilitate picture naming, likely by a priming effect that increased activity in the target area to a level that was optimal for task performance (e.g., Topper and others 1998). In contrast, TMS impaired performance when applied during picture naming (e.g., Flitman and others 1998; Wassermann and others 1999).

Brain state–dependent effects further shape the impact of plasticity-inducing NIBS protocols on learning and training studies. For example, it was demonstrated that anodal tDCS applied during or after motor learning improves motor consolidation (e.g., Reis and others 2009; Stagg and others 2011). In contrast, when given before learning, tDCS decreased motor learning (Stagg and others 2011). The latter effect may be explained in terms of regulatory metaplasticity, which refers to the variation of synaptic plasticity depending on the history of a neuron's postsynaptic activity and is thought to prevent cortical

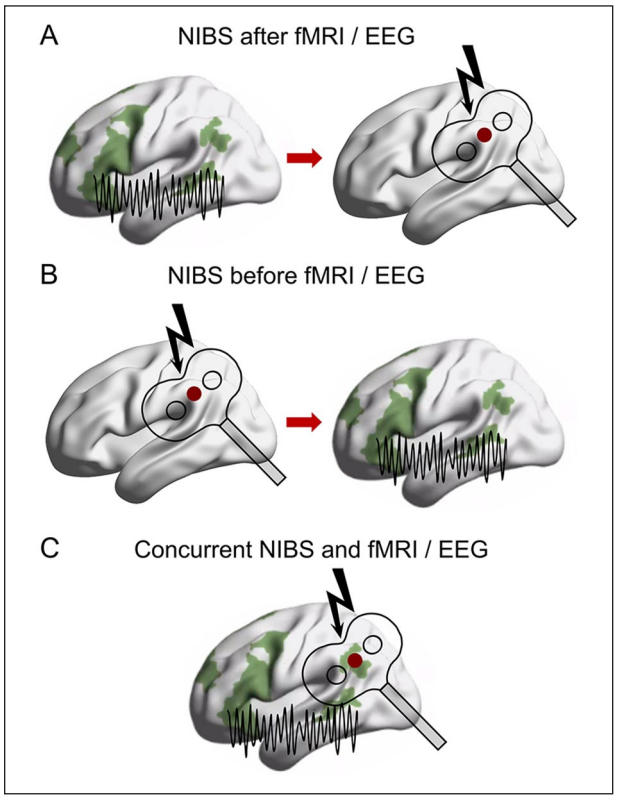

Figure 3. Combination of noninvasive brain stimulation (NIBS) with neuroimaging (green maps) or electrophysiologic readouts (oscillations). (A) NIBS can be given after functional magnetic resonance imaging (fMRI) or electroencephalography (EEG) to probe the functional relevance of a specific area or electrophysiologic parameter (e.g., neural oscillations, event-related potentials) for a given task. (B) Plasticity-inducing NIBS can be applied before fMRI or EEG to map lasting after-effects at the neural network level. Subsequent combinations in A and B can also be combined with magnetoencephalography. (C) Concurrent combination of NIBS with fMRI or EEG can be used to map the immediate consequences of the stimulation at the neural network level. All combinations illustrated for transcranial magnetic stimulation.

network destabilization (Abraham and Bear 1996). While the impact of metaplasticity on NIBS effects is not well understood, homeostatic metaplasticity may explain why the application of the same priming and test rTMS protocols may reverse the effect of the test protocol, whereas priming with the opposite protocol may increase the effect of a test protocol (Mastroeni and others 2013; Murakami and others 2012). Yet, depending on the timing of the application, repeated rTMS protocols may also have additive effects on motor excitability (Goldsworthy and others 2015). How such effects interact with NIBS during cognitive processes remains to be explored.

Particularly important for the study of cognition, a previous task may modulate the effects of a subsequent NIBS protocol. Stefan and others (2006) demonstrated that the capacity of the motor cortex to undergo long-term potentiation-like plasticity induced by paired associative stimulation was abolished immediately after a motor training. This example illustrates the impact of a previous task on the outcome of a subsequently applied NIBS protocol. Such effects are usually ignored in the study of cognition, despite their potential relevance, especially for training and therapeutic applications that rely on plasticity-inducing NIBS protocols.

Given the discussed results, we suggest that the impact of stimulation timing on the observed outcome can be explained by differences in the current brain state. For example, the impact of online and offline protocols may differ because the brain state changes from rest to activation. Such state-dependent effects are impressive examples for the interaction between external and internal factors.

Moreover, it is reasonable to assume that state-dependent NIBS effects are strongly influenced by internal cognitive and emotional factors such as attention, fatigue, or arousal. Indeed, the subject's attentional focus has been shown to influence the magnitude of stimulation effects (see Ridding and Ziemann 2010 for an overview). One study found that a cognitive task during tDCS reduced stimulation-induced changes in motor cortical excitability in response to facilitatory and inhibitory protocols applied over the motor cortex (Antal and others 2007). These effects were suggested to reflect a deactivation of cortical areas that were not engaged in the task, which might have interfered with stimulation-induced plasticity. However, such effects are hard to control and are subject to strong interindividual variability. Their impact is usually ignored in NIBS studies.

