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Studying and modifying brain function with non-invasive brain stimulation

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In the past three decades, our understanding of brain–behavior relationships has been significantly shaped by research using non-invasive brain stimulation (NIBS) techniques. These methods allow non-invasive and safe modulation of neural processes in the healthy brain, enabling researchers to directly study how experimentally altered neural activity causally affects behavior. This unique property of NIBS methods has, on the one hand, led to groundbreaking findings on the brain basis of various aspects of behavior and has raised interest in possible clinical and practical applications of these methods. On the other hand, it has also triggered increasingly critical debates about the properties and possible limitations of these methods. In this review, we discuss these issues, clarify the challenges associated with the use of currently available NIBS techniques for basic research and practical applications, and provide recommendations for studies using NIBS techniques to establish brain–behavior relationships.

Some of the main goals of neuroscience are to understand how the brain controls cognition, emotion and behavior. With the advent of neuroimaging technologies in the last century, it became possible to study the structural and functional brain correlates of behavior and underlying cognitive functions. Establishing these correlations, at various levels of description (cells, circuits and system), continues to teach us much about brain–behavior relationships. However, there is increasing awareness that correlative links alone cannot establish that a measured brain process is indeed necessary or sufficient for a behavior or mental process to occur. This limitation may be particularly relevant in applied settings, where the possible diagnostic and therapeutic usefulness of a neural measure depends on whether it reflects mechanisms that are causally involved in pathological disruption and treatment-induced improvements of behavior. Progress on these questions therefore requires methods that allow researchers to directly assess how experimentally induced changes in neural processes affect behavior and the underlying mental operations.

In animal models, such assessments are usually performed with invasive methods such as pharmacological interventions[1], reversible cooling deactivation[2], targeted microstimulation[3] and, more recently, optogenetics[4]. These approaches can provide detailed demonstrations of brain–function relations with high degrees of spatial precision, encompassing even cell-type-specific effects. Unfortunately, many of these methods cannot be applied in a routine fashion in healthy humans. Most human studies on the causality of brain–behavior relationships therefore employ purely non-invasive brain stimulation techniques. These methods originated over 30 years ago, when Merton and Morton demonstrated that running brief electrical currents through the human scalp can activate the underlying cortex and thereby affect behaviors corresponding to the activated brain areas[5]. This demonstration was a breakthrough, as it established that human brain function can be electrically influenced without opening the skull. The protocol did not catch on widely as it was painful to the participants (currents with intensities of ~20 A were applied through the scalp[5]), but it paved the way for the development of more comfortable methods of transcranial brain stimulation. Since then, two such methods have emerged as mainstays of NIBS in both basic and clinical contexts: transcranial magnetic stimulation (TMS), which is based on principles of electromagnetism, and transcranial electrical stimulation (tES), which harnesses weak, painless electrical currents applied to the scalp (current intensities of ~1–2 mA).

The number of publications using these methods (and variations thereof) is growing exponentially (Fig. 1b), perhaps reflecting the field's recognition that solid knowledge of brain–behavior relations needs converging evidence from neuroimaging and causal demonstrations. However, the growing popularity of these methods is accompanied by increasingly critical debates about their putative physiological mechanisms of action, proper application, and potential for clinical or applied use. These debates are important, since they indicate that NIBS methods may have come of age enough to warrant more detailed investigations of their potential and possible limitations. At the same time, some of these debates may reflect a lack of widely accepted standards for guiding, evaluating, and interpreting methodological aspects of NIBS studies on brain–behavior relations (guidelines mainly exist for the physiologically safe application of these methods[6,7]).

In this review article, we outline the possibilities and limitations of NIBS methods for investigations of brain–behavior relationships. In the first part, we present a concise overview of the spatiotemporal properties of NIBS effects and the implications of these properties for the use of these methods. In the second part, we will summarize and discuss recent debates about the use of NIBS methods and provide recommendations for how these debates may be addressed productively. Finally, we provide guidelines that may help to increase both the conclusiveness of NIBS studies of brain–behavior relations and the potential usefulness of NIBS protocols for possible translational applications.

Establishing brain–behavior relations with NIBS

While the evidence provided by brain imaging methods is purely correlative, it is invaluable for identifying neural processes that may be targeted with causal manipulation methods. In general, methods

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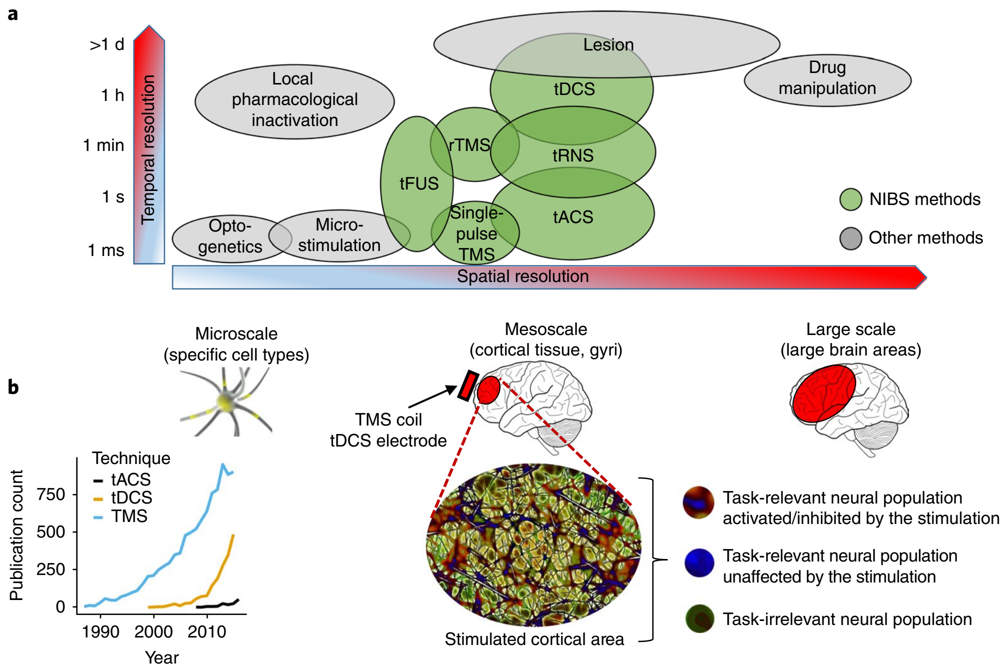


Fig. 1 | Overview of NIBS methods. a, The temporal and spatial resolution at which different causal brain interventions work. NIBS methods work at the mesoscale level, and the temporal resolution varies between high and low depending on the specific NIBS protocol. NIBS necessarily involves the relatively indiscriminate activation of large numbers of neurons; the apparent temporal and spatial specificity seen in NIBS studies is thus unlikely to reflect the anatomical and temporal specificity of the stimulation. Instead, it may indicate disruption of behaviorally relevant operations that are carried out by a relatively small number of cell groups[107] within larger brain regions. **b**, The exponentially growing number of citations per year for TMS, tDCS and tACS (source: http://ncbi.nlm.nih.gov/pubmed/; search dates from 1980 to 2016).

to causally manipulate neural activity can operate at different levels of spatial specificity (micro-, meso- and large-scale) and temporal resolution (from milliseconds to days or even longer). In both these dimensions, NIBS methods generally cover the middle ground, but specific ways of applying these methods differ in their precise properties (Fig. 1a). In terms of spatial resolution, the two most popular methods (TMS and tES) lead to electric fields that span relatively large areas of tissue compared to the effects of other, invasive methods (Fig. 1a and Box 1). Therefore, claims about the spatial focality of the effects need to be interpreted with care and should, whenever possible, be validated with combinations of neuroimaging methods and computational modeling (we discuss this in more detail in the recommendations section, below). Despite the relatively wide spatial spread of the electric fields across large numbers of neurons, the effective spatial resolution for modulating various types of behaviors is thought to be somewhat higher (Box 1). This may reflect the possibility that the behaviorally critical neural processes affected by the stimulation can themselves be restricted to a relatively small number of cell groups within larger brain regions, and that the stimulation can have different effects on neurons that are at rest or activated by ongoing behavior[8,9]. The functionally relevant spatial resolution of NIBS methods may therefore differ across different task contexts and may depend on the spatial extent of the task-related ongoing neural processing. Moreover, different ways of applying the same NIBS method can differ in their precise physical properties, which can set different limits on their mechanism of action, physiological effects, and spatial and temporal specificity. Different ways of applying NIBS methods are therefore suited to testing different types of hypotheses regarding interactions between physiology and behavior or cognition.

