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Noninvasive brain stimulation: from physiology to network dynamics and back

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Abstract

Noninvasive brain stimulation techniques have been widely used for studying the physiology of the CNS, identifying the functional role of specific brain structures and, more recently, exploring large-scale network dynamics. Here we review key findings that contribute to our understanding of the mechanisms underlying the physiological and behavioral effects of these techniques. We highlight recent innovations using noninvasive stimulation to investigate global brain network dynamics and organization. New combinations of these techniques, in conjunction with neuroimaging, will further advance the utility of their application.

In the last two decades, modern noninvasive brain stimulation (NIBS) techniques have made remarkable contributions to neuroscience. The two most commonly used forms of NIBS are transcranial magnetic stimulation (TMS; Fig. 1a) and transcranial direct current stimulation (tDCS; Fig. 1b). Both TMS and tDCS are safe for use in human subjects and have been widely used to test hypotheses about the physiology of the CNS. They identify causal links between specific brain structures supporting cognitive, affective, sensory and motor functions. They also offer insight into local and global brain network organization, dynamics and experience-dependent plasticity.

Abundant evidence supports the use of NIBS techniques as tools for enhancing motor skills and cognitive function in healthy subjects and as therapeutic agents for patients with neurological and psychiatric disorders[1,2]. Despite the unquestionable contribution of NIBS to cognitive, systems and translational neuroscience, the specific underlying mechanisms of stimulation-induced behavioral and physiological effects remain largely unknown. Still, evidence accumulated from animal models, sophisticated experimental designs involving neuropharmacological manipulations in humans, and the combination of NIBS with

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neuroimaging techniques has elucidated some of the possible neurophysiological underpinnings of NIBS effects. Here we review established and emerging NIBS techniques and propose underlying mechanisms. We also highlight more recent findings related to the effect of NIBS on brain network dynamics across spatial scales.

Brief historical overview

A series of experiments conducted by Faraday in 1831 led to the discovery of electromagnetic induction, in which an alternating magnetic field induces an electric current. More than 150 years later, it was shown that when a coil connected to a magnetic stimulator is placed on the human scalp over the motor cortex, current flow and neural activation in the targeted cortex are induced and movements of the contralateral upper or lower limb are easily elicited[3]. Since this seminal study, TMS has rapidly developed into a widely used technique for noninvasive exploration of human brain physiology, with emerging clinical implications. However, the biophysical mechanisms influenced by TMS are still not completely understood. The prevailing hypothesis is that axons are the most effective conductors in the CNS because they have the highest density of ion channels. Therefore, they are preferentially affected by the TMS pulse, which may activate both inhibitory and excitatory neurons[4]. TMS may suppress neural signal or generate random neuronal noise; however, its effects have been suggested to be activity dependent, suppressing the most active neurons and changing the balance between excitation and inhibition[5,6].

The growing interest in noninvasive brain stimulation generated by TMS led to the revitalization of tDCS, a technique applied to animal models in the 1960s[7]. In 2000 it was demonstrated that tDCS induces cortical excitability changes in the human motor cortex[8]. This work used a battery-driven stimulator delivering weak (≤1 mA) currents between a pair of saline-soaked surface sponge electrodes, with one placed on the scalp over the motor cortex and the other over a reference location. Anodal stimulation produced excitation; cathodal stimulation, inhibition. Subsequent studies suggested that the immediate effects of tDCS on corticospinal excitability primarily depend on subthreshold resting membrane potential changes, whereas aftereffects of tDCS are due to shifts in intracortical inhibition and facilitation, and interactions with facilitatory corticospinal waves[9]. tDCS effects have been shown in a wide range of processes, spanning motor and sensory to cognitive functions[7].

Stimulation protocols

TMS is commonly applied in single, paired or repetitive trains (Fig. 2a). Initial applications of TMS focused on the motor system and enabled mapping of functional representations in primary motor cortex (M1), with single-pulse TMS to M1 producing muscle contractions measured as motor-evoked potentials (MEPs)[10]. Single-pulse TMS has also been extended to the visual system: suprathreshold stimulation of occipital cortex (mainly primary visual cortex, V1) induces phosphenes (bright spots of light in the visual field) and transient scotomas, and TMS of area V5 enables the study of motion perception[10]. Furthermore, it has become standard practice to use these responses to inform the selection of appropriate

stimulation parameters for other brain areas, from which there is no noninvasively measurable physiological response[11].