Role of Baseline Performance

Recent work emphasizes the crucial role of *baseline performance* for the stimulation outcome (e.g., Silvanto and others 2017). In that study, a color detection task was combined with TMS over the early visual cortex to probe the interaction between baseline activity and stimulation intensity (Fig. 4). In each trial, participants were presented with a visual prime (a grating with a specific combination of color and orientation), which was followed by the target grating (Fig. 4A). The target grating could be fully congruent with the prime (color and orientation matched), fully incongruent (color and orientation differed), or partially congruent (either color or orientation of the target matched that of the prime). Single-pulse TMS was applied over the early visual cortex (Fig. 4B) within the "classic" TMS-masking time window, 100 ms after target onset. The results showed that at the group level, TMS facilitated the detection of fully incongruent targets, while having no statistically significant effect on other stimulus types (Fig. 4C). Such a selective effect on

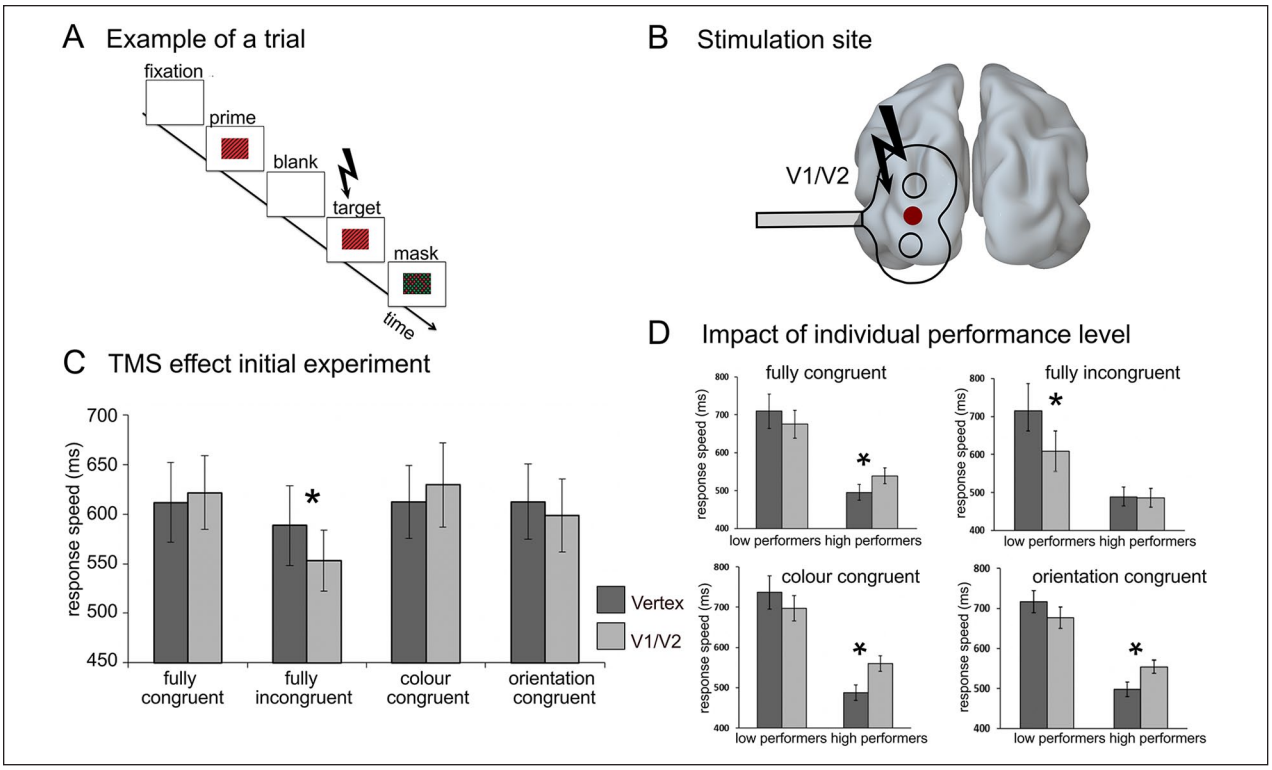

Figure 4. Using transcranial magnetic stimulation (TMS) to probe state dependency. Illustration of two studies on visual priming that used TMS to probe the interaction of brain state and stimulation intensity. (A) Experimental paradigm. Illustration of a fully congruent trial (prime and target match for color and orientation). Each trial started with a fixation screen (500 ms). Participants were then presented with a prime (100 ms) that was either a red-black or green-black grating, tilted either clockwise or counterclockwise. A blank screen (300 ms) was followed by a target (20 ms) that could be fully congruent with the prime (the same stimulus), fully incongruent (color and orientation differed), or partially congruent (either color or orientation matched the prime). A mask was presented after the target until response initiation. Participants had to indicate the color of diagonals of the stimulus target (red or green). Single-pulse TMS was delivered at 100 ms after target onset over V1/V2 or over the vertex (baseline). (B) Stimulation site over the left visual cortex (area V1/V2). (C) Stimulation effects in the initial experiment (Silvanto and others 2017). Relative to vertex stimulation, TMS over V1/V2 significantly delayed the median response speed for correct trials in the fully incongruent condition. (D) Reanalysis based on individual baseline performance (Silvanto and others 2018). TMS had differential effects in high and low performers, as illustrated in the different panels. Values are presented as median response times +/− 1 SEM. *$P < 0.05$. Adapted from Silvanto and others (2018).

a specific congruency category is the hallmark of state-dependent TMS effects and was taken as evidence for priming modulation of early visual cortical activity.

How "selective" are such effects? Further analyses (Silvanto and others 2018) revealed a significant linear relationship between baseline performance and the direction and magnitude of the induced TMS effect. Specifically, low baseline performance was associated with TMS-induced facilitation and high baseline performance with impairment (Fig. 4D). In other words, as performance level increased, TMS effects turned from facilitation to impairment. The key finding was that this relationship was present for all prime-target congruencies: the TMS effect was no longer selective for fully incongruent trials, as had been originally concluded. Incongruent trials did however differ from other trial types in terms of the transition point from TMS-induced facilitation to impairment: facilitation was obtained until a higher level of performance than for other prime-target congruencies.

