



Transcranial brain stimulation: closing the loop between brain and stimulation

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Purpose of review

To discuss recent strategies for boosting the efficacy of noninvasive transcranial brain stimulation to improve human brain function.

Recent findings

Recent research exposed substantial intra- and inter-individual variability in response to plasticity-inducing transcranial brain stimulation. Trait-related and state-related determinants contribute to this variability, challenging the standard approach to apply stimulation in a rigid, one-size-fits-all fashion. Several strategies have been identified to reduce variability and maximize the plasticity-inducing effects of noninvasive transcranial brain stimulation. Priming interventions or paired associative stimulation can be used to 'standardize' the brain-state and hereby, homogenize the group response to stimulation. Neuroanatomical and neurochemical profiling based on magnetic resonance imaging and spectroscopy can capture trait-related and state-related variability. Fluctuations in brain-states can be traced online with functional brain imaging and inform the timing or other settings of transcranial brain stimulation. State-informed open-loop stimulation is aligned to the expression of a predefined brain state, according to prespecified rules. In contrast, adaptive closed-loop stimulation dynamically adjusts stimulation settings based on the occurrence of stimulation-induced state changes.

Summary

Approaches that take into account trait-related and state-related determinants of stimulation-induced plasticity bear considerable potential to establish noninvasive transcranial brain stimulation as interventional therapeutic tool.

Keywords

brain plasticity, brain rhythms, closed-loop brain stimulation, noninvasive transcranial brain stimulation (NTBS), open-loop brain stimulation, state dependence

INTRODUCTION

A range of noninvasive transcranial brain stimulation (NTBS) techniques is widely used in neuroscience and clinical settings. Transcranial magnetic stimulation (TMS) relies on 'inductive' electrical stimulation of the brain via a strong time-varying electromagnetic field, while transcranial current stimulation (TCS) passes electrical currents directly through the skull to stimulate the brain. Depending on the type of current, TCS is called transcranial direct current stimulation (TDCS) or transcranial alternating current stimulation (TACS). Although TMS induces electrical currents that are sufficiently strong to induce action potentials in axonal structures close to the hemispherical surface, TDCS and TACS generate weaker electrical currents that produce slight shifts in the membrane potential, and hereby modulate intrinsic neural activity without directly inducing action potentials.

TMS, TDCS and TACS can influence brain activity beyond the stimulation period, although their biophysical properties differ substantially in

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KEY POINTS

- Trait-related and state-related factors determine the responsiveness to the plasticity-inducing effects of NTBS. This motivates the use of individualized protocols, which adjust for these trait-related or state-related determinants.
- Trait-related factors can help to identify individuals with similar responsiveness to NTBS, whereas state-related determinants can inform manipulations to ‘standardize’ the brain state at the time of NTBS in order to homogenize the group response.
- State-informed open-loop NTBS allows to apply NTBS conditional upon the expression of specific state-related determinants. Initial studies indicate that state-triggered stimulation boosts LTP-like or LTD-like effects of NTBS.
- Adaptive closed-loop NTBS dynamically adjusts stimulation settings to state changes induced by NTBS. This approach is still in its infancy and its plasticity-inducing potential remains to be explored.

terms of generated current strength, focality and temporal stimulation pattern [1,2]. The physiological after-effects of interventional NTBS are far from being understood, but there is consensus that NTBS can induce long term potentiation (LTP)-like and long term depression (LTD)-like effects [3], homeostatic-like plasticity [4], as well as cause lasting changes in effective connectivity at the brain network level [5]. The plasticity-inducing potential of NTBS attracted considerable clinical interest as a relatively safe and pain-free tool to improve brain function in various brain disorders and prompted substantial efforts in the last two decades to exploit the various NTBS techniques therapeutically [6]. Yet, therapeutic studies have only provided sufficient level-A evidence of definite efficacy for the antidepressant effect of high-frequency repetitive TMS (rTMS) of left dorsolateral prefrontal cortex and the analgesic effect of high-frequency rTMS of the primary motor cortex (M1) contralateral to the affected side in neuropathic pain [6,7]. Currently, a major obstacle for the broad therapeutic use of interventional NTBS is that most after-effects show strong inter-individual and intra-individual variability [8].