Using the high temporal resolution of TMS, application of pulses during task execution can provide insights into the underlying neural substrates, and the time points during which such are engaged, in relation to the specific task performed[12]. For example, single-pulse TMS was used to show that a specific area in the parietal cortex mediates spatial orienting during distinct time periods after the onset of the behavioral event, suggesting that fast and slow visual pathways are necessary for orienting spatial attention[13]. Single-pulse TMS has also contributed to understanding mechanisms of motor learning[14].

Paired-pulse TMS protocols enable further measurements of cortical physiology. Paired-pulse TMS can be used to study functional interactions within a single brain region or between two connected brain areas[15]. Single-region paired-pulse TMS is typically limited to M1 and involves the application of both a subthreshold conditioning stimulus and suprathreshold test stimulus to the same region. Variation of the precise latency between the conditioning and test stimuli can result in intracortical inhibitory (if the conditioning stimulus precedes the test stimulus by <5 ms) or intracortical facilitory (if the conditioning stimulus precedes the test stimulus by latencies between 6 and 25 ms, or if the conditioning stimulus succeeds the test stimulus at 1.5-ms intervals between approximately 1 and 4.5 ms) effects on corticospinal output[10,16]. Paired-pulse TMS can also be used to investigate interactions between two spatially distinct brain regions (Fig. 2b). In this model, a conditioning stimulus applied over one cortical area is followed by a test stimulus applied over a second, anatomically connected area. In the motor system, inhibitory or facilitatory effects on MEP sizes can be obtained when the test stimulus applied over M1 is preceded by a conditioning stimulus over contralateral M1, cerebellum, premotor and parietal regions[17–19]. In the visual system, the effects of paired-pulse TMS on phosphene threshold have been used to evaluate functional connectivity among V1, V5 and the frontal eye field[20,21].

Repetitive TMS (rTMS) refers to a family of widely used NIBS techniques. rTMS can be applied using protocols in which stimulation and task performance are dissociated in time. In the most common approach, rTMS is applied over a site of interest for several minutes. The induced effects outlast the period of stimulation, giving insight into the role of the specific stimulated brain regions in plasticity and behavior. For example in the motor system, low-frequency (1 Hz) rTMS inhibits cortical excitability, creating a transient ‘virtual lesion’[22]. This resembles a reversible pharmacological lesion classically used in animal models to study the function of the targeted brain area in motor learning by applying inhibitory rTMS at different time points and to different brain regions along the learning process[23–25]. Alternatively, high-frequency (5–20 Hz) rTMS produces an increase in cortical excitability[26], which can facilitate motor sequence learning[27], though the effects may vary[28]. rTMS has been extended to probe cognitive processes as well, including spatial attention, working memory, episodic memory and decision making[11,29,30].

Patterned stimulation protocols represent another established form of rTMS. Theta-burst stimulation (TBS), which involves the application of a burst of three 50-Hz pulses in trains

repeated at 200-ms intervals, is the primary protocol in this class. Three TBS variants have been extensively explored. Continuous TBS (cTBS) involves the application of burst trains for 20–40 s and has an inhibitory effect on corticospinal excitability. Conversely, for intermittent TBS (iTBS), burst trains with a duration of 2 s are applied over a total of 190 s, with the trains repeating every 10 s. Intermediate TBS, a third variant including 5-s burst trains repeated every 15 s for a total of 110 s, is typically used as a negative control for cTBS and iTBS as it shows no effects on corticospinal excitibility[31]. These patterned stimulation protocols induce longer-lasting effects than conventional rTMS paradigms.

tDCS is most commonly applied at 1–2 mA for 5–20 min using 5-cm^2 saline-soaked sponge electrodes and has been shown to have effects across various functions[7]. For example, anodal tDCS facilitates visual perception[32], spatial tactile acuity[33], visuospatial attention[34] and also higher order cognitive functions[35]. Notably, beyond its short-term effects, application of tDCS in conjunction with task execution may result in prolonged improvements in performance. For example, application of anodal tDCS over M1 during multiple sessions enhanced motor skill learning[36], and bilateral tDCS over posterior parietal cortex has been shown to enhance numerical processing[37]. Thus, overall, the underlying logic has been to induce by NIBS neural patterns that facilitate learning by coupling this activity with motor practice or perceptual stimulation, or modulate state-dependent activity (Box 1). This coupling might be useful for recalibrating or ameliorating neural functioning in clinical conditions.