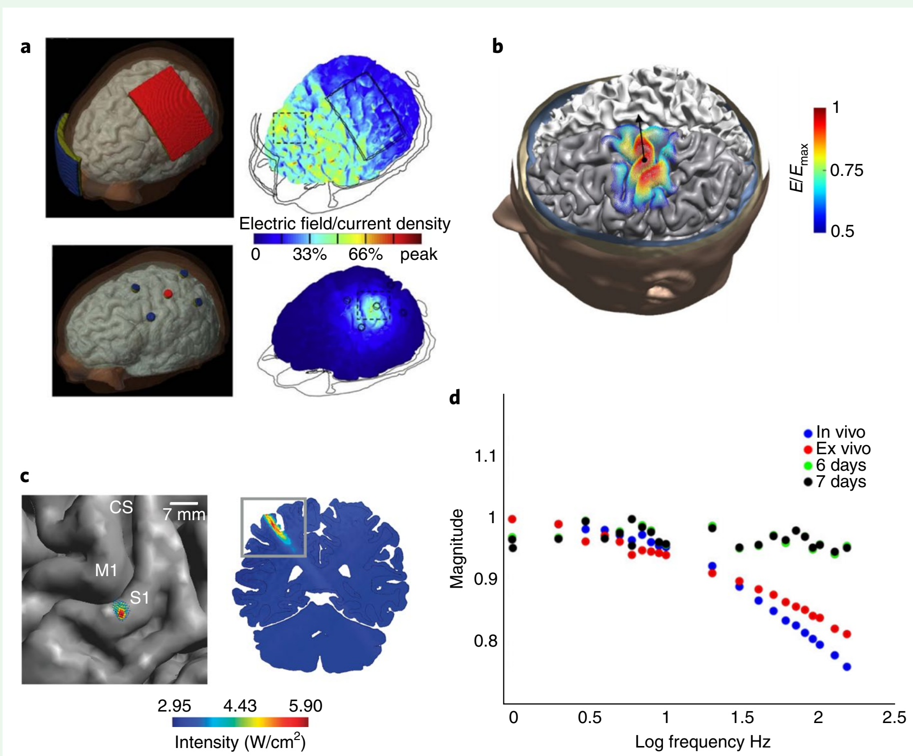
For instance, online application of TMS (i.e., single- or double-pulse TMS, or short bursts of TMS[10]) elicits temporally restricted bursts of action potentials. The application of such TMS pulses during task performance can be used to selectively interfere with ongoing neuronal processes to study the temporal dynamics of brain function with high temporal resolution (on the order of milliseconds). For examples, TMS pulses applied over V1 at a specific latency from the onset of a visual stimulus can induce suppression of conscious visual perception of this stimulus[11] and TMS pulses applied over cortical language production areas can produce speech arrest within a specific timeframe[12]. Additionally, simultaneous application of TMS pulses over different interconnected brain areas[13] or during concurrent neuroimaging[14,15] (Fig. 2c) allows tests of how action potentials elicited in one brain area influence processing in interconnected areas in a top-down and/or context-sensitive manner; this makes it possible to study how brain networks dynamically operate at high temporal resolution and to stimulate deep cortical or subcortical areas indirectly via interconnected areas[14,15]. Moreover, online TMS protocols that apply pulses at specific frequencies may facilitate corresponding oscillations, thus allowing tests of the causal link between brain rhythms and behavior[16–18]. Taken together, these studies demonstrate that online TMS protocols exert influences on neural processing in a highly task-, context- and time-dependent manner; these protocols can therefore be tailored to affect specific aspects of neural activity.

Other applications of TMS have focused on neuromodulatory after-effects following repetitive TMS protocols[10] (rTMS). Depending on their specific frequency and/or patterning, different rTMS protocols result in excitatory or inhibitory after-effects lasting several minutes, which have been linked to long-term potentiation or long-term depression (LTP or LTD, respectively; see Box 2). These after-effects are thought to reflect rTMS influences on the strength of glutamatergic synapses via NMDA receptor, AMPA receptor and calcium channel effects[10,19–21]. Other possible mediators of these effects may reflect nonlinear time-dependent influences on inhibitory GABAergic neurons, nonsynaptic mechanisms

Box 1 | Which aspects of neural processing are influenced by NIBS methods?

The results of research on basic neurophysiological NIBS effects have inspired many researchers to use NIBS techniques to investigate brain–behavior relationships. While the corresponding studies have led to a general consensus on the basic biophysical principles underlying each NIBS method, there is an ongoing debate about the precise neurophysiological processes that are stimulated by these techniques. Most studies on these issues have been conducted in primary motor cortex, so caution must be used when extrapolating this knowledge to other cortical areas. For instance, it was originally suggested that TMS primarily excites the axons of superficial cortical interneurons, which then activate cortical output neurons[141]. However, this notion may not apply to all cortical areas because which neurons are activated by an electrical current depends on the direction of the electrical field relative to the neuron, the sensitivity of a given type of neuron, the intensity of stimulation, the depth of penetration into excitable tissue and other factors[142]. The situation is further complicated by the fact that the gyrification of the human brain can vary between individuals and even within the same functionally defined area.

One strategy that has been proposed to address these issues is to estimate computational models of the most likely induced electric fields, which has led to the development of novel electrode configurations[137] that may help to predict NIBS-induced effects with greater accuracy[106,111] (see figure a,b,c). For instance, modeling work suggests that conventional electrode montages might induce effects not only under the electrodes but also between them, with the strongest fields for some montages predicted to actually not lie directly under the electrodes (a, top). While these efforts at modeling tES-induced electric fields and effects on neurons may ultimately prove crucial for optimizing the efficiency of NIBS protocols, such models do need to be physiologically validated[9,36,106] and will need to be able to fully account for the well-established effects induced by more traditional protocols[36]. For instance, neurophysiological work shows that both classic and novel electrode montages shown in panel a reliably induce cortical excitability that depends on the stimulation polarity, with the conventional electrode montage inducing stronger effects immediately after stimulation but the ring electrode configuration effects being more prominent 30 min after the end of stimulation[36]. Moreover, while the modeling sometimes suggests that the peak electric field in the classic montage may lie between rather than under the electrodes (a), the physiological data show that the induced effect is in fact maximal



Box Fig. 1 | Spatial focality of NIBS methods estimated by electric field (EF) models. a, Conventional tDCS electrode montage for anodal stimulation of M1 with the cathodal electrode over the contralateral orbit (top left) and a newly proposed 4 × 1 ring electrode configuration designed to improve the focality of the induced cortical EF (bottom left). EF simulations based on a finite-element model of the human head predict that the conventional electrode montage induces maximum EF mainly between the two electrodes, while the 4 × 1 ring electrode configuration induces more focalized effects over the target area[137]. Adapted with permission from ref. [137], Elsevier. **b**, The predicted EF induced by a TMS coil positioned above left M1 with an orientation relative to central sulcus of 45°. The induced EF is relatively focal, but comparable to the EF induced by the tDCS 4 × 1 ring electrode configuration[138]. Adapted with permission from ref. [138], Elsevier. **c**, The acoustic intensity field (AIF) of a transcranial focused ultrasound stimulation (tFUS) beam projected from above the primary somatosensory cortex. The AIF calculations suggest that tFUS should be much more focal than both TMS and tDCS as its effects are expressed in less than 1 cubic centimeter[139]. Adapted with permission from ref. [139], Springer Nature. **d**, Frequency response of intracranially measured voltages differ across different tACS frequencies between in vivo (blue) and ex vivo (red, green, and black) states[140]. Notably, any tACS frequency dependency is largely absent for the ex vivo measurements several days after death (green and black dots). Adapted with permission from ref. [140], National Academy of Sciences.

