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DOI: https://doi.org/10.1038/s41593-017-0054-4

REVIEW

Studying and modifying brain function with non-invasive brain stimulation

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Abstract

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.

MAIN TEXT

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 a lot 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 on the scalp (current intensities of ~1-2 mA).

The number of publications utilizing these methods (and variations thereof) is currently growing exponentially (Figure 1b), perhaps reflecting the field's recognition that solid knowledge on 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 methodical 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. We start with a concise overview of the spatio-temporal 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 on 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 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 (Figure 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 (Figure 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 modelling (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 and Box Figure 1). This may reflect 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/temporal specificity. Different ways of applying NIBS methods are therefore suited to test different types of hypotheses regarding physiology-behavior/cognition interactions.

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 (in 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] (Figure 2c) allows tests of how action potentials elicited in one brain area impact on processing in interconnected areas in a

top-down and/or context-sensitive manner; this allows direct study of how brain networks dynamically operate at high temporal resolution and may make it possible 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/LTD, see Box 2), respectively. 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 non-linear time-dependent influences on inhibitory GABAergic neurons, non-synaptic mechanisms including alterations of the 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 study the causal contributions of cortical regions to behavior in both health[24–26] and disease[27–29]. Studies employing this approach measure

178 behavioral alterations in the immediate aftermath of the rTMS protocol, thereby testing
179 the functional consequences of the temporary excitability modulation for behavior.

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

198 While tDCS has low temporal resolution and is indiscriminate as to which aspects
199 of neural processing are modulated, other variants of tES methodology can be used to
200 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 crossmodal 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 (Figure 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 starts 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 (DBS). However, there are attempts to develop specific TMS hardware – e.g. 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 exactly these protocols affect oscillatory activity. Work in anesthesized animals and computational modelling suggests 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[58,59]. Thus, the

investigation of how tACS entrains or modulates oscillatory activity in the human brain will require the development of multi-modal 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 minutes of tRNS applied over M1 can enhance motor cortex excitability for about 60 minutes 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] (Figure 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 – e.g., 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 – e.g., 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 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 methodical 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

294 logically coherent sets of effects generated with the same well-defined methodical
295 procedures in the same task contexts. Preliminary attempts at quantifying effect sizes
296 associated with NIBS methods *per se*[93,94] have therefore been inconclusive, as they have
297 mostly pooled many different studies using this research method in very different ways.

298 The sources of the reported variability of NIBS effects have hardly been explored
299 systematically, but include brain-intrinsic, task-related, and methodological factors.
300 Relevant *brain-intrinsic factors* may include trait and state variables such as sex, age,
301 diurnal variations, genetic polymorphisms, attention, pharmacology, and synaptic
302 history[95] (Figure 3). For example, NIBS-induced plasticity has been shown to be related
303 to BDNF polymorphisms[96] and is altered by enhancement or reduction of dopaminergic
304 neuromodulation in a non-linear, dosage- and receptor-dependent manner[97–99].
305 Therefore, the individual variability of NIBS effects is not surprising, as NIBS protocols
306 induce plasticity by affecting glutamatergic, calcium-dependent mechanisms that are
307 affected by various neuromodulatory agents. By definition, these effects will therefore
308 vary between different tasks and brain regions (see below). As for *methodological*
309 *aspects*, variations of NIBS protocols in terms of intensity, duration, electrode position,
310 and coil orientation can alter stimulation effects, even in a non-linear fashion[100,101] (see
311 also Box 1). Additionally, the physiological effect of NIBS methods can strongly depend
312 on characteristics of the testing situation, as clearly illustrated by the fact that even MEPs
313 elicited from motor cortex following modulatory NIBS protocols can differ in strength
314 depending on what participants were doing at the time of stimulation (e.g., whether they
315 engaged in motor behavior or not[102]). Finally, subject-specific aspects can also play a
316 role, such as differences in arousal or attentional state, ceiling or floor effects with regard

317 to task performance, or differences in group size, just to name a few[103]. However, it is
318 important to highlight that many of these sources of variability are not unique to NIBS
319 studies and equally apply to many other research approaches attempting to relate
320 physiology and behavior in the biological and social sciences[104] (Figure 3).

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

329 The sources of physiological variability discussed above show that one cannot
330 assume that protocols known to result in enhancement or reduction of primary motor
331 cortex excitability – the most frequently-used assay of physiological NIBS effects – will
332 have the same physiological effect when applied to another brain area. Another factor
333 that may affect the variability of NIBS effects relates to possible non-linear interactions
334 with task-related neural processing. For instance, if NIBS methods and task performance
335 have synergistic effects on the same neuronal populations, neurons may be activated too
336 strongly, thereby resulting in antagonistic NIBS effects[101,107]. Finally, the link between
337 behavioral performance and physiological measures – such as TMS-generated
338 excitability measures or cerebral activation monitored by functional imaging – may in itself
339 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 that the selectivity of task-relevant networks has increased[43]. NIBS protocols may therefore affect performance in opposite ways during different stages of learning, as shown e.g. for visuo-motor coordination[110].