Basic neurophysiological mechanisms

Although these two techniques are capable of producing similar physiological and behavioral effects, TMS and tDCS are believed to operate by different mechanisms. In searching for a feasible mechanistic framework underlying TMS, studies have mainly explored similarities with activity-dependent synaptic plasticity. Repetitive electrical stimulation of adult hippocampus in *in vitro* animal models induces NMDA receptor–dependent long-term potentiation (LTP) or depression (LTD)[38,39]. High frequency stimulation results in persistent increases in synaptic strength, whereas long trains of low frequency stimulation result in a lasting decrease in synaptic efficacy. In humans, similar *in vivo* LTP-like and LTD-like plasticity effects in the neocortex are largely reproduced by rTMS, with sustained changes in MEP amplitudes serving as a noninvasive probe for cortical excitability. Solid evidence linking human rTMS with LTP-like and LTD-like plasticity comes from studies using TBS protocols[31,40], which are based on LTP and LTD stimulation protocols used in animal models. Another stimulation protocol, widely used for demonstrating LTP-like and LTD-like plasticity, is paired associative stimulation (PAS)[41], in which low-frequency median nerve stimulation is coupled with TMS over the contralateral motor cortex. PAS protocols are of particular relevance because they demonstrate some of the characteristics of spike timing–dependent plasticity[42], wherein the order and precise temporal interval between presynaptic and postsynaptic spikes determine the sign and magnitude of LTP-like or LTD-like synaptic changes[43]. More recently, PAS-like protocols have been extended to corticocortical pathways using repetitive paired-pulse TMS applied to directly connected cortical regions, producing similar effects[44,45].

Pharmacological interventions provide further information about the possible mechanisms underlying TMS. The NMDA receptor antagonist memantine blocks the inhibitory effect of cTBS and the facilitory effect of iTBS[46]. Similarly, dextromethorphan, another NMDA receptor antagonist, blocks PAS-induced facilitation of MEP amplitudes[47]. It thus appears that, overall, the LTP-like and LTD-like effects of rTMS rely on NMDA receptor–mediated glutamatergic function.

The mechanisms by which tDCS exerts its effects are yet to be fully determined[48]. Unlike TMS, which is believed to induce action potentials in and around the stimulated neuronal tissue, tDCS is considered to have a modulatory effect, biasing cortical excitability[8]. More specifically, animal studies have established that anodal stimulation seems to increase neuronal excitability and spontaneous firing rate by depolarizing resting membrane potentials, whereas cathodal stimulation hyperpolarizes membrane potentials, leading to decreased neuronal firing rate and excitability. These effects are time and intensity dependent[49]. Similar polarity-specific shifts in cortical excitability have been observed in humans[8], despite the added complexity associated with transcranial, rather than direct, application of stimulation.

Here too, pharmacological interventions have facilitated our understanding of the possible mechanisms of tDCS effects in humans, specifically helping to differentiate between short-lasting effects and longer-lasting aftereffects. In particular, ion-channel blockers seem to have differential polarity-specific effects on cortical excitability. Administration of the voltage-dependent sodium channel blocker carbamazepine[50,51] or calcium channel blocker flunarizine[51] eliminates only anodal LTP-like plasticity, both during and after stimulation[51]. Alternately, administration of the NMDA receptor antagonist dextromethorphan hinders the post-stimulation effects of tDCS in a non-polarity-specific manner[51].