‘VARIABILITY’ AS AN EMERGING THEME

Interventional NTBS protocols are commonly applied in a rigid, ‘one-size-fits-all’ fashion (Fig. 1). With the exception of stimulus intensity in the case of TMS, all NTBS variables are usually preprogrammed and applied in an open-loop

manner. The NTBS protocol is kept constant across individuals and throughout the course of stimulation. This rigid approach ignores both intra-individual and inter-individual variations in the neurobiology of the brain and may be the reason for the considerable variability of the brain response to current NTBS protocols [8]. Indeed, recent neurophysiological studies in relatively large cohorts of healthy individuals have consistently shown that inter-individual variability of NTBS after-effects is not the exception but the rule, and the size of inter-individual variability has been considerably underestimated in previous research. A number of studies on the plasticity-inducing effects of NTBS targeting area M1 have shown that the number of responders, showing the expected LTP-like or LTD-like effect can be lower than 50% with similar percentages showing reversed LTP-like or LTD-like effects [9–12].

In good agreement with these results, another recent line of research showed that a wide range of neuroanatomical, neurochemical and neurophysiological factors could determine the after-effects of NTBS [13,14] (Fig. 2). Neuroanatomical determinants include cortical and skull thickness [15,16], differences in gyral shape and white matter structure [17,18]. Neurochemical determinants include factors like neurotransmitter availability and hormone levels [19–22]. Neurophysiological determinants involve attention state [23], activity history [4,24] and endogenous oscillatory patterns [25,26]. These determinants are not mutually independent, can modulate each other [27], and can be modified by other variables such as age [28] or genetic traits [29]. Some plasticity-determining factors exert relatively stable invariant effects on the individual responsiveness to NTBS, including demographic, genetic, and neuroanatomical characteristics, but also stable neurophysiological traits such as the individual alpha rhythm frequency. Because these trait-related determinants contribute to inter-individual variability, it may be possible to reduce inter-individual variability by preselecting participants or adjusting NTBS variables to the individually expressed ‘trait’. For instance, circadian fluctuations in the responsiveness to NTBS can be controlled by applying NTBS at a fixed time of the day [30]. Functional connectivity patterns have also been used to predict the therapeutic effect of TMS. Using resting-state MRI (rs-MRI), several groups reported that rs-connectivity of the subgenual cingulate cortex, measured days before therapy onset, predicted the therapeutic effect of a 5-week high-frequency rTMS intervention in major depressive disorder [30–33].

In contrast to ‘trait-related’ determinants, the modifying effects of other plasticity-determining