One crucial, currently 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 should lie between the electrodes for some montages (Box 1). Such computational models of tES-induced electric fields may ultimately prove crucial 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 effects on areas under the electrodes as induced by traditional protocols[36] (see a more detailed discussion on this topic in 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 needed for everyday use of NIBS remain unaddressed. Most of the existing NIBS studies were conducted in controlled

363 laboratory settings, did not specifically aim for maximal and homogeneous effects, did not
364 explore long-term (and possibly performance-reducing) effects, and did not focus on
365 possible late-occurring side effects or side effects that might be caused by intensified use.
366 Obviously, this cautionary statement does not mean that NIBS will never be suitable for
367 neuro-enhancement purposes; future translational approaches of the basic laboratory
368 studies may offer this possibility if they take state- and task-dependent effects into
369 account, possibly as closed-loop systems[52].

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

Overcoming NIBS limitations

Some of the problems discussed in the previous section might relate to the variability of methodical 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 methodical procedures 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 (Figure 4). For instance, 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 studies to result in the highest level of variability in effect size. On the other hand, most conclusive (and least exploratory) about a brain-behavior relation may be studies that incorporate the following methodical procedures: First, neuro-navigation in order to more precisely locate the NIBS region of interest in each participant, e.g. based on functional neuroimaging evidence or based on clearly defined anatomical criteria. This

409 is arguably more critical for TMS studies than for studies employing tES with its relatively
410 coarser spatial resolution. However, tES studies may also benefit from this step since this
411 ensures more homogenous positioning of the areas of interest in the induced fields, in
412 particular for emergent tES protocols that offer higher spatial resolutions (see BOX 1 for
413 a discussion on this topic). Second, control tasks or behavioral measures that ascertain
414 that the NIBS effects are indeed specific for the behavior under study. Third, stimulation
415 of control regions/frequencies in order to test the functional specificity of the target
416 area/neural process of interest. Fourth, combination with neuroimaging in order to directly
417 quantifiy the strength of the NIBS effect on the local neural effect of interest, and to
418 measure how connected brain networks are affected by the application of the stimulation.
419 Fifth, characterization of the NIBS-induced changes with theory-driven models whose
420 mechanistic latent variables can capture changes in both behavioral and brain activity
421 modulations.

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

429 Adopting the type of multi-method strategies mentioned above are labor-intensive
430 and challenging, but this approach is increasingly adopted and therefore feasible[18,117–119].
431 One example study[118] that utilized many of the methodical procedures suggested in

Figure 4 tested the hypothesis that working memory information is temporarily stored via "activity silent" synaptic mechanisms (Figure 5a). This study used fMRI to localize cortical areas that represent category specific working memory contents, and TMS combined with EEG to characterize the temporal dynamics of the hypothesized memory reactivation. Another study[18] utilizing similar procedures investigated the causal role of theta oscillations (~6 Hz) on the dorsal stream for working memory maintenance (Figure 5b). The authors used MEG 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 (TPJ) in guiding strategic social behavior, by combining computational modeling of behavior, neural activity recordings with fMRI, and transcranial magnetic stimulation (TMS) guided by neuronavigation (Figure 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 methodical framework similar to the one illustrated in Figure 4.

Combining NIBS methods with other imaging techniques such as magnetic resonance spectroscopy (MRS) 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

455 instance, it has been shown that anodal tDCS over M1 reduces the concentration of
456 GABA, whereas cathodal stimulation results in a significant decrease in the concentration
457 of both glutamate and GABA[123]. This is consistent with the notion that LTP-like plasticity
458 in the neocortex – thought to be affected by tDCS – critically depends on GABA
459 modulation[124]. Based on these findings, a recent study employed tDCS to test for cortical
460 rebalancing of excitatory and inhibitory influences during associative learning[119]. The
461 researchers administered anodal tDCS to induce a local reduction in cortical GABA while
462 using fMRI to track the representational overlap between learned associations over time.
463 As hypothesized, the new experiment revealed that cortical memories were re-exposed
464 during anodal tDCS, thereby illustrating how NIBS in combination with different
465 neuroimaging modalities (MRS and fMRI) can be used to reveal a more comprehensive
466 picture of the neurophysiological mechanisms underlying cognitive processes.

467 Shifting the field from more exploratory behavioral demonstrations to the multi-
468 method approaches illustrated above requires careful planning of all stages of a NIBS
469 study (Figure 6). That is, during the *design stage* of the experiments, the researchers
470 must already clearly define the area that should be stimulated, the cognitive process that
471 should be modulated, and how this NIBS influence on behavior can be measured
472 conclusively. This latter step requires *a-priori* considerations of including a control
473 task/behavioral measure to establish context-specificity and selecting a control brain
474 region to test the spatial selectivity of the intervention effect. Additionally, in order to
475 reduce problems with type I errors and improve reproducibility[125], NIBS studies (and all
476 other studies) should employ adequate sample sizes[126]. This may be achieved by power
477 analyses[126] and the consideration 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, the researchers should try to maximize the reliability of the NIBS-induced modulations, e.g., by using neuro-navigation 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 the majority of the NIBS methods induce somato-sensory effects (e.g. in TMS auditory effects of the "coil click"[128], in tDCS the skin sensations due to the current flow over the scalp[129], and in tACS the perception of phosphenes[130]), it is crucial that the authors take care of blinding the NIBS intervention and to properly control for placebo effects.