These findings were further elaborated in a recent *ex vivo* animal study in mice, in which anodal DCS applied to M1 slices was coupled with low-frequency synaptic stimulation inducing long-term synaptic plasticity[52]. Notably, these effects required activity-dependent brain-derived neurotrophic factor (BDNF) secretion[52], a finding that is in agreement with previous demonstrations of the role of BDNF in NIBS-induced plasticity[53,54] and its modulatory role in NMDA receptor-dependent LTP and LTD[55,56]. Other studies in humans have implicated the GABAergic system in tDCS-induced plasticity[57,58]. In particular, polarity-specific changes in GABA concentration, occurring with tDCS, were documented using magnetic resonance spectroscopy[58]. Taken together, these results indicate that the lasting aftereffects of tDCS may indeed reflect LTP-like and LTD-like plasticity, possibly through membrane polarization[50,51]. The excitatory effects of anodal tDCS seem to primarily involve NMDA receptor–dependent LTP but may also be mediated by a reduction in GABAergic inhibition[58]. Conversely, the inhibitory effects of cathodal tDCS seem to mainly reflect reduction in excitatory glutamatergic neurotransmission.

Recent studies have extended this mechanistic framework to establish the effect of certain neuromodulators on NIBS-induced plasticity. Although effects have been documented for the cholinergic, serotonergic and adrenergic systems, most investigations have focused on the dopaminergic system[59]. For example, administration of the D2 receptor antagonist

sulpiride blocks the excitatory and inhibitory effects of iTBS and cTBS, respectively[60]. Similarly, low and high dosage l-DOPA administration abolishes tDCS-induced LTP-like and LTD-like plasticity[61]. Overall, these findings demonstrate that dopaminergic neurotransmission is required for NIBS-induced LTP-like and LTD-like plasticity, findings that are congruent with animal models[59].

Inter-individual differences: challenges and possibilities

Given the complex set of biophysical interactions that NIBS rely on, it is perhaps not surprising that stimulation-induced behavioral, physiological and therapeutic effects are not uniform and tend to substantially vary among individuals. Indeed, several factors have been shown to modulate the magnitude of NIBS effects, including variation in brain and skull morphology, local brain oscillations, age, physical fitness and sex, to name a few[62].

The presence of inter-individual difference in stimulation-induced effects poses a real challenge for studies and future therapeutic intervention using NIBS. Yet with careful methodological adjustments, the presence of such variation, rather than being a source of possible confounding effects, can be exploited as a source of information for gaining a greater mechanistic understanding of NIBS. For example, polymorphisms in genes related to dopamine[63] and BDNF[54] explain some of the variation in NIBS-induced plasticity and have thus pointed to mediation by these mechanisms. Furthermore, models of cortical surface folding patterns and white matter fiber architecture derived from structural neuroimaging data have recently been used to inform quantitative physical models of induced electrical fields generated by NIBS in individual subjects[64]. Thus, in the future, initial profiling of individuals that takes into account the presence of such gene polymorphisms or morphological structure could help inform individualized NIBS-based therapeutic interventions and improve possible outcomes.

Modulation of cortical network dynamics

The human brain is a complex neural network hierarchically organized on multiple, overlapping spatial scales[65]. One crucial principle of this organization is the strict competitive balance between segregated and integrated information exchange and processing, which is achieved through transient or long-lasting synchronization of oscillatory activity[66]. Experimental evidence obtained in both animals and humans suggests that NIBS techniques are capable of modulating such cortical oscillatory activity at each spatial scale[67]. Thus, they serve as powerful and complementary tools for investigating causal interactions in brain networks[68].

At the small end of the spatial scale spectrum lie cortical microcircuits, which consist of layer V pyramidal neurons connected to glutamatergic corticocortical and corticofugal projection neurons and to heterogeneous GABAergic interneurons distributed in columnar fashion across different cortical laminae[69]. Several structural similarities exist between cortical microcircuits and central pattern generators classically identified with the spinal cord and brainstem, which support intrinsic and spontaneous oscillatory dynamics that can be modified by external inputs[70]. Paired-pulse TMS protocols that apply both stimuli to M1

through the same coil interrogate these intra- and inter-microcircuit dynamics. More recently, some researchers have begun using triple-pulse TMS protocols (which apply a combination of two standard conditioning stimuli) to gain insight into how different local network oscillations interact with one another[71].