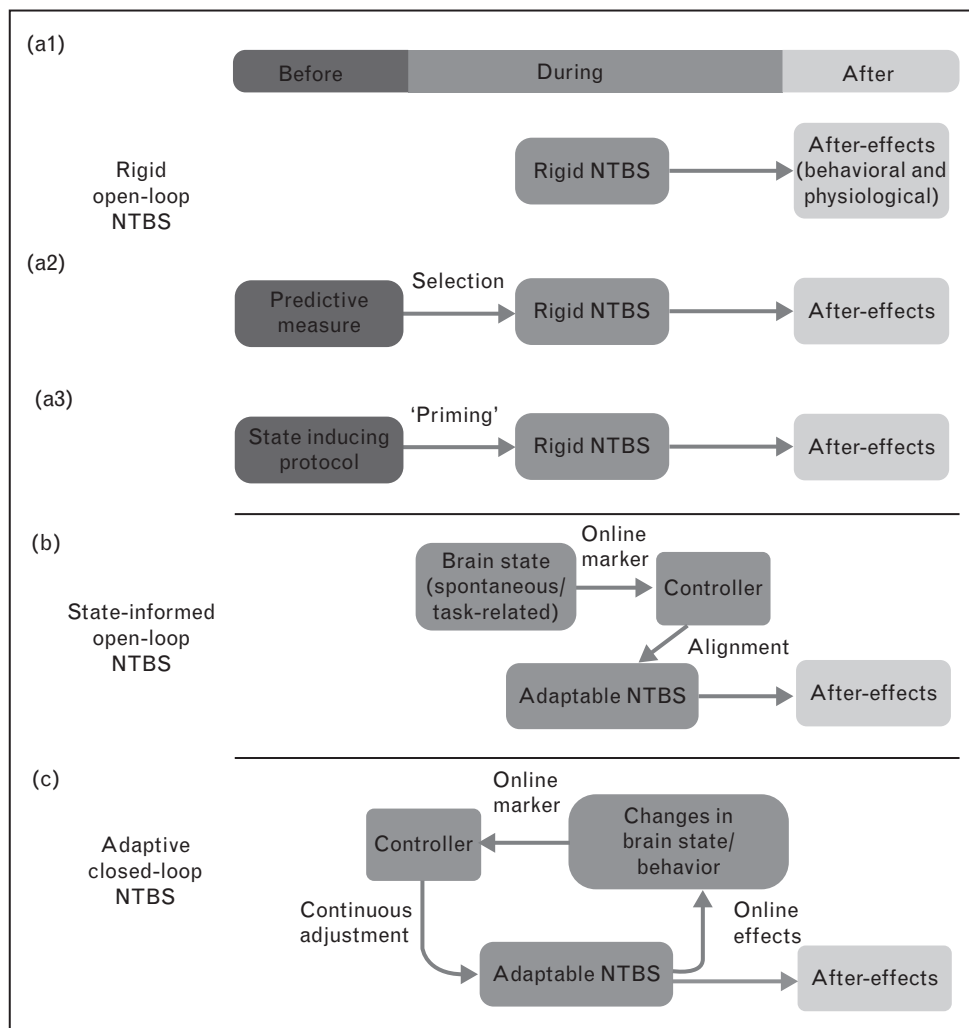


FIGURE 1. Towards closed-loop NTBS. (a1) Standard application of NTBS. The protocol is selected based on its known average impact on physiological or behavioral variables. It is applied stereotypically in all patients or participants. (a2) The best protocol among some alternatives is selected based on prior measurements of markers, which have been demonstrated to be predictive of individual outcome. (a3) A combination of protocols is used to stabilize outcome. Initially, a protocol is applied which is known to 'set' the brain in a state that renders it sensitive to the main NTBS protocol. (b) Markers of a preselected brain state are continuously read out and used to align the application of the NTBS protocol. Electroencephalography (EEG) band activity is a feasible marker with good temporal resolution. This approach cannot only be applied during rest, but also to align the NTBS protocol with task-related activity. (c) Full closed-loop application of an adaptable NTBS protocol. In this setting, neuroimaging (or another readout) is used to assess markers of the immediate effects of the NTBS protocol on brain activity. These markers are then used for on-the-fly adaptations of the protocol.

factors are tightly linked to the physiological state expressed by the brain at the time of stimulation, such as the phase or amplitude of oscillatory brain activity [1]. These 'state-related' determinants are liable to rapid within-session and between-session changes over the course of the NTBS intervention and thus, contribute to both inter-individual and intra-individual variability in responsiveness to NTBS. Fast-fluctuating neurophysiological determinants have mainly been identified by post-hoc grouping of NTBS trials based on concurrently

recorded electroencephalography (EEG) signals, providing correlational evidence for the importance of oscillatory phase and amplitude for NTBS outcome [34–41].

Previous work has often tried to deal with state-associated factors by using rigorous standardization, matching state-related factors like attention, time of day and preintervention motor-activity constant across individuals [13,42]. However, rigorous standardization of state-related determinants may not be applicable in a clinical setting.