Finally, for the *analysis/report* stage, the investigators should have a clear plan for the statistical analyses used to evaluate whether the targeted cognitive process was specifically impacted by the NIBS intervention. This analysis plan should include statistical comparisons with control tasks, brain regions and clearly defined neuro-computational latent variables to identify the specificity of the hypothesized NIBS-induced effect on behavior and neural function. Last but not the least, in order 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 methodical practices 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 always 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 develop and identify 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

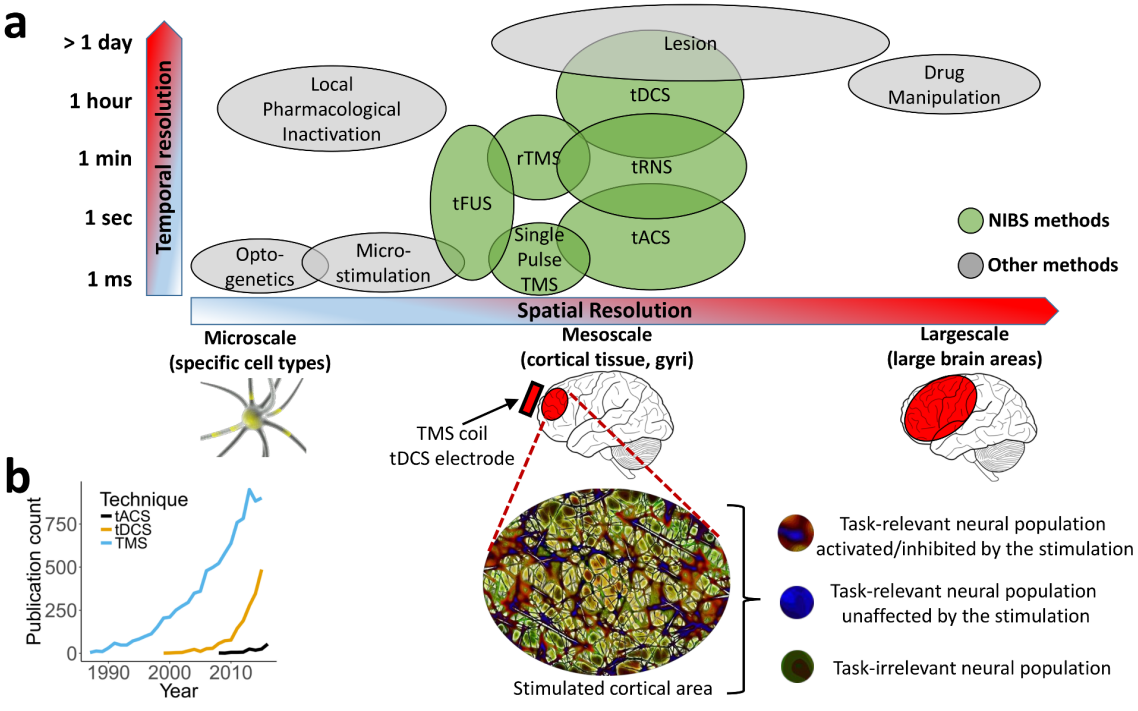
would have to be derived with combinations of brain stimulation, neuroimaging, solid experimental designs, and modeling work (as attempted e.g. in computational psychiatry[135]). Such initial studies in healthy participants should lead to further translational treatment-validation studies that should 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 should importantly 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 multi-center 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 more basic and less research-oriented 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 that the use of NIBS for research purposes requires responsible scientific practice. This may necessitate a shift in focus from simplistic assumptions about how NIBS methods generally affect the brain towards more physiologically informed multi-method approaches that test specific hypotheses about how NIBS influences 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 interpretations and future summary of the data. Of course, these considerations are not only important for NIBS research but also for other fields of experimental sciences. But the current debates highlight 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.

Figure Legends

Figure 1. a) The scheme shows the temporal and spatial resolution at which different causal brain interventions work. NIBS methods work at the meso-scale 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)** This plot shows the exponentially-growing number of citations per year for TMS, tDCS and tACS (source: ncbi.nlm.nih.gov; search dates from the year 1980 to 2016).