Box 1 | Which aspects of neural processing are influenced by NIBS methods? (Continued)

under the stimulating electrode[36]. This puzzling discrepancy will need to be resolved and shows that, while modeling will be useful to help optimizing NIBS protocols, physiological validation is crucial before jumping to conclusions about the spatial specificity and effectiveness of any NIBS protocol[143,144].

Another promising route to deal with the relatively low degree of spatial focality offered by tDCS (a) and TMS (b) focuses on the development of new methods with improved spatial resolution. One such promising technology may be transcranial focused ultrasound stimulation (tFUS), which can induce cortical excitability changes with a resolution of millimeters as suggested by theoretical modeling and empirical work[145] (c). However, the neurophysiological underpinnings of these tFUS-induced changes of cortical excitability still need to be understood in much more detail before this method can be put to safe routine use.

In an attempt to answer the question "which aspects of neural processing are influenced by NIBS?", researchers have tried to measure the neurophysiological influences of NIBS using a variety of methods, including in vitro[144], in vivo[9,40,143] and ex vivo preparations[146]. However, the results of these studies are variable. Therefore, it is crucial to investigate to what extent the results obtained from different approaches (for example, in vitro and ex vivo) can be directly extrapolated to NIBS-induced effects in the healthy living human brain. In a recent study, researchers measured electric fields in the brain of nonhuman primates during tDCS/tACS both in vivo and ex vivo[140]. They found significant differences in electrical field strength between in vivo and ex vivo measurements (d), which may relate to biophysical changes of brain and head tissues that naturally accompany death. These results provide crucial evidence that accurate evaluation of the biophysical properties of NIBS techniques critically depend on in vivo measurements[9,140,143] and that conclusions derived from ex vivo experiments need to be interpreted with care.

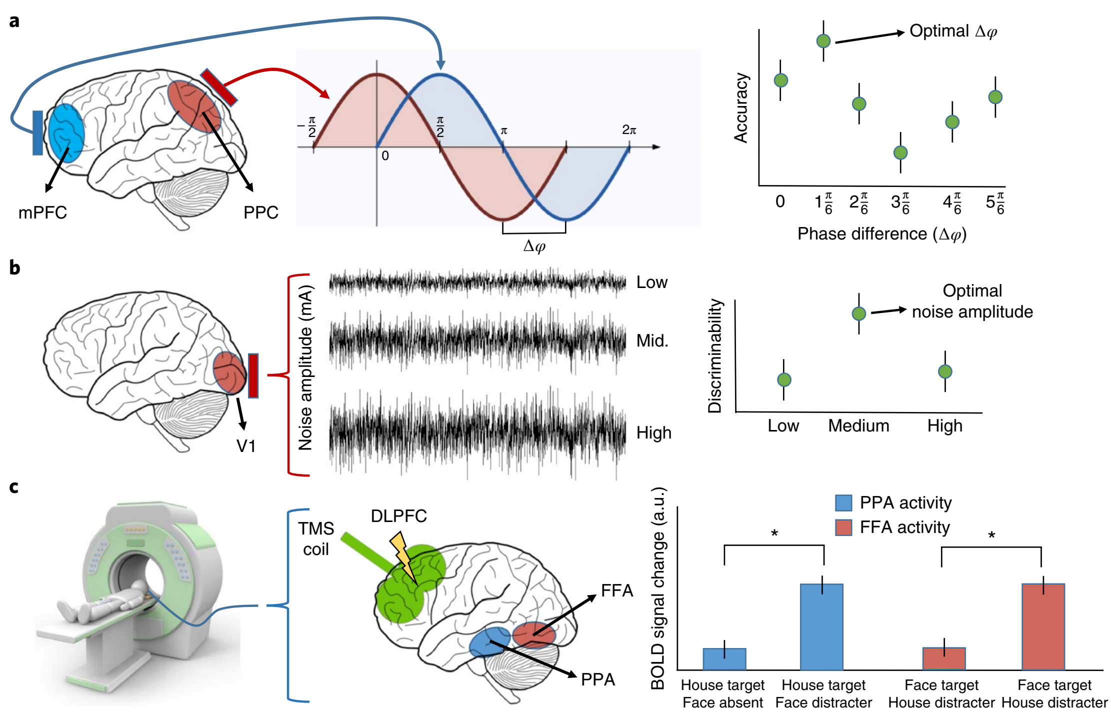


Fig. 2 | Examples of NIBS methods to study brain–function relationships. a, tACS applied with multi-electrode setups can be used to investigate how oscillatory coherence between spatially distinct nodes of functional networks underlies behavior. In the example experiment presented in this panel, tACS electrodes were mounted over the medial prefrontal cortex (mPFC) and posterior parietal cortex (PPC), two brain regions identified in an EEG experiment to show phase-coupling that was related to the consistency of preference-based decisions[136]. In a subsequent tACS experiment[48], tACS was applied over the mPFC and PPC at the frequencies identified in the EEG experiment at six different lags (Δφ). This showed that full anti-phase stimulation leads to poorer performance compared to tACS applied at full in-phase stimulation. Crucially, the optimal phase difference for task performance indicated that information may flow from frontal to parietal cortex (right panel), illustrating that tACS can be used to make inferences about the direction of information flow between segregated nodes of functional brain networks. **b**, tRNS may be useful for investigating the stochastic dynamics of neuronal processing. In the example presented in this panel[14], tRNS was applied over the primary visual cortex (V1, left) at different noise amplitudes (middle) to investigate the stochastic resonance phenomenon (see Box 2). Consistent with the assumption that there are optimal noise levels for neural processing, only intermediate (but not high or low) levels of noise led to higher discriminability in a signal detection task (right). This illustrates how tRNS can elucidate stochastic dynamics of neural circuits in the intact human brain. **c**, TMS can be combined with fMRI to reveal functional influences in brain networks underlying behavior. In the example study presented in this panel, the investigators tested different theories about the role of dorsolateral prefrontal cortex (DLPFC) in stabilizing working memory during external distraction[14]. Subjects had to memorize face or house stimuli that activated the fusiform face area (FFA; for faces) and parahippocampal place area (PPA; for houses) while distractor stimuli from the opposite category were present or not. TMS pulses given to DLPFC during fMRI led to increased BOLD signals (a.u., arbitrary units) in FFA and PPA only when distracters were present. Critically, these influences were only observed in regions representing the current memory targets (right), thus providing causal evidence that neural signals from DLPFC can enhance working memory representations in posterior brain areas during external distraction.

Box 2 | Definitions of NIBS-relevant terminology

Brain-derived neurotrophic factor (BDNF): A protein encoded by the *BDNF* gene that is highly relevant for NIBS research as it is known to be involved in various forms of synaptic plasticity, including LTP and LTD (see below). Crucially, NIBS-induced neuroplasticity has been shown to depend on secretion of this protein in animal studies[147]. In humans, *BDNF* gene polymorphisms have been shown to have an impact on NIBS-induced plasticity[148]. Thus, BDNF is one of the many factors that should be taken into account when considering potential sources of behavioral and physiological variability in NIBS-induced effects (Fig. 3).