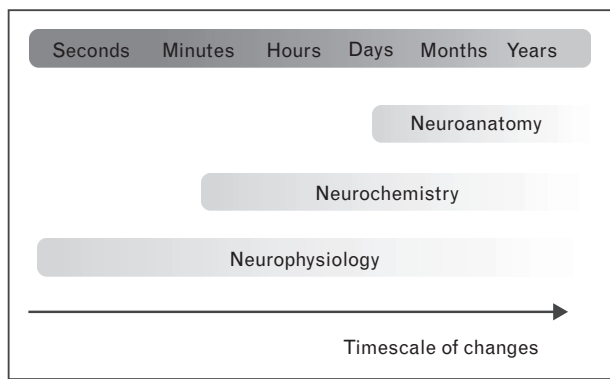


FIGURE 2. Timescales of changes in neuroanatomy, neurochemistry and neurophysiology determining the ability of NTBS to induce long-term potentiation (LTP)-like or long term depression (LTD)-like plasticity. Neuroanatomical changes on the microscopic level (such as myelination) and the macroscopic level (such as cortical thickness or folding pattern) are slow and it can be assumed that neuroanatomical features remain constant for the duration of a brain stimulation protocol. Neurochemical changes can be faster and can be influenced by the time of the day (which is an easily controllable factor), but also faster acting factors such as motivation. Neurochemical features can undergo changes during the administration of NTBS. Neurophysiological changes can occur on the sub-second time scale. For example, attentional changes or changes of the involvement of the stimulated area in the time course of a behavioral task can be very fast. They lend themselves best for the usage in online control settings based on central and peripheral markers of brain state. NTBS, noninvasive transcranial brain stimulation.

Individually adjusted open-loop noninvasive transcranial brain stimulation

Stable trait-related factors or very slowly changing state-related factors that determine plasticity-inducing efficacy of NTBS can be used to individually adjust the variables of rigid NTBS protocols (Fig. 1). In this context, ‘open-loop NTBS’ covers all NTBS protocols consisting of a predefined set of stimulation variables that are kept constant during the administration of NTBS.

Most studies use neurophysiologic traits to individually adjust open-loop NTBS. For M1, the timing of intracortical facilitation can be probed within the sub-millisecond time range using paired-pulse TMS [43]. Adjusting the inter-pulse interval of repetitive TMS to the intrinsic rhythmicity of intracortical facilitation enhances the LTP-inducing capabilities of specific TMS protocols [44]. EEG can also readily provide subject-specific information about endogenous oscillatory patterns. Both repetitive TMS and TACS are often given at a stimulation rate of 10 Hz, a frequency close to the endogenous alpha

rhythm (8–12 Hz). Several groups have boosted electrophysiological and behavioral effects when the frequency of rTMS or TACS was adjusted to the preferred individual alpha rhythm [45,46,47]. In clinical studies, attempts to specifically target the individual alpha frequency (IAF) yielded mixed results. In patients with schizophrenia, two studies compared the effectiveness of IAF-stimulation to rigid-state, 10 Hz stimulation and found a significantly greater therapeutic effect for IAF-stimulation [48,49], whereas two trials on treatment of major depression could not find a significant advantage of IAF-stimulation [50,51].

We are not aware of any study, which prospectively used neuroanatomical or neurochemical determinants to individually adjust the variables of rigid NTBS protocols. Profiling neuroanatomical and neurochemical factors often exceeds the scope of a short ‘calibration’ experiment. This hampers the integration of these factors into an individual adjustment routine. At least with respect to neuroanatomical profiling, individualization of NTBS is within reach in the foreseeable future. Macroscopic neuroanatomical features are readily revealed by neuroimaging. Additionally, software solutions become increasingly available which can use the neuroimaging data to model the impact of variations in the shape and volume of the targeted cortical gyrus on the distribution of the induced electrical fields in the cortical target and surrounding cortical areas [52,53].

State control of open-loop noninvasive transcranial brain stimulation

Preselection of individuals or individually adjusted rigid NTBS is not an option, if one wants to control the influence of state-related factors that vary on a time scale of minutes or shorter. One strategy to ‘homogenize’ the individual response to the NTBS intervention is to secure that all participants express a comparable neurophysiological or neurochemical state at the time of NTBS [4]. For instance, a priming intervention may be applied to achieve ‘state control’, including a preceding NTBS [54], pharmacological manipulation [55] or a preceding period of physical (in)activity [24] (Fig. 1).