Other work suggests that lower initial baseline performance predicts stronger tDCS-induced modulation of verbal learning, highlighting a possible mediator of between-subject variability in stimulation response (Perceval and others 2020). When attempting to explain such effects, the consideration of NIBS effects as an interaction between an external stimulus and ongoing brain activity is important, with the outcome depending on the strength of the stimulus and the response sensitivity of the brain.

Role of Sex, Genetics, and Age

Variability in response to NIBS protocols has been associated with sex differences, genetic polymorphisms, and age-related changes in brain structure and functions

(e.g., Ridding and Ziemann 2010). These factors are generally not well understood and likely show complex interactions with modulatory NIBS effects. Sex-dependent differences in cortical excitability and in response to different plasticity-inducing NIBS protocols may be related to differences in brain anatomy and hormone levels (e.g., Kuo and others 2006). Such differences affect cognitive performance. For example, previous work reported sex differences in response to prefrontal tDCS in verbal working memory, with female subjects demonstrating behavioral improvements under right prefrontal stimulation while male participants selectively benefited from left hemispheric tDCS (Meiron and Lavidor 2013). This double dissociation emphasizes the impact of sex differences in cerebral lateralization on the individual responsiveness to NIBS. While numerous previous findings point toward sex differences in response to NIBS with females being often somewhat more responsive (Ridding and Ziemann 2010), their impact is rarely investigated in cognitive NIBS studies.

Genetic factors have been associated with differences in response to NIBS protocols. Genetic polymorphisms of neurotrophins significantly influence the induction of plasticity by NIBS over the motor cortex (Ridding and Ziemann 2010). For example, carriers of common single-nucleotide polymorphisms in the brain-derived neurotrophic factor gene do not show the expected depression of motor cortical excitability after cTBS (e.g., Cheeran and others 2008). Brain-derived neurotrophic factor modulates glutamatergic transmission in the striatum and is associated with several cognitive processes, including learning, memory, and reward processing. With respect to the impact of genetic polymorphisms on NIBS effects in cognitive studies, it was suggested that the individual genetic profile may also modulate behavioral effects of plasticity-inducing NIBS protocols (Wiegand and others 2016). Considering individual differences in genetic patterns may help to increase the behavioral efficiency of different NIBS approaches.

Another important modulatory factor for the individual responsiveness to NIBS protocols is age. Aging is generally associated with impairments in learning and memory as well as executive functions. Such changes may be related to an overall altered capacity for synaptic plasticity. Indeed, some studies indicate that the capacity for NIBS-induced plasticity decreases with age (see Perceval and others 2016 for review), and the response to neurostimulation is more variable in the aging brain. Likewise, older participants often show higher resting motor thresholds, reflecting a general hypoexcitability (Bhandari and others 2016). Accordingly, tDCS montages, which usually improve performance in young participants, did not significantly influence behavior or even resulted in impairments in older adults in some previous studies (Perceval and others 2016). Such changes likely reflect alterations in brain function and structure, including changes in activity patterns and cortical atrophy. However, some studies show that older adults seem to profit equally or even stronger than young participants from certain plasticity-inducing NIBS protocols (e.g., Meinzer and others 2013). These effects likely reflect differences in baseline performance, with older subjects benefiting more due to an overall lower performance level while younger subjects may perform closer to ceiling. Accordingly, some of the neural changes associated with aging may entail the potential for greater effect sizes of NIBS protocols in older adults because the aging brain may perform further away from a homeostatic optimum (Habich and others 2020). Indeed, Meinzer and others (2013) demonstrated that a single session of anodal tDCS over the left prefrontal cortex improved performance in a word generation task in older subjects to the level of a young control group. Moreover, behavioral improvements were associated with reduced bilateral hyperactivity during fMRI and a normalization of network interactions toward a more "youth-like" pattern at rest.

Such age-related differences in response to plasticity-inducing NIBS protocols are particularly relevant for interventions against age-related cognitive decline. However, one challenge when planning NIBS applications in older participants is to identify whether age-related changes in task-related activity and connectivity patterns reflect compensatory reorganization or general dedifferentiation due to aging. Perturbation approaches may help to disentangle such mechanisms at the behavioral level.

A Framework for State-Dependent NIBS Effects

As outlined in the previous sections, many variables influence and mediate the impact of brain stimulation on motor excitability and cognitive performance. How can one bring these together in a common framework? We propose that to develop such a framework, one requires a conceptualization of brain stimulation effects as an interaction between an external stimulus and ongoing brain activity. The neural and behavioral outcome depends on the strength of the stimulus and the susceptibility of the brain to be activated by it—in other words, neural excitability. When we look at the wide range of variables listed earlier, all of them can be reduced to an increase or decrease of neural excitability (i.e., the ability of a neuron to be activated) or the strength of the external stimulus (i.e., the intensity of brain stimulation).

A particular reason why it is so important to consider NIBS effects as an interaction between internal and external factors is the nonlinear nature of their interaction.