Long-term potentiation (LTP): A facilitation of synaptic transmission that is considered to be one of the main mechanisms underlying learning and memory formation. The opposite phenomenon, **long-term depression (LTD)**, refers to inhibition of synaptic transmission. LTP and LTD might be expressed at every synapse in the mammalian brain[149]. Long-lasting neurophysiological facilitation or inhibition induced by NIBS (for example, depending on the method and protocol used and other factors such as brain state and cognitive task) is believed to relate to LTP- or LTD-like changes.

Motor-evoked potentials (MEPs): Electrical potentials recorded from peripheral muscles in response to single-pulse electrical or magnetic stimulation of M1. MEP amplitudes are typically used to assess the level of cortico-spinal excitability induced by NIBS protocols. Excitatory or inhibitory NIBS protocols increase or decrease MEP amplitudes, respectively.

Phosphene: Transient visual percept resembling light flashes that can be induced by suprathreshold TMS pulses over V1[26] or by tACS in the ~8–35 Hz range, depending on the amount of light in the environment[130]. For tACS in this frequency range, such phosphenes need to be properly controlled for as they are difficult to differentiate from genuine neural entrainment. Moreover, whether the origin of tACS-induced phosphenes is cortical or retinal remains a matter of debate[8,150].

Stochastic resonance: A phenomenon referring to a situation in which a signal that is too weak to be detected by a sensor is enhanced by adding an optimal level of noise. For instance, it has been shown that visual detection performance can be increased by adding the right amount of noise to the visual stimulus; too much or too little noise results in poor detection performance or misperception of the visual stimulus. Recent studies have suggested that tRNS can be used as a tool to investigate the stochastic resonance principle in the human cortex[63].

including alterations of brain-derived neurotrophic factor (BDNF; see Box 2) and even neurogenesis[22]. Given these modulatory impacts of rTMS protocols on brain physiology, their effects by definition critically depend on brain state during the stimulation[23]. The duration of the physiological aftereffects makes these 'offline' rTMS protocols well-suited to studying the causal contributions of cortical regions to behavior in both health[24–26] and disease[27–29]. Studies employing this approach measure behavioral alterations in the immediate aftermath of the rTMS protocol, thereby testing the functional consequences of the temporary excitability modulation for behavior.

The second family of methods, tES, produces its neuromodulatory effects not via magnetic fields (as TMS does) but rather by means of weak electrical currents applied to the scalp. The most popular variant is transcranial direct current stimulation (tDCS), introduced about two decades ago (Fig. 1b). This method applies a weak tonic direct current between electrodes mounted on the head, which partially passes through the cortical tissue and affects relatively large cortical areas (on the order of centimeters; see Box 1). This current de- or hyperpolarizes neuronal resting membrane potentials and thereby alters cortical excitability[30,31]. The primary effects of tDCS do not include synaptic mechanisms but instead involve voltage-dependent ion channels[32]. However, stimulation extending over a few minutes leads to LTP- or LTD-like plasticity[32,33] that can extend to interconnected cortical and subcortical structures[34,35]. The temporal resolution of this technique is low, as the online neuromodulatory effects start to take place a few seconds after the start of the stimulation and continue throughout current application, whereas the physiological aftereffects can last for several hours and even days if accompanied by pharmacological interventions[32]. Thus, considering the physiology and neuromodulatory characteristics of tDCS, the functional specificity of the intervention largely relates to its capability to modulate task-related neural processing rather than to the spatial and temporal specificity of the electric fields produced by the stimulation itself[36].

While tDCS has low temporal resolution and is indiscriminate as to which aspects of neural processing are modulated, other variants of tES methodology can be used to target more specific aspects of neural function at higher temporal scales. One such method was specifically developed to investigate the role of neural oscillations in designated frequency bands for behavior[37]. This technique, known as transcranial alternating current stimulation (tACS), employs oscillatory electrical stimulation with the aim of facilitating neuronal activity in specific frequency bands[38–40], thereby allowing study of causal links between brain rhythms and specific aspects of behavior[41–44]. For instance, tACS can be used to study the causal role of theta–gamma cross-frequency coupling for working memory performance[45], the contributions of beta and gamma oscillations to motor behavior[41,43], the role of frontal gamma oscillations during high-level cognitive tasks[46] or the causal contributions of alpha oscillations to the generation of visual and cross-modal perceptual illusions[42,44].

tACS can also be used to investigate how oscillatory coherence between spatially distinct nodes of functional networks contributes to behavior[47–50], by simultaneously applying oscillatory currents over distinct regions at the same frequency but using different oscillatory phases to facilitate or hamper synchronization in the functional networks (Fig. 2a). As mentioned before, the link between rhythmic oscillations and behavior can also be investigated using rTMS protocols that apply pulses at specific frequencies to facilitate corresponding oscillations[16–18]. Crucially, emerging work is starting to suggest that TMS pulses may have very different effects if they are applied at different phases of ongoing neural oscillations[51]. This shows directly that some of the variability of neural NIBS effects may relate to the precise temporal relation between the NIBS protocol and ongoing neural activity, suggesting that this information could be used to design more efficient stimulation protocols in the context of closed-loop systems[52–54].

A limitation of the frequency-specific protocols mentioned above (and tES methods in general) is that they can only directly affect activity in cortical regions. Direct stimulation of deeper structures typically requires invasive procedures—for example, deep brain stimulation. However, there are attempts to develop specific TMS hardware, such as the TMS H-coil[55], to modulate the excitability of brain areas lying further away from the cortical surface (possibly up to 6 cm)[56]. Moreover, a recent study showed in mice that a new NIBS protocol, termed temporal interference (TI), allows entrainment of oscillatory neuronal activity in subcortical structures (such as the hippocampus) without recruiting neurons of the overlying cortex[57]. Future extension of this TI-NIBS protocol to humans, if at all possible, may therefore overcome the constraint that only superficial structures may be directly affected.

While numerous studies have demonstrated selective and frequency-specific effects of tACS on behavior, it is debated how

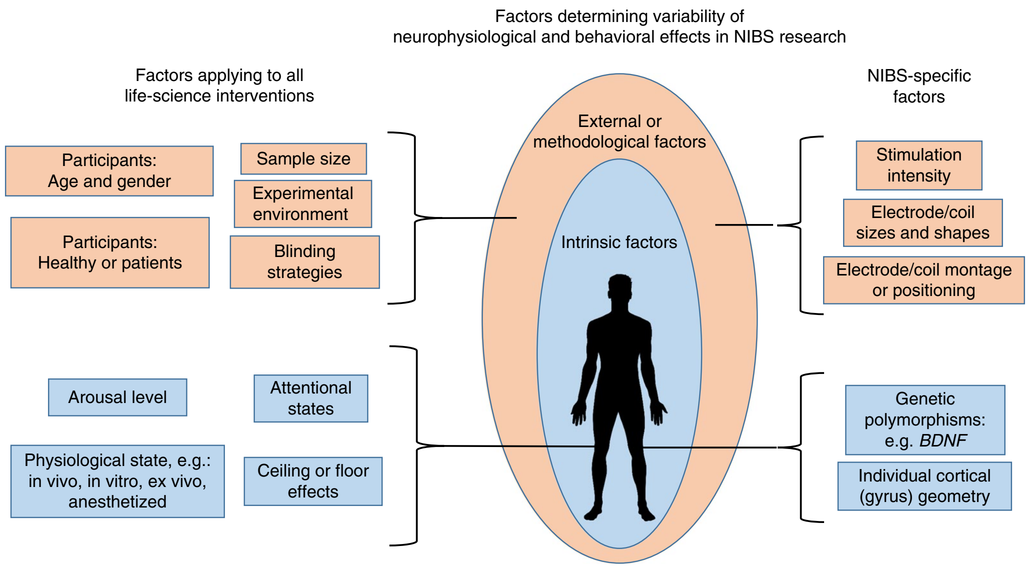


Fig. 3 | Example factors determining the variability of neurophysiological and behavioral NIBS effects. Many sources of variability in NIBS effects reflect factors that similarly affect the variability of other experimental interventions in the life sciences. However, there are NIBS-specific factors that should be taken into account in both experimental studies and studies employing meta-analytic techniques. The latter also need to ensure that studies are selected for inclusion based on overlap in conceptual aims and well-defined methodological criteria[93,104].