Another mean of ‘standardizing’ the brain state at the time of stimulation is associative pairing. Associative pairing exploits Hebbian principles of spike-time dependent-like neural plasticity. Pairing electrical nerve stimulation with single-pulse TMS, paired associative stimulation (PAS), has long been used to induce spike-timing dependent-like plasticity in human M1 [56]. Recently, the concept of peripheral-cortical PAS was successfully

transferred to other NTBS techniques by pairing brief trains of peripheral afferent stimulation with short bursts of high frequency (≥ 80 Hz) TACS over contralateral M1 [57[•]]. In addition to peripheral-cortical PAS, dual-site cortico-cortical PAS has been used to induce spike-time dependent-like neural plasticity, for instance by associative pairing of TMS over the left and right hand area of M1 [58] or over pairing of TMS to parietal or frontal areas and M1 [59,60]. Associative cortico-cortical pairing of NTBS has also been demonstrated outside of M1. Polania *et al.* [61[•]] showed that antiphase pairing of frontal and parietal TACS influenced behavior in a value-based choice task, whereas in-phase pairing was not different from sham-stimulation. Whether in-phase dual-site TACS also can be used to induce Hebbian LTP-like after-effects in the stimulated areas and whether this is related to Hebbian principles of plasticity remains to be addressed in future studies. An innovative extension of the PAS approach was recently introduced in patients with Parkinson's disease, in which deep brain stimulation (DBS) of the subthalamic nucleus (STN) was paired with single-pulse TMS of M1 [62^{••}].

STATE-INFORMED OPEN-LOOP NONINVASIVE TRANSCRANIAL BRAIN STIMULATION

Another possibility to deal with time-varying state-related determinants of NTBS-induced plasticity is the 'temporal neuronavigation' of NTBS by adjusting the timing of NTBS to the expression of a given cortical state like the phase or power of cortical oscillatory activity (Fig. 1). This requires that endogenous fluctuations of relevant state-markers are continuously read out and are used to trigger NTBS in a feed-forward manner. The feasibility of activity-dependent stimulation has been illustrated in a proof-of-principle study [63] in which EEG-derived phase information was exploited to temporally navigate single TMS pulses into the up-state and down-state of slow-wave oscillations during non-rapid eye movement sleep. Using this state-informed NTBS approach, the authors showed that the motor evoked potential, triggered by TMS was significantly larger when the pulse was given in the up-phase than when the pulse was given in the down phase of slow-wave sleep oscillations. Although this study showed the feasibility of 'on-demand' state-informed NTBS, it remains to be clarified whether such state-triggered stimulation can more reliably induce LTP-like plasticity than state-naïve NTBS.

An encouraging proof-of-concept study has demonstrated that state-triggered NTBS can induce

LTP-like changes in corticospinal excitability [64[•]]. In that study, on-line EEG triggered the administration of single-pulse TMS, which depended on task-related desynchronization of beta-band oscillatory activity during a motor imagery task. State-triggered single-pulse TMS induced a stable LTP-like increase in corticospinal excitability, whereas the same number and pattern of stimuli applied in a brain-state independent fashion decreased corticospinal excitability. Brain-state independent single-pulse TMS was given at rest in the absence of motor imagery. Since the effects of motor imagery alone were not assessed, it is unclear whether the LTP-like increase in corticospinal excitability was caused by state-triggered single-pulse TMS, by motor imagery, or the combination of motor imagery and state-triggered single-pulse TMS. Based on a single-case study in a patient with motor stroke, it was suggested that a similar approach might be used to increase M1 excitability during neurorehabilitation [65]. Fluctuating neural states might not only be useful to define the time point of NTBS (i.e., state-triggered NTBS). State-informed NTBS may also be used to adjust other NTBS variables (e.g., intensity) according to a prespecified rule that is based on the expressed brain state.

Adaptive, closed-loop noninvasive transcranial brain stimulation

Standardizing the state of the brain at the time of NTBS can reduce the intra-individual and inter-individual variability and induce associative Hebbian plasticity. Another way to exploit online 'read-outs' of the brain state is to monitor the functional impact of NTBS online during stimulation. These acute changes may be predictive of NTBS after-effects and yield important information that can be used to dynamically adjust the stimulation settings in order to maximize its plasticity-inducing potential in each individual (Fig. 1).