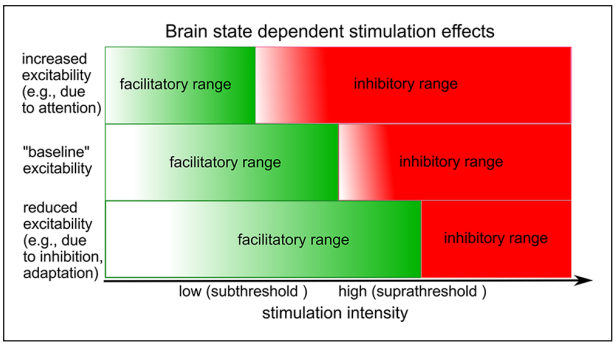

Figure 5. A model for state dependency in noninvasive brain stimulation studies. Noninvasive brain stimulation has distinct ranges of behavioral/neural facilitation as a function of the strength of the applied current, illustrated for transcranial magnetic stimulation. These ranges are shifted by changes in neural excitability. Consequently, at a given transcranial magnetic stimulation intensity, either facilitation or impairment can be obtained, depending on current neural excitability level. Adapted from Silvanto and Cattaneo (2017).

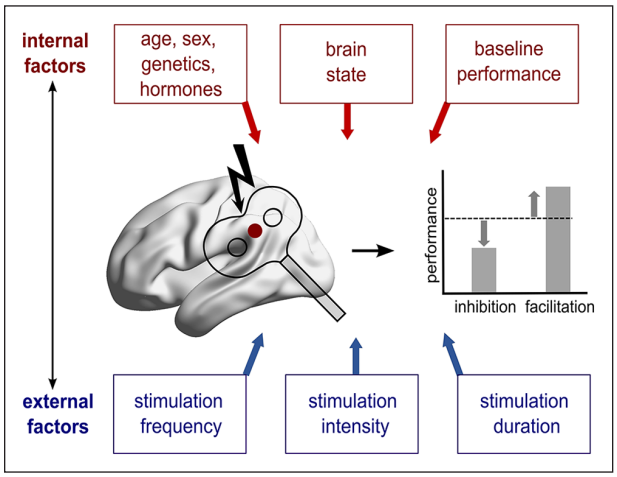

Figure 6. Different factors that influence the impact of noninvasive brain stimulation on task performance. Internal factors are illustrated in red and external factors in blue. These factors strongly interact and influence each other and the outcome of a given noninvasive brain stimulation protocol, which may result in inhibition or facilitation of task performance. Illustrated for transcranial magnetic stimulation.

Changes in intensity, task difficulty, or state of adaptation can turn a disruptive effect of brain stimulation into facilitation. Nonlinearites have also been observed in the neural effects of TMS in single-cell recordings. As discussed earlier, low-intensity TMS can induce a facilitation in early visually induced neural firing, which turns into a suppression of neuronal activity at high TMS intensities (Moliadze and others 2003). To explain the nonlinear interactions between stimulation intensity and neural excitability, Silvanto and Cattaneo (2017) proposed a model in which the combination of stimulation strength and neural excitability determines whether behavioral responses are facilitated or impaired. This model is shown in Figure 5. It is based on the idea that there are specific intensity ranges at which TMS either enhances or inhibits neural activity and behavior. The key issue is that these ranges are shifted by changes in neuronal excitability. As illustrated on the right side of the model, a consequence of excitability reduction induced by adaptation is the shift of facilitatory-inhibitory ranges toward higher-stimulation intensities. If excitability is increased by engagement of attention, lower intensities are needed to obtain similar effects than is the case at "baseline." The outcome is that a TMS intensity, which at "baseline" facilitates behavior, can have a disruptive effect when excitability has been increased. This occurs because the shift in the facilitatory-inhibitory range modulates whether a given TMS intensity is facilitatory or suppressive.

We argue that this model can be generalized to other NIBS protocols as the underlying mechanisms reflect general interactions between the current brain state and the modulatory input of a given NIBS protocol. While intensity is usually kept constant in transcranial electrical stimulation studies, some previous work points to nonlinearities in response to different tDCS and tACS intensities (Moliadze and others 2012) and a strong interaction with the current cognitive task (Antal and others 2007). Moreover, as outlined earlier, other external factors such as stimulation frequency and stimulation duration have been demonstrated to interact with internal factors and are thus crucial for the observed outcome (Fig. 6). However, research on brain state–dependent NIBS effects is still at its infancy, and it is too early to make strong predictions regarding the exact outcome of such interactions in different experimental settings.

Conclusions and Future Directions

NIBS protocols are powerful tools for the modulation of motor and cognitive functions in the human brain. As outlined in this review, the impact of a specific protocol strongly depends on the complex interaction of internal factors (e.g., brain state, age, sex, attention, and fatigue) and external factors (e.g., stimulation intensity, duration, and frequency), which often results in unexpected findings or null effects. Considering such interactions may explain effects that have been traditionally considered paradoxical, such as unexpected facilitation of behavioral responses. Future studies in large cohorts are required to explore the impact of such interactions and identify those factors that contribute to the strong interindividual variability in motor and cognitive tasks. We note that our conclusions are limited because we did not perform a

systematic review of all NIBS studies on cognition that support our conceptualization of NIBS effects as an interaction between external and internal factors. While a systematic review was beyond the scope of our article, a future study would benefit from such an approach to illustrate the influence of these factors on the outcome of NIBS effects. Our framework currently lacks precision because there are no ways to measure cortical excitability validly and objectively outside the motor cortex in the human brain. However, this does not preclude a systematic investigation of the impact of different stimulation intensities or different brain states on the observed outcome. The discussed examples suggest that this would be a crucial next step for the implementation of our framework. For example, future studies could vary task load and stimulation intensity for standardized cognitive tasks and test the impact of such modulations at the outcome level.

Importantly, brain state–dependent effects should not only be considered at the behavioral level but also the neural network level. The notion that a given NIBS protocol will have its strongest impact at the stimulated area appears to be too simple because strong remote effects in distant connected areas have been demonstrated already for single-pulse TMS (e.g., Bestmann and others 2003) and the behavioral relevance of remote effects has been shown for different cognitive processes (e.g., Hartwigsen and others 2017). The combination of NIBS with different neuroimaging and electrophysiologic techniques can provide insight into such effects beyond the behavioral level.