582 **Figure 2**. Examples of NIBS methods to study brain-function relationships. **(a)** tACS
583 applied with multi-electrode setups can be used to investigate how oscillatory coherence
584 between spatially distinct nodes of functional networks underlies behavior. In the example
585 experiment presented in this panel, tACS electrodes were mounted over the medial
586 prefrontal cortex (mPFC) and posterior parietal cortex (PPC), two brain regions identified
587 in an EEG experiment to show phase-coupling that was related to the consistency of
588 preference-based decisions[136]. In a subsequent tACS experiment[48], tACS was applied
589 over the mPFC and PPC at the frequencies identified in the EEG experiment at six
590 different lags ($\Delta\varphi$). This showed that full anti-phase stimulation leads to poorer
591 performance compared to tACS applied at full in-phase stimulation. Crucially, the optimal
592 phase difference for task performance indicated that information may flow from frontal to
593 parietal cortex (see right panel), illustrating that tACS can be used to make inferences
594 about the direction of information flow between segregated nodes of functional brain
595 networks. **(b)** tRNS may be useful for investigating the stochastic dynamics of neuronal
596 processing. In the example presented in this panel[63], tRNS was applied over the primary
597 visual cortex (V1, left panel) at different noise amplitudes (middle panel) to investigate the
598 stochastic resonance phenomenon (SR, see BOX 2). Consistent with the assumption that
599 there are optimal noise levels for neural processing, only intermediate (but not high or
600 low) levels of noise led to higher discriminability in a signal detection task (right panel).
601 This illustrates how tRNS can elucidate stochastic dynamics of neural circuits in the intact
602 human brain. **(c)** TMS can be combined with fMRI to reveal functional influences in brain
603 networks underlying behavior. In the example study presented in this panel, the
604 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 in FFA and PPA only when distracters were present. Critically, these influences were only observed in in regions representing the current memory targets (right panel), thus providing causal evidence that neural signals from DLPFC can enhance WM representations in posterior brain areas during external distraction.

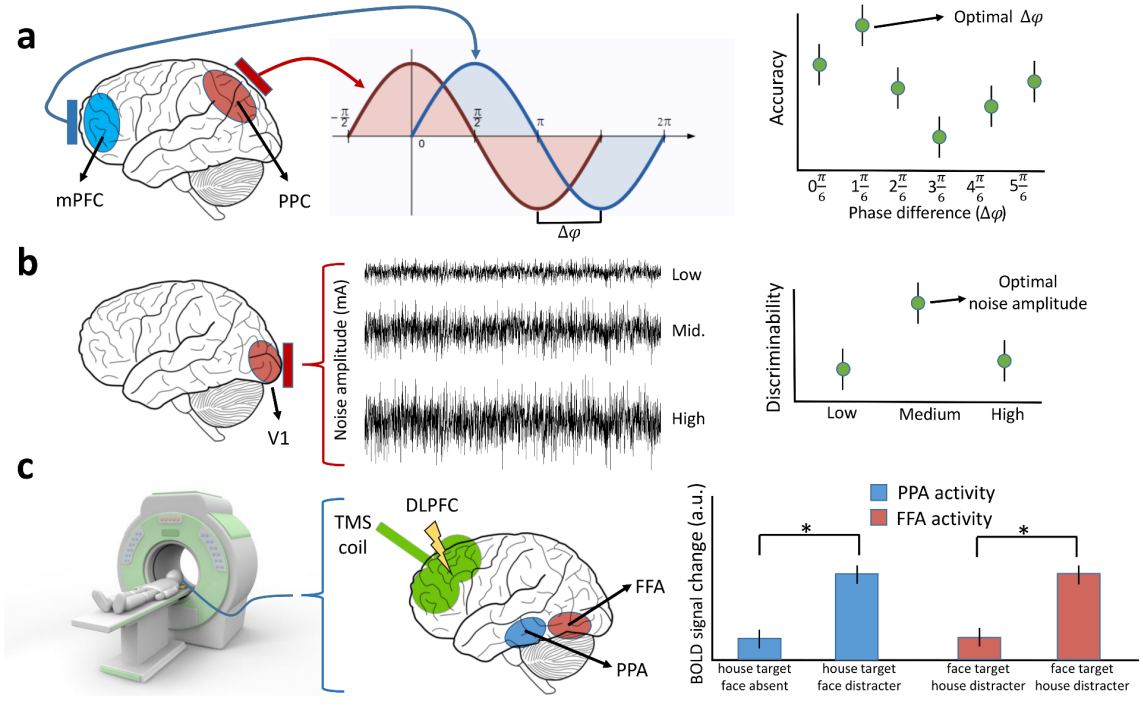


Figure 3. Example factors determining the variability of neurophysiological and behavioral NIBS effects. Many sources of variability in NIBS effects reflect factors that similarly affect the variability of other experimental interventions in the life sciences. However, there are NIBS-specific factors 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 methodical criteria[93,104].