Adaptive closed-loop neurostimulation that dynamically reacts to the occurrence of distinct neural activity patterns has already made significant progress in recent years in the field of invasive brain stimulation using implanted devices [66,67]. For instance, DBS of the STN that is dynamically controlled by STN-beta power resulted in approximately 30% greater clinical improvements than standard open-loop DBS in a small group of patients with Parkinson's disease [68^{••}]. A 'on demand' closed-loop stimulation device may deliver stimulation more efficiently by limiting stimulation only when brain function is impaired or aberrant neural activity is present [69].

Although this experience motivates the use of adaptive, closed-loop approaches in the field of NTBS, this is still in its infancy. Therefore, the label ‘closed-loop’ should be used very carefully. Especially, the use of state-triggered NTBS that lacks an adaptive property based on the NTBS-induced state changes should not be labeled as ‘closed-loop’ NTBS [64]. A real ‘closed-loop’ approach requires that several major challenges are solved. First, a state marker has to be identified which reliably signals the dynamic changes induced by NTBS. That is, rather than merely detecting the occurrence of a brain state to adjust the temporal application of the NTBS protocol to, we are interested in reading out the ongoing changes in the brain state because of NTBS. It should be noted that stable change detection requires integration over longer time windows, so that adaptive closed-loop will be slower than mere brain-state detection. Second, it has to be demonstrated that changes in the state marker are truly predictive of NTBS-induced after-effects of interest such as LTP-like or LTD-like plasticity or specific functional improvement. Finally, it has to be demonstrated that the iterative modification of selected stimulation settings does efficiently influence the identified state marker in a controlled way.

A first proof-of-principle example for closed-loop NTBS used TACS to target M1 at the individual tremor frequency in patients with Parkinson’s disease to suppress tremor amplitude [70]. The individual tremor frequency was taken as a peripheral proxy for endogenous oscillatory activity and the goal was to weaken these spontaneous oscillations by phase-cancellation with exogenously applied TACS oscillations. To this end, the phase of TACS was constantly adjusted, informed by the ongoing tremor activity, to maintain the optimal phase-delay between TACS and the endogenous tremor rhythm as determined from simultaneous actigraphy measures. Using this method, the authors achieved tremor suppression of around 50%. Although this study is very encouraging, the demonstration that plasticity-inducing after-effects of NTBS can be improved by closed-loop adjustment of the stimulation settings is still missing.

CONCLUSION

The substantial intra-individual and inter-individual variability in the responsiveness to NTBS has given rise to a critical reflection on the conventional approach to apply NTBS in an ‘open-loop’ one-size-fits-all fashion. Many trait-related or state-related factors determine this variability and prompted novel strategies to reduce variability and maximize the plasticity-inducing effects of NTBS. Trait-related

determinants can be identified before NTBS and used for selection of individuals sharing a similar responsiveness to NTBS. State-related determinants can inform priming interventions or PAS protocols to ‘standardize’ the brain state at the time of NTBS. The relevance of distinct brain states in determining the ability to induce a strong LTP-like or LTD-like effect motivates the use of state-informed open-loop NTBS where administration of NTBS is conditional upon the expression of predefined brain states. Adaptive closed-loop NTBS that dynamically adjusts stimulation settings to the occurrence of an NTBS-induced state change is another promising option to exploit state-dependent determinants and eventually boost plasticity-inducing effects of NTBS. Both, informed open-loop NTBS as well as adaptive closed-loop NTBS, are still in their infancy, and it remains to be shown whether they outperform the plasticity-inducing properties of standard rigid open-loop approaches.

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Conflicts of interest

H.R.S. has served on a scientific advisory board for Lundbeck A/S, Valby Denmark, has received honoraria as speaker from Biogen Idec, Denmark A/S, Genzyme, Denmark and Merck Serono, Denmark, has received honoraria as editor from Elsevier Publishers, Amsterdam, The Netherlands and Springer Publishing, Stuttgart, Germany, has received travel support from MagVenture, Denmark, and has received a research fund from Biogen Idec. The remaining authors have no conflicts of interest.

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- of special interest
- of outstanding interest

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