exactly these protocols affect oscillatory activity. Work in anesthetized animals and computational modeling suggest that direct neural entrainment is possible[39,40], but there is little evidence in humans that this is indeed the case. However, studies are starting to investigate the neural consequences of tACS in vivo. For instance, 10-Hz tACS applied over the motion-sensitive area (MT) attenuates visual motion adaptation in humans[8] and reduces spike-frequency adaptation of MT neurons in macaques[9]. These findings provide a direct demonstration that weak alternating electric fields applied to the scalp, which change motion adaptation behaviorally, in fact significantly affect neural processing in a frequency-specific manner. However, this study could not directly demonstrate neural entrainment due to technical complications with recording during externally applied electrical fields. Thus, the investigation into how tACS entrains or modulates oscillatory activity in the human brain will require the development of multimodal NIBS-recording techniques and well-validated artifact rejection methods capable of identifying neural oscillations during stimulation[58,59].

Another related tES technique called transcranial random noise stimulation (tRNS) focuses on the link between behavior and frequency-specific noise inherent in neural processing[60]. Compared to other stimulation methods, relatively little is known about the physiological impact of this method. However, only 10 min of tRNS applied over primary motor cortex (M1) can enhance motor cortex excitability for about 60 min after the end of stimulation, suggesting that this method may induce neuroplastic effects[60] of similar strength as those induced by anodal tDCS. Applied in conjunction with cognitive tasks, tRNS protocols may enhance learning performance even more strongly than anodal tDCS does[61,62]. Interestingly, the effects of tRNS are strongest when used at intensities thought to induce optimal noise levels[63] (Fig. 2b), consistent with the stochastic resonance principle (see Box 2). tRNS may thus prove useful for investigating the stochastic dynamics of neuronal processing in the intact human brain[64].

Standard NIBS studies using the approaches mentioned above typically apply these protocols in purely behavioral settings, targeting brain areas identified by previous neuroimaging research and assuming that the NIBS methods exert uniform and clearly interpretable physiological effects on these areas. This standard approach has been used for studying causal brain—function relationships in numerous domains, including vision[65], audition[66], motor[67–69], somatosensation[70], language[71,72], attention[73,74], memory[75,76], reasoning[46,77], decision making[78–80] and social behavior[81–83]. While this approach continues to yield very interesting demonstrations that specific aspects of behavior can be changed by stimulation and therefore causally relate to the affected neural processes, it has also triggered critical debates about the properties and possible limitations of these methods. We will discuss these in the following section.

Current controversies associated with the use of NIBS

Over the past few years, critical discussions have arisen about the replicability of effects reported in various scientific fields[84,85]. For studies using NIBS, this discussion has focused on both physiological and behavioral effects of these techniques. However, this general discussion often has not explicitly differentiated between deterministic and neuromodulatory NIBS approaches. The former methods—for example, single- or double-pulse TMS, or short bursts of TMS[10]—directly elicit action potentials that may have relatively uniform physiological and behavioral effects (even though some intra- and interindividual variability can be observed[86]). The latter—for example, offline rTMS or tES methods—mainly operate by modulating ongoing brain activity, so that the effects of these methods will by definition depend critically on brain state and task context. This state-dependency of neuromodulatory NIBS effects is confirmed by animal studies showing, for instance, that the ability to induce LTP and LTD is critically shaped by the previous learning experience of the targeted cortical area[87]. Indeed, in humans, the effects of rTMS and tES on cortical excitability (as monitored by TMS-generated motor evoked potentials (MEPs)) varies between individuals, as do stimulation effects on other physiological and cognitive-behavioral variables[88–92]. However, precise estimates of this variability are so far lacking, as the objectives and methodological procedures of NIBS applications differ considerably between studies. This severely complicates the use of meta-analytic procedures to estimate effect sizes associated with NIBS applications: Such procedures can only validly be applied to logically coherent sets of effects generated with the same well-defined methodological procedures in the same task

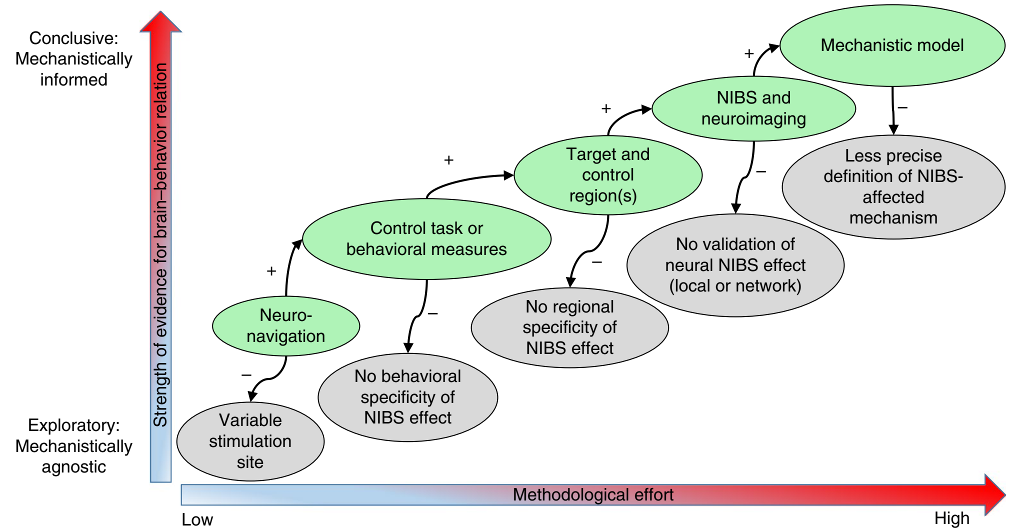


Fig. 4 | The conclusiveness of NIBS results on brain–behavior relations depends on the degree of methodological effort. Here we show an example decision tree to illustrate how the successive inclusion of methodological procedures in a given study can lead to increasingly conclusive and mechanistically informed evidence for the relationship between behavior and a well-defined neural process (for examples, such a scheme was followed in refs [18,117,118]; see also Fig. 5). It is important to note that the scheme is illustrative rather than fully prescriptive, as the precise order of these procedures is not necessarily the same for all studies and as one or several of the illustrated procedures may not apply or be available in particular contexts. Moreover, it should be noted that clinical or translational studies may not necessarily need to employ these procedures if they follow well-validated protocols. However, the more of these methodological procedures that can be included in a given study, the more conclusive and mechanistically informed the resulting evidence.

contexts. Preliminary attempts at quantifying effect sizes associated with NIBS methods per se[93,94] have therefore been inconclusive, as they have mostly pooled many different studies using this research method in very different ways.