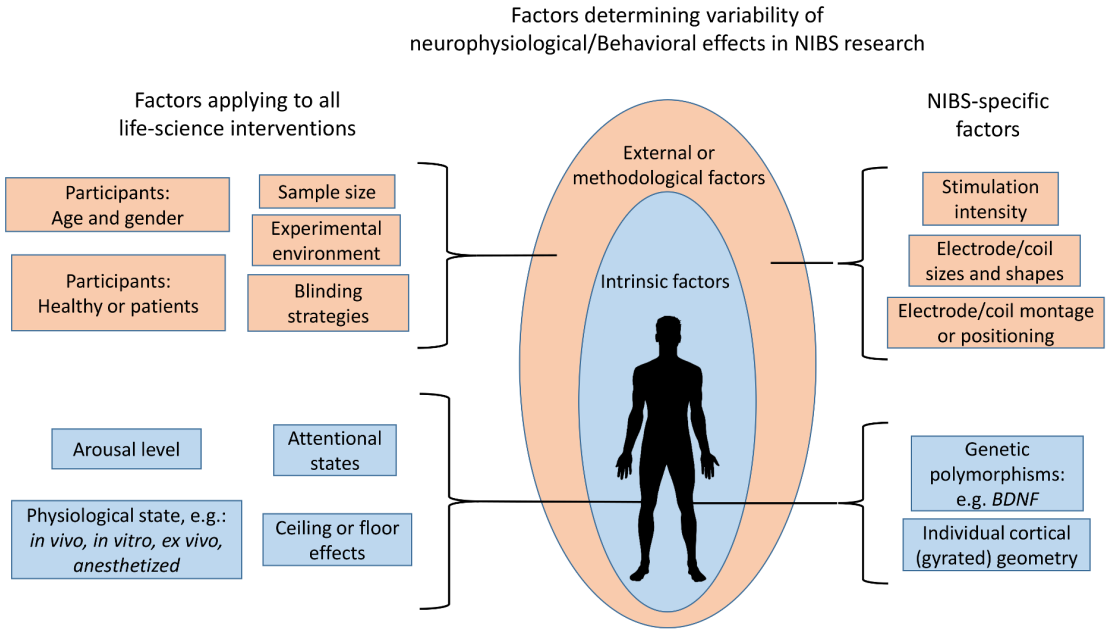
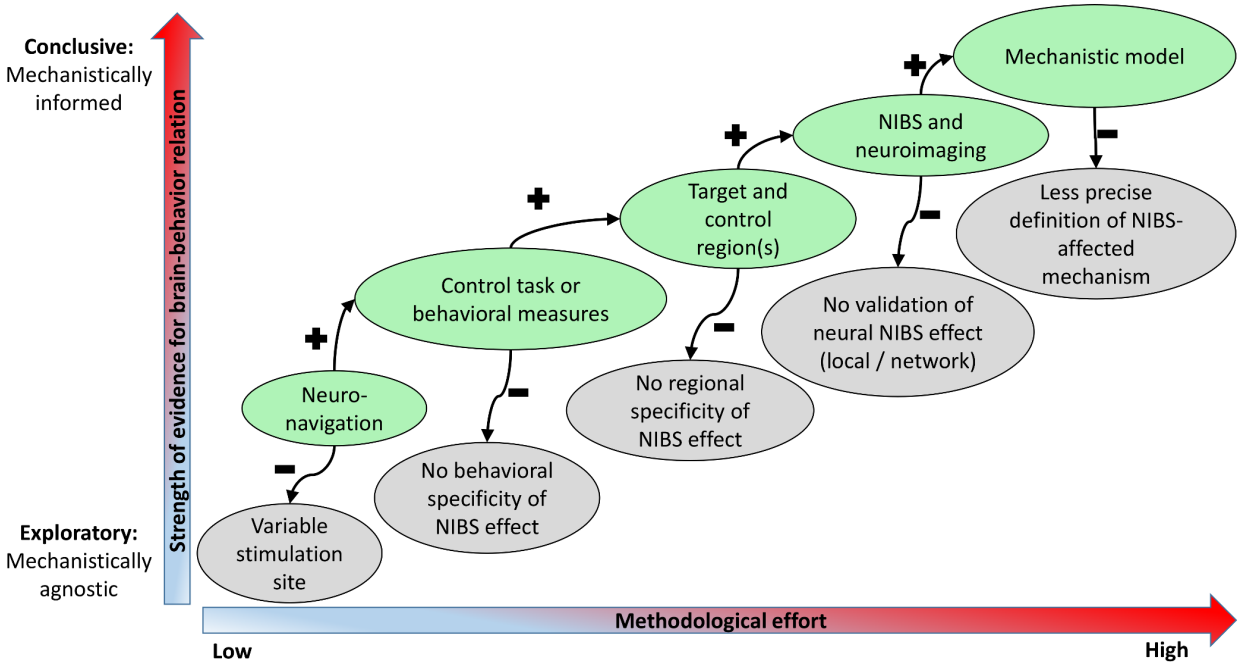


Figure 4. The conclusiveness of NIBS results on brain-behavior relations depends on the degree of methodological effort. Here we show an example decision tree to illustrate how the successive inclusion of methodical procedures in a given study can lead to increasingly conclusive and mechanistically-informed evidence for the relationship

between behavior and a well-defined neural process (for examples, such a scheme was followed in REFs. 18, 117 and 118; see also Figure 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 benefit from following these procedures if they apply well-validated protocols. However, the more of these methodical procedures that can be included in a given study, the more conclusive and mechanistically informed the resulting evidence.