Additionally, directly comparing the impact of NIBS on different brain states, such as rest and task, at the neural level can provide insight into state-dependent effects at the network level. Indeed, it has been suggested that stimulation-induced modulation of network activity may be different for task and rest states, as reflected in the modulation of different large-scale networks during either state (Li and others 2019). Future approaches may consider individual response patterns during different brain states and relate individual response profiles at rest to the modulation of task-related activity and connectivity. Such approaches could help to identify responders and individual-specific response profiles.

Statistical models that may be used to infer different states in a system may help to better characterize network effects and interindividual variability in response to different NIBS protocols. First applications suggest that only few spontaneous brain states may be susceptible to tACS-induced modulation (Kasten and Herrmann 2020). Identifying such brain states may increase the current understanding of stimulation effects and may, in the long run, contribute to increasing the stimulation efficiency.

Another way forward will include more precise and realistic modeling of the induced electrical field of different NIBS protocols to increase the reliability and reduce the variability observed in neurostimulation studies. Recent advances in biophysical modeling have considerably improved the localization of the cortical area effectively stimulated by NIBS (e.g., Saturnino, Madsen, and others 2019; Weise and others 2019). Such approaches should be transferred from the motor cortex to other areas and cognitive domains in future studies. Electrical field simulations have also been used to predict intersubject variability after NIBS at the electrophysiologic level. For example, a recent study showed that the variability in response to tACS-induced power increases in the alpha band could be predicted by the variability of the individual electrical field induced by the stimulation (Kasten and others 2019). This example illustrates the relevance of individualizing stimulation parameters to optimize targeting and dosing of a given NIBS protocol. Optimized targeting is particularly relevant when studying cognitive functions where no direct output can be induced by the stimulation, precluding functional localization. A priori modeling of the induced electrical field at the individual subject level may help to individually guide coil and electrode placement and calibrate the stimulation intensity to a level that may be optimal to modulate task performance. Yet, so far, electric field modeling is not a standard procedure in NIBS studies and is, if at all, mainly performed post hoc to localize stimulation effects. Indeed, first post hoc computational simulations of the TMS-induced current flow in cognitive studies have revealed that stronger stimulation of the target area was associated with stronger behavioral impairments in a language task (Kuhnke and others 2020). As a next step, a priori simulations outside the motor cortex would be needed to optimize target localization and dosing. However, dose optimization is tricky because the excitability of areas outside the motor cortex is not known. As a first approximation, it may be helpful to optimize these parameters based on the stimulation intensities in the motor cortex and then systematically test the impact of different intensities for specific target areas and cognitive domains.

Finally, brain state–dependent stimulation effects should be considered for altered brain states—that is, in lesioned and diseased brains. Considering the interaction between internal and external factors may help to advance treatment of network disorders with different NIBS protocols and may be particularly helpful for explaining the strong variability in the observed effects. Such considerations are important steps toward more effective individualized treatment with NIBS.

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References

Abraham WC, Bear MF. 1996. Metaplasticity: the plasticity of synaptic plasticity. Trends Neurosci 19(4):126–30.

Abrahamyan A, Clifford CW, Arabzadeh E, Harris JA. 2011. Improving visual sensitivity with subthreshold transcranial magnetic stimulation. J Neurosci 31(9):3290–4.

Alekseichuk I, Turi Z, Amador de Lara G, Antal A, Paulus W. 2016. Spatial working memory in humans depends on theta and high gamma synchronization in the prefrontal cortex. Curr Biol 26(12):1513–21.

Amassian VE, Maccabee PJ, Cracco RQ. 1989. Focal stimulation of human peripheral nerve with the magnetic coil: a comparison with electrical stimulation. Exp Neurol 103(3):282–9.

Andoh J, Artiges E, Pallier C, Riviere D, Mangin JF, Cachia A, and others. 2006. Modulation of language areas with functional MR image–guided magnetic stimulation. Neuroimage 29(2):619–27.

Andoh J, Artiges E, Pallier C, Riviere D, Mangin JF, Paillere-Martinot ML, and others. 2008. Priming frequencies of transcranial magnetic stimulation over Wernicke's area modulate word detection. Cereb Cortex 18(1):210–6.

Andoh J, Paus T. 2011. Combining functional neuroimaging with off-line brain stimulation: modulation of task-related activity in language areas. J Cogn Neurosci 23(2):349–61.

Antal A, Terney D, Poreisz C, Paulus W. 2007. Towards unravelling task-related modulations of neuroplastic changes induced in the human motor cortex. Eur J Neurosci 26(9):2687–91.

Bergmann TO, Hartwigsen G. 2021. Inferring causality from noninvasive brain stimulation in cognitive neuroscience. J Cogn Neurosci 33(2):195–225.

Bergmann TO, Karabanov A, Hartwigsen G, Thielscher A, Siebner HR. 2016. Combining non-invasive transcranial brain stimulation with neuroimaging and electrophysiology: current approaches and future perspectives. Neuroimage 140:4–19.

Bestmann S, Baudewig J, Siebner HR, Rothwell JC, Frahm J. 2003. Subthreshold high-frequency TMS of human primary motor cortex modulates interconnected frontal motor areas as detected by interleaved fMRI-TMS. Neuroimage 20(3):1685–96.

Bestmann S, Feredoes E. 2013. Combined neurostimulation and neuroimaging in cognitive neuroscience: past, present, and future. Ann N Y Acad Sci 1296:11–30.