The sources of the reported variability of NIBS effects have hardly been explored systematically, but include brain-intrinsic, task-related and methodological factors. Relevant brain-intrinsic factors may include trait and state variables such as sex, age, diurnal variations, genetic polymorphisms, attention, pharmacology and synaptic history[95] (Fig. 3). For example, NIBS-induced plasticity has been shown to be related to BDNF polymorphisms[96] and is altered by enhancement or reduction of dopaminergic neuromodulation in a nonlinear, dosage- and receptor-dependent manner[97–99]. Therefore, the individual variability of NIBS effects is not surprising, as NIBS protocols induce plasticity by affecting glutamatergic, calcium-dependent mechanisms that are affected by various neuromodulatory agents. By definition, these effects will therefore vary between different tasks and brain regions (see below). As for methodological aspects, variations of NIBS protocols in terms of intensity, duration, electrode position and coil orientation can alter stimulation effects, even in a nonlinear fashion[100,101] (see also Box 1). Additionally, the physiological effect of NIBS methods can strongly depend on characteristics of the testing situation, as clearly illustrated by the fact that even MEPs elicited from motor cortex following modulatory NIBS protocols can differ in strength depending on what participants were doing at the time of stimulation (for example, whether they were engaged in motor behavior or not[102]). Finally, subject-specific aspects can also play a role. These include differences in arousal or attentional state, ceiling or floor effects with regard to task performance, or differences in group size, just to name a few[103]. However, it is important to note that many of these sources of variability are not unique to NIBS studies and equally apply to many other research approaches attempting to relate physiology and behavior in the biological and social sciences[104] (Fig. 3).

The variability of reported NIBS effects need not be disadvantageous, but may instead provide important information about how interventions may be personalized and optimized[105,106]. Moreover, this natural variability may help to identify factors that affect naturally-occurring plasticity, thereby further elucidating the brain physiology underlying cognitive processes. Future meta-analyses of NIBS effects should therefore attempt to systematically identify the factors that determine the variability of NIBS effects; at the very least, these analyses should only pool studies that indeed investigated the same specific brain–behavior relationship with closely comparable NIBS procedures[93,104].

The sources of physiological variability discussed above show that one cannot assume that protocols known to result in enhancement or reduction of primary motor cortex excitability—the most frequently used assay of physiological NIBS effects—will have the same physiological effect when applied to another brain area. Another factor that may affect the variability of NIBS effects relates to possible nonlinear interactions with task-related neural processing. For instance, if NIBS methods and task performance have synergistic effects on the same neuronal populations, neurons may be activated too strongly, thereby resulting in antagonistic NIBS effects[101,107]. Finally, the link between behavioral performance and physiological measures, such as TMS-generated excitability measures or cerebral activation monitored by functional imaging, may in itself not always be straightforward. For instance, improved performance during motor learning is known to result in activity reductions in motor cortex networks[108,109]. However, these reductions obviously do not indicate that the functional relevance of this network has decreased; instead, they may reflect an increase in the selectivity of task-relevant networks[43]. NIBS protocols may therefore affect performance in opposite ways during different stages of learning, as shown, for example, for visuo-motor coordination[110].

One crucial unresolved issue is the question whether tES protocols always elicit their strongest effects under the electrodes, since computational models suggest that the peak of the electric field may lie between the electrodes for some montages (Box 1). Such computational models of tES-induced electric fields may ultimately prove important for optimizing the efficiency of NIBS protocols[106,111], but it will be crucial to validate their computational predictions both physiologically and behaviorally and to fully account for well-established

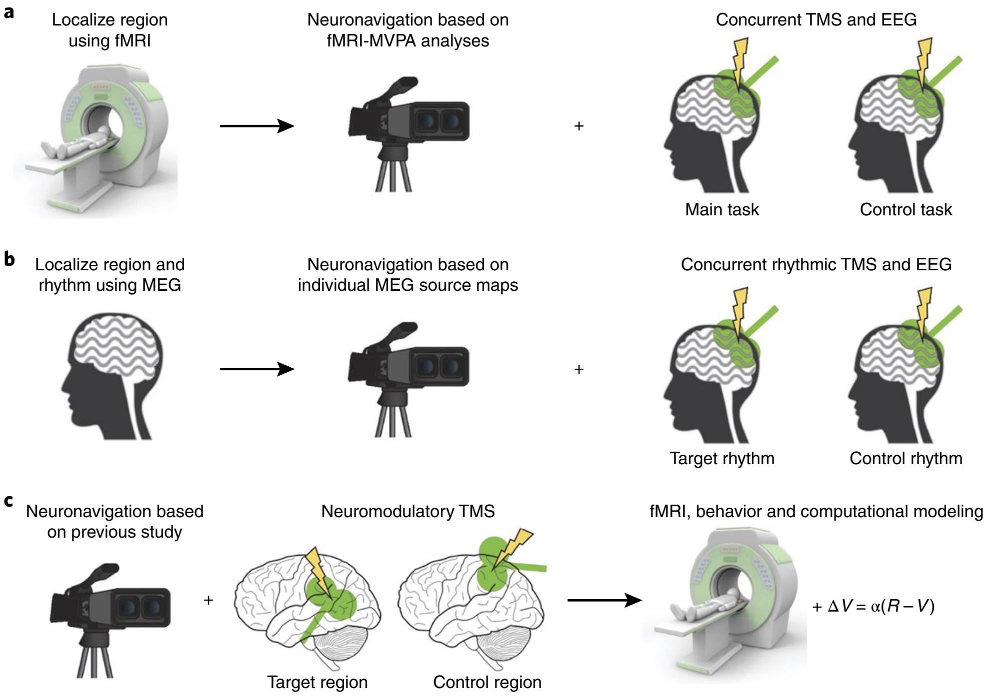


Fig. 5 | Example workflows of studies employing NIBS methods in a multimethods approach to establish brain–behavior relations. a, This study tested the hypothesis that working memory information is temporarily stored via 'activity-silent' synaptic mechanisms[118]. The authors first used fMRI to precisely localize cortical areas that represent category-specific working memory contents. Afterwards, they used EEG in order to characterize the temporal dynamics of the hypothesized memory reactivation via single pulse TMS at the locations identified in the fMRI experiment. They observed that a TMS pulse during the retention period re-expressed latent working memories of unattended memory items. **b**, This study tested the causal role of theta oscillations (~6 Hz) for working memory maintenance. The authors first identified, for each individual, the cortical generators of theta oscillations related to memory maintenance via magnetoencephalography (MEG). Then the authors replicated their findings in a new experiment using EEG, which conveniently allows tracking of oscillatory neural entrainment via rhythmic TMS[120]. Using this multi-method approach, the investigators demonstrated that by artificially entraining theta oscillations via TMS, it was possible to augment working memory performance. **c**, This study investigated how the human brain represents beliefs about how our choices will influence those of others with whom we interact[117]. The authors first identified the region of interest using fMRI and computational modeling. They then used rTMS to inhibit the activity of the right temporoparietal junction (rTPJ), which was hypothesized to implement the social influence signal. They also used a remote control region (vertex) to test the regional specificity. After rTMS, participants performed the social task during fMRI and used computational modeling to study how mechanistic latent variables of behavior where affected by the inhibitory rTMS protocol to the rTPJ compared to the control region. This multi-method approach thus allowed the authors to reveal a regional and functional specific causal role of the rTPJ in computing social influence signals.

effects on areas under the electrodes as induced by traditional protocols[36] (Box 1).

Another focus of recent debate is the application of NIBS techniques in a do-it-yourself manner, mainly for the purpose of neuro-enhancement. Several companies have begun to produce stimulators specifically for this type of application; for technical and financial reasons, such stimulators are more widely available for tDCS than TMS. It is questionable whether the effects of NIBS approaches are sufficiently uniform and understood to be readily applied for neuro-enhancement purposes in everyday life[112]. Critics believe that it may be too early to employ NIBS methods as routine neuro-enhancement tools because the physiological effects vary between individuals (see above) and because important translational questions that would need to be answered for everyday use of NIBS remain unaddressed. Most of the existing NIBS studies were conducted in controlled laboratory settings, did not specifically aim for maximal and homogeneous effects, did not explore long-term (and possibly performance-reducing) effects, and did not focus on possible late-occurring side effects or side effects that might be caused by intensified use. Obviously, this cautionary statement does not mean that NIBS will never be suitable for neuro-enhancement purposes; future translational approaches of the basic laboratory studies may offer this possibility if they take state- and task-dependent effects into account, possibly as closed-loop systems[52].