642 **Figure 5.** Examples of studies employing NIBS methods in a multi-methods approach to
643 establish brain-behavior relations. **(a)** This study tested the hypothesis that working
644 memory information is temporary stored via "activity silent" synaptic mechanisms[118]. The
645 authors first used fMRI to precisely localize cortical areas that represent category specific
646 working memory contents (left panel). Afterwards, they used EEG in order to characterize
647 the temporal dynamics of the hypothesized memory reactivation via single pulse TMS at
648 the locations identified in the fMRI experiment (middle panel). They observed that a TMS
649 pulse during the retention period, re-expressed latent working memories of unattended
650 memory items (right panel). **(b)** This study tested the causal role of theta oscillations (~6
651 Hz) for working memory maintenance. The authors first identified for each individual the
652 cortical generators of theta oscillations related to memory maintenance via MEG (left
653 panel). Then the authors replicated their findings in a new experiment using EEG, which
654 conveniently allows tracking of oscillatory neural entrainment via rhythmic TMS[120] (middle
655 panel). Using this multi-method approach, the investigators demonstrated that by
656 artificially entraining theta oscillations via TMS, it was possible to augment working
657 memory performance (right panel). **(c)** This study investigated how the human brain
658 represents beliefs about how our choices will influence those of others we interact with[117].
659 The authors first identified the region of interest using fMRI and computational modelling
660 (left panel). The authors then used rTMS to inhibit the activity of the right temporoparietal
661 junction (rTPJ), which was hypothesized to implement the social influence signal (middle
662 panel). Additionally, the authors also used a remote control region (vertex) to test the
663 regional specificity. After rTMS, participants performed the social task during fMRI and
664 used computational modelling to study how mechanistic latent variables of behavior

where affected by the inhibitory rTMS protocol to the rTPJ compared to the control region (right panel). This multimethod approach, thus, allowed the authors to reveal a regional and functional specific causal role of the rTPJ in computing social influence signals.

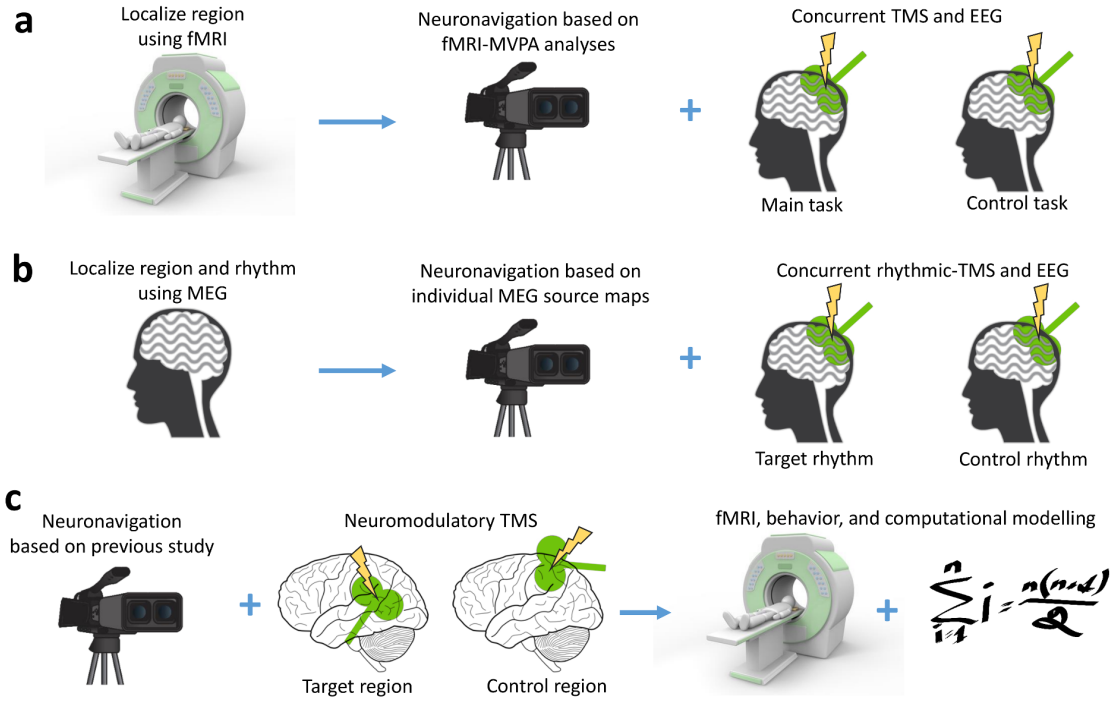
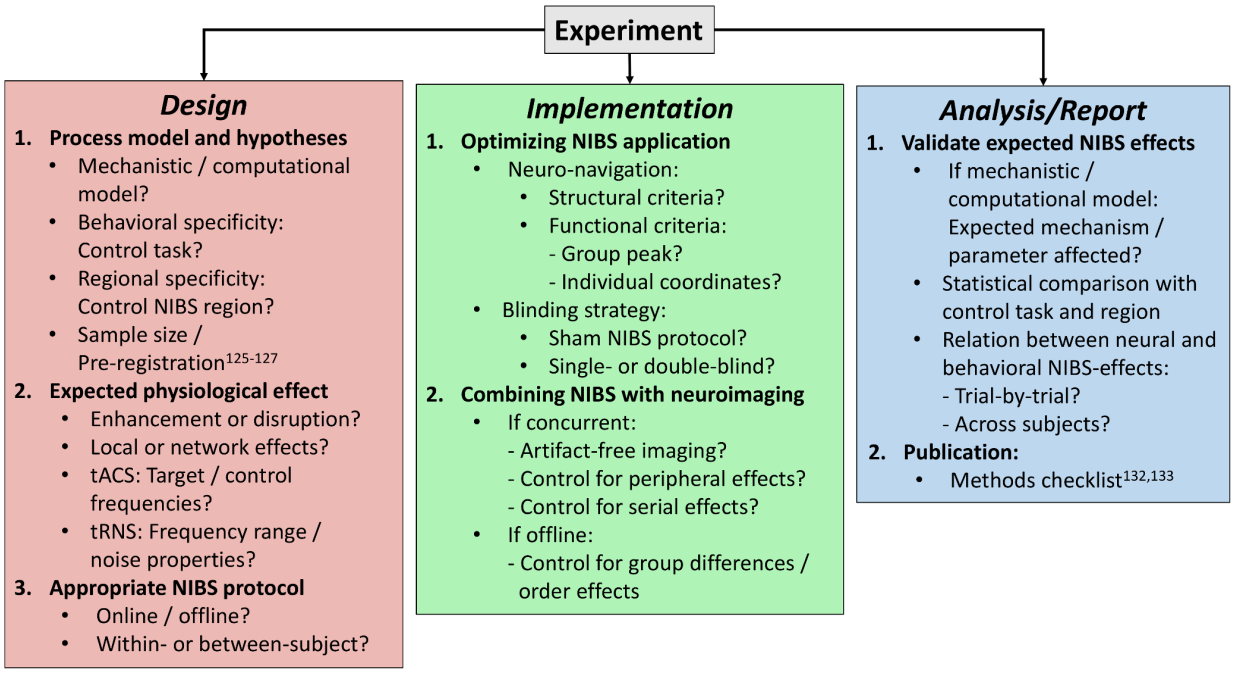