Paired- and triple-pulse techniques have also been used to interrogate networks on larger spatial scales, through the multi-regional protocols described previously. A single supra-threshold TMS pulse generates very high frequency, short-lasting and spatially specific oscillations that are phase-locked to the stimulus[4]. This combination of properties makes TMS useful for probing functional connectivity between connected brain regions, as distinct oscillations generated by a conditioning stimulus applied to a cortical region and a test stimulus applied to M1 can interact sufficiently to modulate motor output only in a small temporal window. Furthermore, the degree to which the phases of these oscillations are coupled determines the degree of modulation[67]. Initial applications along these lines studied interactions between right and left M1 (ref. 15). However, a pioneering application of paired-pulse stimulation[72], as well as concurrent TMS–functional magnetic resonance imaging studies in which TMS applied to M1 or dorsal premotor cortex produces robust blood oxygen level–dependent modulation in remote, but connected, regions, laid the groundwork for expansion to other regions connected directly or indirectly to M1 (ref. 73).

Thus far, several interactions between M1 and other areas have been experimentally probed using this technique. These regions include ventral[17,74] and dorsal premotor cortex[75], pre-supplementary motor area[76], dorsolateral prefrontal cortex[77], posterior parietal cortex[78] and the cerebellum[79]. Interactions between frontal eye fields and extrastriate visual cortex have also been explored using this technique[21]. Additionally, triple-pulse studies have made it possible to explore the effects of inter-regional inputs on local processing within M1 circuits[71].

Across all of these studies, several consistent and robust findings have emerged[17,74,76]. First, inter-regional paired-pulse stimuli only show significant modulation of MEP amplitude at highly specific interstimulus intervals. For two regions that are directly connected anatomically, these effects are most common when the stimuli are separated in time by 6 or 8 ms. Although the interstimulus latencies producing significant modulation remain consistent whether measured at rest or in the context of a behavioral task, the sign of the modulation typically differs. In most cases, inter-regional paired-pulse stimulation results in inhibitory modulation of motor output (reduced MEP amplitude) when probed at rest[74] but switches to facilitatory modulation when applied during a behavioral task[75]. Finally, the observed modulation during behavioral tasks is highly context specific[17,74–76]. Interpretation of the mechanisms mediating inhibitory and facilitatory modulation remains difficult, but it is clear that more expansive network interactions are crucial[17].

The use of NIBS techniques in which stimulation and task performance are dissociated in time has yielded substantial information regarding functional specificity of individual network nodes during specific tasks through a ‘perturb and measure’ approach[80–82]. This approach has been used, for example, by combining TMS and subsequent neuroimaging measurements[82] or by using low-frequency rTMS to modulate MEPs during specific

tasks[80,81]. tDCS was also used in this manner to investigate changes in global inter-regional phase coupling at multiple frequency bands[83]. As expected, owing to the nonspecific frequency nature of tDCS, anodal tDCS applied to M1 resulted in increased synchronization within task-related networks across multiple frequency bands. When the effects of stimulation were assessed at rest, decreased synchronization was observed in the default-mode network[83].

Recently, two NIBS techniques have been developed to gain a better understanding of the function of frequency-specific local and global cortical oscillatory dynamics in the production of behavior. Rhythmic TMS[67] entrains specific brain oscillations by applying rTMS at the same frequency, resulting in a progressive increase in power in that band (Fig. 3a). Thus far, this technique has been used to successfully perturb theta, alpha, beta and gamma oscillatory activity[67,84,85]. Even more notably, it has for the first time allowed specific features of oscillatory dynamics to be causally linked to distinct perceptual processes in human subjects[67,85].

In a separate experiment, transcranial alternating current stimulation, a second NIBS technique capable of influencing network dynamics in a frequency-specific manner, was used to investigate the effect of theta-band synchronization/desynchronization of parietofrontal regions on performance in a working memory task[86]. Synchronization resulted in performance improvement, whereas anti-phase desynchronization resulted in performance decreases relative to sham stimulation. In a similar vein, borrowing from methodologies developed in PAS protocols that pair cortical TMS with electrical stimulation of peripheral nerves, repetitive cortico-cortical paired-pulse TMS protocols have shown the ability to facilitate or inhibit specific pathways between two connected brain regions[44,45] (Fig. 3b,c). This technique has yet to be implemented in combination with neuroimaging, however, so it is unknown how global network effects of repetitive cortico-cortical paired-pulse TMS on global network interactions differ from rTMS techniques targeting functional brain regions. Thus, this presents a new method that can be used to investigate the influences of specific functional connectivity pathways on network dynamics underlying a wide variety of behaviors.