Bhandari A, Radhu N, Farzan F, Mulsant BH, Rajji TK, Daskalakis ZJ, and others. 2016. A meta-analysis of the effects of aging on motor cortex neurophysiology assessed by transcranial magnetic stimulation. Clin Neurophysiol 127(8):2834–45.

Bungert A, Antunes A, Espenhahn S, Thielscher A. 2017. Where does TMS stimulate the motor cortex? Combining electrophysiological measurements and realistic field estimates to reveal the affected cortex position. Cereb Cortex 27(11):5083–94.

Caulfield KA, Li X, George MS. 2021a. Four electric field modeling methods of dosing prefrontal transcranial magnetic stimulation (TMS): introducing APEX MT dosimetry. Brain Stimul 14(4):1032–4.

Caulfield KA, Li X, George MS. 2021b. A reexamination of motor and prefrontal TMS in tobacco use disorder: time for personalized dosing based on electric field modeling? Clin Neurophysiol 132(9):2199–207.

Cheeran B, Talelli P, Mori F, Koch G, Suppa A, Edwards M, and others. 2008. A common polymorphism in the brain-derived neurotrophic factor gene (BDNF) modulates human cortical plasticity and the response to rTMS. J Physiol 586(23):5717–25.

Chung SW, Hill AT, Rogasch NC, Hoy KE, Fitzgerald PB. 2016. Use of theta-burst stimulation in changing excitability of motor cortex: a systematic review and meta-analysis. Neurosci Biobehav Rev 63:43–64.

Faisal AA, Selen LP, Wolpert DM. 2008. Noise in the nervous system. Nat Rev Neurosci 9(4):292–303.

Fiori V, Kunz L, Kuhnke P, Marangolo P, Hartwigsen G. 2018. Transcranial direct current stimulation (tDCS) facilitates verb learning by altering effective connectivity in the healthy brain. Neuroimage 181:550–9.

Flitman SS, Grafman J, Wassermann EM, Cooper V, O'Grady J, Pascual-Leone A, and others. 1998. Linguistic processing during repetitive transcranial magnetic stimulation. Neurology 50(1):175–81.

Gamboa OL, Antal A, Moliadze V, Paulus W. 2010. Simply longer is not better: reversal of theta burst after-effect with prolonged stimulation. Exp Brain Res 204(2):181–7.

Gentner R, Wankerl K, Reinsberger C, Zeller D, Classen J. 2008. Depression of human corticospinal excitability induced by magnetic theta-burst stimulation: evidence of rapid polarity-reversing metaplasticity. Cereb Cortex 18(9):2046–53.

Goldsworthy MR, Muller-Dahlhaus F, Ridding MC, Ziemann U. 2015. Resistant against de-depression: LTD-like plasticity in the human motor cortex induced by spaced cTBS. Cereb Cortex 25(7):1724–34.

Habich A, Feher KD, Antonenko D, Boraxbekk CJ, Floel A, Nissen C, and others. 2020. Stimulating aged brains with transcranial direct current stimulation: opportunities and challenges. Psychiatry Res Neuroimaging 306:111179.

Hallett M. 2000. Transcranial magnetic stimulation and the human brain. Nature 406(6792):147–50.

Hanley CJ, Alderman SL, Clemence E. 2020. Optimising cognitive enhancement: systematic assessment of the effects of tDCS duration in older adults. Brain Sci 10(5):304.

Hartwigsen G. 2015. The neurophysiology of language: insights from non-invasive brain stimulation in the healthy human brain. Brain Lang 148:81–94.

Hartwigsen G. 2016. Adaptive plasticity in the healthy language network: implications for language recovery after stroke. Neural Plasticity 2016:9674790.

Hartwigsen G, Bzdok D, Klein M, Wawrzyniak M, Stockert A, Wrede K, and others. 2017. Rapid short-term reorganization in the language network. Elife 6:e25964.

Hassanzahraee M, Nitsche MA, Zoghi M, Jaberzadeh S. 2020. Determination of anodal tDCS duration threshold for reversal of corticospinal excitability: an investigation for induction of counter-regulatory mechanisms. Brain Stimul 13(3):832–9.

Herz DM, Christensen MS, Bruggemann N, Hulme OJ, Ridderinkhof KR, Madsen KH, and others. 2014. Motivational tuning of fronto-subthalamic connectivity facilitates control of action impulses. J Neurosci 34(9):3210–7.

Holland R, Leff AP, Josephs O, Galea JM, Desikan M, Price CJ, and others. 2011. Speech facilitation by left inferior frontal cortex stimulation. Curr Biol 21(16):1403–7.

Horvath JC, Forte JD, Carter O. 2015. Evidence that transcranial direct current stimulation (tDCS) generates little-to-no reliable neurophysiologic effect beyond MEP amplitude modulation in healthy human subjects: a systematic review. Neuropsychologia 66:213–36.

Jamil A, Batsikadze G, Kuo HI, Labruna L, Hasan A, Paulus W, and others. 2017. Systematic evaluation of the impact of stimulation intensity on neuroplastic after-effects induced by transcranial direct current stimulation. J Physiol 595(4): 1273–88.

Kasten FH, Duecker K, Maack MC, Meiser A, Herrmann CS. 2019. Integrating electric field modeling and neuroimaging to explain inter-individual variability of tACS effects. Nat Commun 10(1):5427.

Kasten FH, Herrmann CS. 2020. The hidden state-dependency of transcranial alternating current stimulation (tACS). Preprint. bioRxiv. doi:10.1101/2020.12.23.423984

Klink K, Passmann S, Kasten FH, Peter J. 2020. The modulation of cognitive performance with transcranial alternating current stimulation: a systematic review of frequency-specific effects. Brain Sci 10(12):932.