Figure 6. Multi-method approaches can be used to gain fundamental and more reliable insights on brain-behavior relations via NIBS. However, in order to carry out such studies involving high methodological effort (see Figure 4), it is crucial to have a clear work plan before conducting the study. This scheme shows an example of important aspects to consider in such a work plan before, during and after the execution of NIBS studies.


Experiment
Design
1. Process model and hypotheses
• Mechanistic / computational model?
• Behavioral specificity: Control task?
• Regional specificity: Control NIBS region?
• Sample size / Pre-registration[125-127]
2. Expected physiological effect
• Enhancement or disruption?
• Local or network effects?
• tACS: Target / control frequencies?
• tRNS: Frequency range / noise properties?
3. Appropriate NIBS protocol
• Online / offline?
• Within- or between-subject?
Implementation
1. Optimizing NIBS application
• Neuro-navigation:
• Structural criteria?
• Functional criteria:
- Group peak?
- Individual coordinates?
• Blinding strategy:
• Sham NIBS protocol?
• Single- or double-blind?
2. Combining NIBS with neuroimaging
• If concurrent:
- Artifact-free imaging?
- Control for peripheral effects?
- Control for serial effects?
• If offline:
- Control for group differences / order effects
Analysis/Report
1. Validate expected NIBS effects
• If mechanistic / computational model: Expected mechanism / parameter affected?
• Statistical comparison with control task and region
• Relation between neural and behavioral NIBS-effects:
- Trial-by-trial?
- Across subjects?
2. Publication:
• Methods checklist[132,133]

676

677

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 for investigating 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 needs to be taken 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[137]. 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[138]. 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[139] that may help to predict NIBS-induced effects with greater accuracy[106,111] (Box Figure 1a,b,c). For instance, modelling work suggests that conventional electrode montages might induce effects not only under the electrodes but also between them, and that for some montages the strongest fields may actually not lie under the electrodes (Box Figure 1a, top). While these efforts at modelling

tES-induced electric fields and effects on neurons may ultimately prove crucial for optimizing the efficiency of NIBS protocols, it is important to note that such models 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 Box Figure 1a reliably induce cortical excitability that depends on the stimulation polarity, with the conventional electrode montage inducing stronger effects immediately after stimulation but the novel ring electrode configuration effects being more prominent 30 minutes after the end of stimulation[36]. Moreover, while the modelling sometimes suggests that the peak electric field in the classic montage may lie between rather than under the electrodes (e.g., see Box Figure 1a), the physiological data show that the induced effect is in fact maximal under the stimulating electrode[36]. This puzzling discrepancy will need to be resolved and shows that while modelling will be useful to help optimizing NIBS protocols, physiological validation is crucial before jumping to conclusions about the spatial specificity and effectivity of any NIBS protocol[140,141].