Apart from these methodological issues, NIBS and all other kinds of neuro-enhancement techniques are subject to ethical considerations. These comprise the question of how the techniques need to be applied in order to be appropriate and safe, the problem that there is only limited knowledge about the effects of NIBS on the developing brain[113] and the fact that it is difficult to detect NIBS-related "neuro-doping"[114] in contexts in which this may be critical (for example, standardized exams or sports competitions). More generally, there is considerable debate about whether neuro-enhancement techniques compromise the autonomy of users, either neurophysiologically or by societal means—for instance, if people are pressured into their use or if the associated expense widens the gap between economically divergent groups[115]. The discussion also encompasses the question whether specific communication strategies[116] may be necessary to ensure sufficient transparency so that potential users and policy makers can make informed decisions about the use of NIBS methods. Finally, it is debated how these methods should be regulated[116] to prevent the widespread use of insufficiently tested interventions while avoiding unnecessary restrictions on the development of promising interventional tools in the scientific domain.

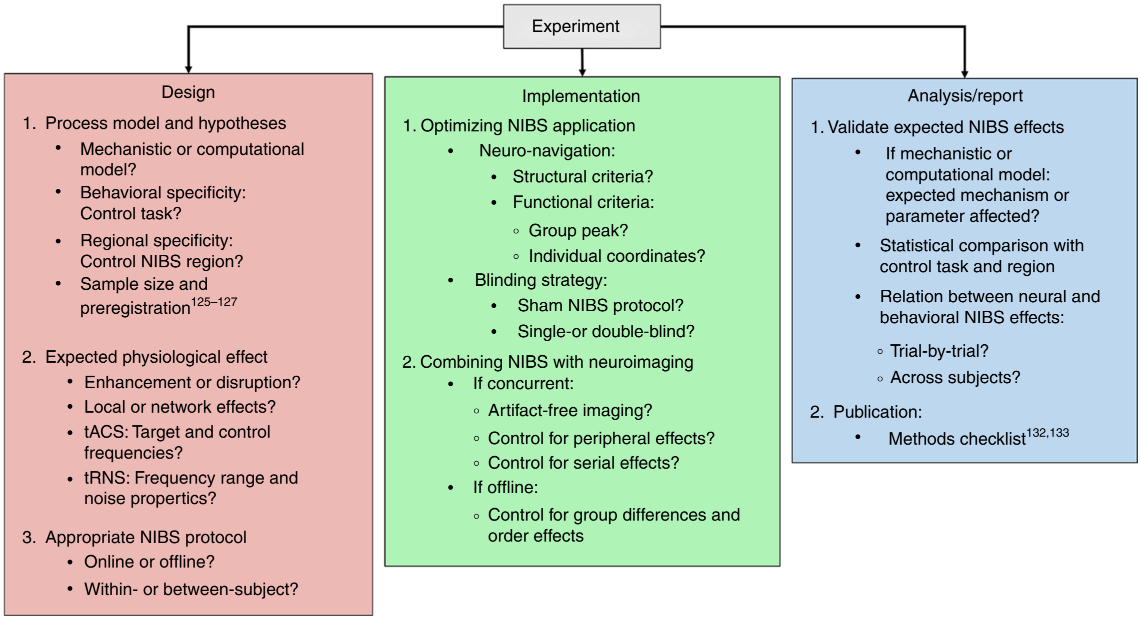


Fig. 6 | Methodical considerations during different stages of NIBS experiments. Multi-method approaches can be used to gain fundamental and more reliable insights on brain–behavior relations via NIBS. To carry out such studies involving high methodological effort (see Fig. 4), it is crucial to have a clear work plan beforehand. This scheme shows an example of important aspects to consider in such a work plan before, during and after the execution of NIBS studies. Not all of these points necessarily apply to all studies, as some studies may have scientific aims that do not require comparisons with control tasks or control sites. However, considering all of the points listed in the figure before running the study will always be beneficial.

Overcoming NIBS limitations

Some of the problems discussed in the previous section might relate to the variability of methodological procedures employed in NIBS studies. This variability may reflect a lack of clear guidelines on how conclusive NIBS evidence can be, given the details of how the specific NIBS method was employed and how the resulting effects are interpreted. In this section, we propose some tentative guidelines that may help in both assessing the strength of evidence for brain–behavior relations in NIBS studies and for designing and conducting NIBS studies. These guidelines may provide a starting point for overcoming some of the limitations discussed in the previous section. Note that we focus these guidelines on studies of brain–behavior relations; our recommendations may be neither sufficient nor necessary for basic neurophysiology research using NIBS methods.

Overcoming the limitations of NIBS methods will require both specific methodology as well as combinations of NIBS procedures with other research methods. In our eyes, the more these two strategies are adhered to in a given NIBS study, the more conclusive the evidence for a specific brain–behavior relation can be (Fig. 4). For instance, the most exploratory and least conclusive may be those studies that acquire only behavioral measures in combination with NIBS application over a target site that is defined purely based on scalp measurements (using, for instance, the 10-20 system). We expect this type of study to result in the highest level of variability in effect size. By contrast, most conclusive (and least exploratory) may be studies that incorporate the following methodology: First, they include neuronavigation in order to more precisely locate the NIBS region of interest in each participant—for example, based on functional neuroimaging evidence or based on clearly defined anatomical criteria. This is arguably more critical for TMS studies than for studies employing tES, with its coarser spatial resolution. However, tES studies may also benefit from this step since it ensures more homogenous positioning of the areas of interest in the induced fields, in particular for emergent tES protocols that offer higher spatial resolutions (Box 1). Second, they include control tasks or behavioral measures that ascertain that the NIBS effects are indeed specific for the behavior under study. Third, they include stimulation of control regions or frequencies in order to test the functional specificity of the target area or neural process of interest. Fourth, they include combination with neuroimaging in order to directly quantify the strength of the NIBS effect on the local neural effect of interest and to measure how connected brain networks are affected by the application of the stimulation. Fifth, they include characterization of the NIBS-induced changes with theory-driven models whose mechanistic latent variables can capture changes in both behavioral and brain activity modulations.

The multi-method approach we propose here may be impractical for clinical use and may have poor ecological validity for standard clinical settings. However, we think it may be decisive for basic research in order to provide conclusive evidence for the effectiveness of a given NIBS protocol. This step appears essential to inform subsequent translational and/or applied clinical use of these methods, which would not have to employ the demanding research pipeline described in Fig. 4 but could either apply other neuroimaging methods or just follow the exact protocol established in prior studies.