Krause B, Marquez-Ruiz J, Cohen Kadosh R. 2013. The effect of transcranial direct current stimulation: a role for cortical excitation/inhibition balance? Front Hum Neurosci 7:602.

Kuhnke P, Beaupain MC, Cheung VKM, Weise K, Kiefer M, Hartwigsen G. 2020. Left posterior inferior parietal cortex causally supports the retrieval of action knowledge. Neuroimage 219:117041.

Kuo MF, Nitsche MA. 2012. Effects of transcranial electrical stimulation on cognition. Clin EEG Neurosci 43(3):192–9.

Kuo MF, Paulus W, Nitsche MA. 2006. Sex differences in cortical neuroplasticity in humans. Neuroreport 17(16):1703–7.

Laakso I, Tanaka S, Koyama S, De Santis V, Hirata A. 2015. Inter-subject variability in electric fields of motor cortical tDCS. Brain Stimul 8(5):906–13.

Li LM, Violante IR, Leech R, Ross E, Hampshire A, Opitz A, and others. 2019. Brain state and polarity dependent modulation of brain networks by transcranial direct current stimulation. Hum Brain Mapp 40(3):904–15.

Luber B, Lisanby SH. 2014. Enhancement of human cognitive performance using transcranial magnetic stimulation (TMS). Neuroimage 85 Pt 3:961–70.

Mastroeni C, Bergmann TO, Rizzo V, Ritter C, Klein C, Pohlmann I, and others. 2013. Brain-derived neurotrophic factor—a major player in stimulation-induced homeostatic metaplasticity of human motor cortex? PLoS One 8(2):e57957.

Meinzer M, Lindenberg R, Antonenko D, Flaisch T, Floel A. 2013. Anodal transcranial direct current stimulation temporarily reverses age-associated cognitive decline and functional brain activity changes. J Neurosci 33(30):12470–8.

Meiron O, Lavidor M. 2013. Unilateral prefrontal direct current stimulation effects are modulated by working memory load and gender. Brain Stimul 6(3):440–7.

Miniussi C, Ruzzoli M, Walsh V. 2010. The mechanism of transcranial magnetic stimulation in cognition. Cortex 46(1):128–30.

Miranda PC, Lomarev M, Hallett M. 2006. Modeling the current distribution during transcranial direct current stimulation. Clin Neurophysiol 117(7):1623–9.

Moliadze V, Atalay D, Antal A, Paulus W. 2012. Close to threshold transcranial electrical stimulation preferentially activates inhibitory networks before switching to excitation with higher intensities. Brain Stimul 5(4):505–11.

Moliadze V, Stenner T, Matern S, Siniatchkin M, Nees F, Hartwigsen G. 2021. Online effects of beta-tACS over the left prefrontal cortex on phonological decisions. Neuroscience 463:264–71.

Moliadze V, Zhao Y, Eysel U, Funke K. 2003. Effect of transcranial magnetic stimulation on single-unit activity in the cat primary visual cortex. J Physiol 553 Pt 2:665–79.

Monte-Silva K, Kuo MF, Hessenthaler S, Fresnoza S, Liebetanz D, Paulus W, and others. 2013. Induction of late LTP-like plasticity in the human motor cortex by repeated non-invasive brain stimulation. Brain Stimul 6(3):424–32.

Murakami T, Muller-Dahlhaus F, Lu MK, Ziemann U. 2012. Homeostatic metaplasticity of corticospinal excitatory and intracortical inhibitory neural circuits in human motor cortex. J Physiol 590(22):5765–81.

Neggers SF, Petrov PI, Mandija S, Sommer IE, van den Berg NA. 2015. Understanding the biophysical effects of transcranial magnetic stimulation on brain tissue: the bridge between brain stimulation and cognition. Prog Brain Res 222:229–59.

Nitsche MA, Fricke K, Henschke U, Schlitterlau A, Liebetanz D, Lang N, and others. 2003. Pharmacological modulation of cortical excitability shifts induced by transcranial direct current stimulation in humans. J Physiol 553 Pt 1:293–301.

Nitsche MA, Paulus W. 2000. Excitability changes induced in the human motor cortex by weak transcranial direct current stimulation. J Physiol 527 Pt 3:633–9.

Nitsche MA, Paulus W. 2001. Sustained excitability elevations induced by transcranial DC motor cortex stimulation in humans. Neurology 57(10):1899–901.

Nitsche MA, Seeber A, Frommann K, Klein CC, Rochford C, Nitsche MS, and others. 2005. Modulating parameters of excitability during and after transcranial direct current stimulation of the human motor cortex. J Physiol 568 Pt 1:291–303.

Opitz A, Fox MD, Craddock RC, Colcombe S, Milham MP. 2016. An integrated framework for targeting functional networks via transcranial magnetic stimulation. Neuroimage 127:86–96.

Opitz A, Paulus W, Will S, Antunes A, Thielscher A. 2015. Determinants of the electric field during transcranial direct current stimulation. Neuroimage 109:140–50.

Pascual-Leone A, Walsh V, Rothwell J. 2000. Transcranial magnetic stimulation in cognitive neuroscience—virtual lesion, chronometry, and functional connectivity. Curr Opin Neurobiol 10(2):232–7.

Perceval G, Floel A, Meinzer M. 2016. Can transcranial direct current stimulation counteract age-associated functional impairment? Neurosci Biobehav Rev 65:157–72.

Perceval G, Martin AK, Copland DA, Laine M, Meinzer M. 2020. Multisession transcranial direct current stimulation facilitates verbal learning and memory consolidation in young and older adults. Brain Lang 205:104788.