Another promising route to deal with the relatively low degree of spatial focality offered by tDCS (Box Figure 1a) and TMS (Box Figure 1b) focusses 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 modelling and empirical work[142] (Box Figure 1c). 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*[141], *in vivo*[9,40,140] and *ex vivo* preparations[143]. However, the results of these studies are rather variable. Therefore, it is crucial to investigate to what extent the results obtained from different approaches (e.g., *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 non-human primates during tDCS/tACS both *in vivo* and *ex vivo*[144]. They found significant differences in electrical field strength between *in vivo* and *ex vivo* measurements (Box Figure 1d), 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[9,140,144] and that conclusions derived from *ex vivo* experiments need to be interpreted with care.

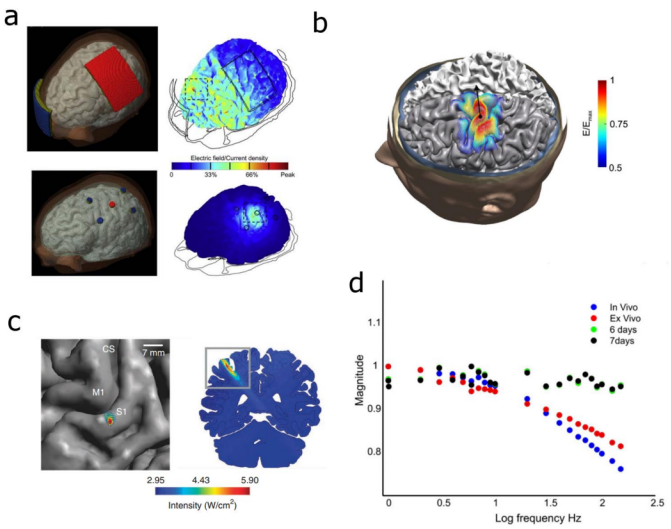
BOX 2: Definitions of NIBS-relevant terminology

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/LTP (see below for a definition). Crucially, NIBS-induced neuroplasticity has been shown to depend on secretion of this protein in animal studies[145]. In humans, brain-derived BDNF gene polymorphisms have been shown to have an impact on NIBS-induced plasticity[146]. Thus, BDNF is one of the many factors that should

746 be taken into account when considering potential sources of behavioral and physiological
747 variability in NIBS-induced effects (Figure 3).
748 **Long-term potentiation (LTP):** A facilitation of synaptic transmission that is considered
749 to be one of the major mechanisms underlying learning and memory formation. The
750 opposite phenomenon, **long-term depression (LTD)**, refers to inhibition of synaptic
751 transmission. LTP and LTD are thought to be expressed at possibly every synapse in the
752 mammalian brain[147]. Long-lasting neurophysiological facilitation or inhibition induced by
753 NIBS (depending on the method and protocol used and additional factors such as brain
754 state and cognitive task) is believed to relate to LTP- or LTD-like changes.
755 **Motor-evoked potentials (MEPs):** Electrical potentials recorded from peripheral
756 muscles in response to single-pulse electrical or magnetic stimulation of M1. MEP
757 amplitudes are typically used to assess the level of cortico-spinal excitability induced by
758 NIBS protocols. Excitatory or inhibitory NIBS protocols increase or decrease MEP
759 amplitudes, respectively.
760 **Phosphene:** Transient visual percepts resembling light flashes that can be induced by
761 supra-threshold TMS pulses over V1[26] or by tACS in the ~8-35 Hz range, depending on
762 the amount of light in the environment[130]. For tACS in this frequency range (~8-35 Hz),
763 such phosphenes need to be properly controlled for as they are difficult to differentiate
764 from genuine neural entrainment. Moreover, whether the origin of tACS-induced
765 phosphenes is cortical or retinal remains a matter of debate[8,148].
766 **Stochastic Resonance (SR):** A phenomenon referring to a situation where a signal that
767 is too weak to be detected by a sensor is enhanced by adding an optimal level of noise.
768 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 SR principle in the human cortex[63].

Box Figure 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 more recent newly proposed 4x1 ring electrode configuration designed to improve the focality of the induced cortical EF (bottom left). The 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 4x1 ring electrode configuration induces more focalized effects over the target area[139]. Adapted with permission from[139]. **(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 4x1 ring electrode configuration[149]. Adapted with permission from[149]. **(c)** The figure shows the acoustic intensity field (AIF) of the 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 cm[150]. Adapted with permission from[150]. **(d)** Frequency response of intracranially measured voltages differ across different tACS frequencies between *in vivo* (blue) and *ex vivo* (red) states[144]. Notably, any tACS frequency dependency is largely absent for the ex vivo measurements (green and black dots).


a
b
c
d
Electric field/Current density
0
33%
66%
Peak
1
0.75
0.5
CS
7 mm
M1
S1
2.95
4.43
5.90
Intensity (W/cm²)
In Vivo
Ex Vivo
6 days
7days
Magnitude
1.1
1
0.9
0.8
0
0.5
1
1.5
2
2.5
Log frequency Hz

792

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