Adopting the type of multi-method strategies mentioned above is labor-intensive and challenging, but this approach is increasingly seen and therefore feasible[18,117–119]. One example study[118] that used much of the methodology suggested in Fig. 4 tested the hypothesis that working memory information is temporarily stored via 'activity-silent' synaptic mechanisms (Fig. 5a). This study used fMRI to localize cortical areas that represent category-specific working memory contents, along with TMS combined with electroencephalography (EEG) to characterize the temporal dynamics of the hypothesized memory reactivation. Another study[18] using similar procedures investigated the causal role of theta oscillations (~6 Hz) on the dorsal stream for working memory maintenance (Fig. 5b). The authors used magnetoencephalography to identify for each individual the cortical generators of theta oscillations related to memory maintenance and then tested the causal role of these temporal-spatial oscillatory signatures supporting working memory maintenance with combinations of rhythmic TMS and EEG that can test for neural entrainment[120]. A third example study[117] demonstrated a causal role for the temporoparietal junction in guiding strategic social behavior, by combining computational modeling of behavior, neural activity recording with fMRI and transcranial magnetic stimulation (TMS) guided by neuronavigation (Fig. 5c). Notably, in all these studies, the documented effects were shown to be specific for a given task context, brain region or stimulation frequency. Thus, these example studies demonstrate that NIBS studies can deliver conclusive evidence for a specific, mechanistically defined brain behavior relationship (rather than being purely exploratory) if researchers employ a methodological framework similar to the one illustrated in Fig. 4.

Combining NIBS methods with other imaging techniques such as magnetic resonance spectroscopy can also provide insight into the specific neurophysiological mechanisms of stimulation effects that go beyond those acquired with pharmacological interventions[121] and that can be linked to cognitive processes[122]. For instance, it has been shown that anodal tDCS over M1 reduces the concentration of GABA, whereas cathodal stimulation results in a significant decrease in the concentrations of both glutamate and GABA[123]. This is consistent with the notion that LTP-like plasticity in the neocortex—thought to be affected by tDCS—critically depends on GABA modulation[124]. Based on these findings, a recent study employed tDCS to test for cortical rebalancing of excitatory and inhibitory influences during associative learning[119]. The researchers administered anodal tDCS to induce a local reduction in cortical GABA while using fMRI to track the representational overlap between learned associations over time. As hypothesized, the new experiment revealed that cortical memories were re-exposed during anodal tDCS, thereby illustrating how NIBS in combination with different neuroimaging modalities (magnetic resonance spectroscopy and fMRI) can be used to reveal a more comprehensive picture of the neurophysiological mechanisms underlying cognitive processes.

Shifting the field from more exploratory behavioral demonstrations to the multi-method approaches illustrated above requires careful planning of all stages of a NIBS study (Fig. 6). During the design stage of the experiments, the researchers must clearly define the area that should be stimulated, the cognitive process that should be modulated, and how this NIBS influence on behavior can be measured conclusively. This last step requires a-priori considerations of including a control task or behavioral measure to establish context specificity and selecting a control brain region to test the spatial selectivity of the intervention effect. Additionally, to reduce problems with type I errors and improve reproducibility[125], NIBS studies (and all other studies) should employ adequate sample sizes[126]. This may be achieved by power analyses[126] and the guideline that studies of standard behavioral tasks aiming at threshold significance levels with sample sizes $n < 20$ are likely to be irreproducible[127]. Finally, during the planning stage, investigators usually have a clear hypothesis of the neural process they want to affect with their protocol. NIBS studies are therefore ideal candidates for pre-registration and we encourage the community to adopt this scientific practice.

During the execution stage of the experiments, the researchers should try to maximize the reliability of the NIBS-induced modulations—for example, by using neuronavigation techniques to identify in each individual the target regions of interest based on prior functional and/or structural neuroimaging (but see the caveat about clinical studies described above). Moreover, given that most NIBS methods induce somatosensory effects (for example, in TMS, auditory effects of the coil click[128]; in tDCS, skin sensations due to the current flow over the scalp[129]; in tACS, the perception of phosphenes[130] (see Box 2)), it is crucial that the authors take care to blind the NIBS intervention and to properly control for placebo effects.

Finally, in the analysis and reporting stage, the investigators should have a clear plan for the statistical analyses used to evaluate whether the targeted cognitive process was specifically affected by the NIBS intervention. This analysis plan should include statistical comparisons with control tasks, brain regions and clearly defined neurocomputational latent variables to identify the specificity of the hypothesized NIBS-induced effect on behavior and neural function. Last but not least, to promote reproducibility in NIBS research, we encourage both researchers and journal editors to provide for every publication involving any type of NIBS intervention a methods-reporting checklist. This type of strategy is already used for studies employing fMRI[131], a research method that has also triggered intense discussions about methodology and reproducibility[85]. Fortunately, corresponding methods-reporting NIBS checklists already exist based on recent international consensus studies for TMS[132] and tES[133]. Such checklist reports would ensure transparent reporting of methodological details concerning NBS application, data collection and data analysis, all of which have clear implication for interpretation and future use of these data[131].

Implications for translational applications

Beyond studies employing NIBS methods to reveal causal brain–behavior relations, important applications of NIBS protocols have attempted to identify and potentially ameliorate pathophysiological mechanisms underlying neurological and psychiatric diseases. The problems discussed above apply in a similar manner to these more clinical and translational applications of NIBS methods. While the use of NIBS for therapeutic applications has been extensively investigated, the corresponding treatment effects have been moderate and variable in most cases; beyond the use of prefrontal rTMS for treatment of major depression, no NIBS protocol has developed into a routinely used treatment tool so far[134]. This does not necessarily reflect limited therapeutic potential of NIBS interventions. However, it does suggest that research strategies in this field so far may not have been well suited to developing and identifying NIBS protocols with optimal efficacy. At least three lines of research may advance the field in this respect. First, it will be important to base any intervention protocol on solid mechanistic knowledge about the causal and specific contribution of brain areas and networks to clinical symptoms. In analogy to basic-science studies on causal brain–behavior relationships, this knowledge would have to be derived with combinations of brain stimulation, neuroimaging, solid experimental designs and modeling work (as attempted, for example, in computational psychiatry[135]). Such initial studies in healthy participants should lead to further translational treatment-validation studies that should not only monitor clinical symptoms but also physiological data, to validate the precise neurophysiological mechanisms causally mediating the intervention effects. Second, promising treatment protocols identified with the strategy discussed above should be further optimized by systematic evaluation of the optimal stimulation areas and parameter settings for the stimulation; this should initially be performed in healthy surrogate populations, but it is important that it be directly validated in the target patient groups (to account for the state dependency of neuromodulatory NIBS protocols discussed above). This optimization of intervention protocols may not be restricted to the group level, but should include individual optimization of the protocols dependent on brain state, lesions, clinical symptoms and other factors. Third, the field is currently characterized by a multitude of studies with relatively small sample sizes. While this may be helpful for exploratory and screening purposes, it is not sufficient for establishing the clinical relevance of an intervention and for decisions about its implementation in clinical routine. Thus, larger and preferably multicenter randomized clinical trials should be conducted to establish with adequate statistical power which protocols may have clinically relevant effects, and on whom. All these steps would be important to provide solid evidence for the usefulness of applying these validated protocols in clinical settings.

Conclusions

In the last 30 years, NIBS methods have become indispensable tools for elucidating how behavior causally depends on specific aspects of neural activity in the healthy human brain. There is presently no alternative to these techniques for the study of causal brain–behavior relationships in humans, but current controversies highlight the necessity for responsible scientific practice in the use of NIBS for research purposes. This may require a shift in focus from simplistic assumptions about how NIBS methods generally affect the brain toward more physiologically informed multi-method approaches that test specific hypotheses about how the influences of NIBS on behavior are mediated by modulation of well-defined neural processes. These approaches should explicitly consider various intrinsic, task-related and methodological factors that can potentially influence the variability of behavioral and physiological outcomes. Moreover, more attention should be devoted to the precise reporting of methods, protocols and results to allow more accurate interpretation and future summary of the data. Of course, these considerations are important not only for NIBS research but also for other experimental sciences. But the current debates show that NIBS research in particular may be at a crossroads where the field would strongly benefit from coordinated methodological efforts to optimize the conclusiveness of findings on brain–behavior relations. This step appears vital for successful translational applications of these methods for cognitive enhancement and improved mental health.

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Competing interests

The authors declare no competing financial interests.

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