Pitcher D, Parkin B, Walsh V. 2021. Transcranial magnetic stimulation and the understanding of behavior. Annu Rev Psychol 72:97–121.

Reis J, Schambra HM, Cohen LG, Buch ER, Fritsch B, Zarahn E, and others. 2009. Noninvasive cortical stimulation enhances motor skill acquisition over multiple days through an effect on consolidation. Proc Natl Acad Sci U S A 106(5):1590–5.

Ridding MC, Ziemann U. 2010. Determinants of the induction of cortical plasticity by non-invasive brain stimulation in healthy subjects. J Physiol 588 Pt 13:2291–304.

Riddle J, McFerren A, Frohlich F. 2021. Causal role of cross-frequency coupling in distinct components of cognitive control. Prog Neurobiol 202:102033.

Romei V, Thut G, Silvanto J. 2016. Information-based approaches of noninvasive transcranial brain stimulation. Trends Neurosci 39(11):782–95.

Ruzzoli M, Marzi CA, Miniussi C. 2010. The neural mechanisms of the effects of transcranial magnetic stimulation on perception. J Neurophysiol 103(6):2982–9.

Salvador R, Wenger C, Miranda PC. 2015. Investigating the cortical regions involved in MEP modulation in tDCS. Front Cell Neurosci 9:405.

Sasaki T, Kodama S, Togashi N, Shirota Y, Sugiyama Y, Tokushige SI, and others. 2018. The intensity of continuous theta burst stimulation, but not the waveform used to elicit motor evoked potentials, influences its outcome in the human motor cortex. Brain Stimul 11(2):400–10.

Saturnino GB, Madsen KH, Thielscher A. 2019. Electric field simulations for transcranial brain stimulation using FEM: an efficient implementation and error analysis. J Neural Eng 16(6):066032.

Saturnino GB, Thielscher A, Madsen KH, Knoesche TR, Weise K. 2019. A principled approach to conductivity uncertainty analysis in electric field calculations. Neuroimage 188:821–34.

Schwarzkopf DS, Silvanto J, Rees G. 2011. Stochastic resonance effects reveal the neural mechanisms of transcranial magnetic stimulation. J Neurosci 31(9):3143–7.

Siebner HR, Hartwigsen G, Kassuba T, Rothwell JC. 2009. How does transcranial magnetic stimulation modify neuronal activity in the brain? Implications for studies of cognition. Cortex 45(9):1035–42.

Silvanto J, Bona S, Cattaneo Z. 2017. Initial activation state, stimulation intensity and timing of stimulation interact in producing behavioral effects of TMS. Neuroscience 363:134–41.

Silvanto J, Bona S, Marelli M, Cattaneo Z. 2018. On the mechanisms of transcranial magnetic stimulation (TMS): how brain state and baseline performance level determine behavioral effects of TMS. Front Psychol 9:741.

Silvanto J, Cattaneo Z. 2017. Common framework for "virtual lesion" and state-dependent TMS: the facilitatory/suppressive range model of online TMS effects on behavior. Brain Cogn 119:32–38.

Stagg CJ, Jayaram G, Pastor D, Kincses ZT, Matthews PM, Johansen-Berg H. 2011. Polarity and timing-dependent effects of transcranial direct current stimulation in explicit motor learning. Neuropsychologia 49(5):800–4.

Stecher HI, Notbohm A, Kasten FH, Herrmann CS. 2021. A comparison of closed loop vs. fixed frequency tACS on modulating brain oscillations and visual detection. Front Hum Neurosci 15:661432.

Stefan K, Wycislo M, Gentner R, Schramm A, Naumann M, Reiners K, and others. 2006. Temporary occlusion of associative motor cortical plasticity by prior dynamic motor training. Cereb Cortex 16(3):376–85.

Topper R, Mottaghy FM, Brugmann M, Noth J, Huber W. 1998. Facilitation of picture naming by focal transcranial magnetic stimulation of Wernicke's area. Exp Brain Res 121(4):371–8.

Vignaud P, Mondino M, Poulet E, Palm U, Brunelin J. 2018. Duration but not intensity influences transcranial direct current stimulation (tDCS) after-effects on cortical excitability. Neurophysiol Clin 48(2):89–92.

Vosskuhl J, Struber D, Herrmann CS. 2018. Non-invasive brain stimulation: a paradigm shift in understanding brain oscillations. Front Hum Neurosci 12:211.

Walsh V, Cowey A. 2000. Transcranial magnetic stimulation and cognitive neuroscience. Nat Rev Neurosci 1(1):73–9.

Walsh V, Pascual-Leone A. 2003. Transcranial magnetic stimulation: a neurochronometrics of mind. Cambridge (MA): The MIT Press.

Wassermann EM, Blaxton TA, Hoffman EA, Berry CD, Oletsky H, Pascual-Leone A, and others. 1999. Repetitive transcranial magnetic stimulation of the dominant hemisphere can disrupt visual naming in temporal lobe epilepsy patients. Neuropsychologia 37(5):537–44.

Wassermann EM, Wedegaertner FR, Ziemann U, George MS, Chen R. 1998. Crossed reduction of human motor cortex excitability by 1-Hz transcranial magnetic stimulation. Neurosci Lett 250(3):141–4.

Weise K, Numssen O, Thielscher A, Hartwigsen G, Knoesche TR. 2019. A novel approach to localize cortical TMS effects. Neuroimage 209:116486.

Wiegand A, Nieratschker V, Plewnia C. 2016. Genetic modulation of transcranial direct current stimulation effects on cognition. Front Hum Neurosci 10:651.