Conclusions and future directions

Technological and methodological advances in NIBS bring about exciting new possibilities, as well as tackling some of the pitfalls associated with these techniques (Box 2 and Fig. 4). New TMS coils are being developed for stimulation of deep neural pathways[87]. Other technological advances have been introduced to generate more realistic sham stimulation conditions[88]. Another emerging trend is the combination of NIBS with other techniques; for instance, with positron-emission tomography and magnetic resonance spectroscopy to study the molecular mechanisms of action[58] and with other imaging modalities (diffusion and functional MRI, electroencephalography or magnetoencephalography) to document large-scale stimulation-induced reorganization of structural and functional networks at rest or during task-related activity. Advances have also been made in applying new stimulation protocols able to increase the functional resolution of NIBS (Box 2).

Other advances have been made in electrical stimulation of the brain, where emerging techniques are used presumably to induce or interfere with oscillations of cortical networks. These state-of-the-art techniques might be able to entrain task-related oscillatory activity, another important physiological determinant of cognitive processes[89]. Of these techniques, transcranial alternating current stimulation, as mentioned above, consists of an alternating current delivered in a frequency-specific fashion[90]. Transcranial random noise stimulation, by contrast, consists of an alternating current delivered to the cortex at random frequencies. Although the noise signal can contain all of the frequencies from 0.1 to 640 Hz, this spectrum can be also divided into the low frequency range (0.1–100 Hz) and high frequency range (100–640 Hz)[91].

We have reviewed key findings that contribute to our understanding of the mechanisms underlying the physiological and behavioral effects of noninvasive brain stimulation techniques. Advances in the field reviewed here, as well as general advances in neuroscience, will lend further insight into these issues. Furthermore, some of these advances represent a paradigmatic shift in systems neuroscience, with a clear focus now on using NIBS to investigate and modulate complex network interactions, which may allow unresolved historical problems to be revisited with a fresh perspective.

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Box 1

State dependency in brain stimulation

The neural impact of an external stimulus is determined not only by the properties of that stimulus but also by the underlying state of the activated brain region. For example, the probability of phosphene perception induced by near-threshold TMS of the occipital cortex depends on the phase of ongoing alpha oscillations[98]. In accordance with the view of state-dependent stimulation effects, a new method called TMS adaptation (TMSA) has been introduced to increase the functional resolution of TMS. TMSA is based on the hypothesis that TMS acts differentially on neurons according to their initial neural activation state. An adapting stimulus, presented for a long time (usually 40–60 s), is used to induce habituation in a subset of cells that encode particular stimulus attributes, therefore making them a selective target for TMS[11,99,100]. TMSA predicts that TMS improves processing of attributes that are adapted, whereas it decreases performance for non-adapted attributes. However, the underlying mechanism of TMS and TMSA are still debated. To investigate these mechanisms, a recent study manipulated the brain state using contrast adaptation, a decrease in visual contrast sensitivity produced by repeated exposure to high-contrast stimuli[6]. TMS impaired perception when the visual cortex was not adapted but facilitated perception after adaptation. It has been proposed that TMS affects excitatory and inhibitory neural populations differentially, and that TMS has an activity-dependent suppressive effect on the inhibitory populations. Thus, overall, state dependency may be important in understanding the biological effects and mechanisms through which NIBS modulates neural activity.

Box 2

Technological challenges

In light of the emerging interest in using paired-pulse TMS to evaluate inter-regional functional interactions, including cortical regions in the same hemisphere, the size of the coils has become a limitation. Mini-coils designed specifically for this application have been developed—for example, to probe connectivity between dorsal premotor cortex and M1 in the same hemisphere[92]. However, more generic developments are required to address this sophisticated challenge. For example, as the size of the coil is decreased, the current necessary for effective stimulation increases[93]. In addition, smaller coils heat more rapidly, limiting the duration and frequency of stimulation. For standard figure-eight coils, the problem of coil heating during repetitive stimulation might be addressed with active cooling system designs. A key technological challenge for TMS is improving stimulation focality and penetration depth, factors that typically show a tradeoff with one another[94]. The standard figure-eight coil is believed to stimulate a surface area ranging from 1 to 2 cm^2, depending on coil type and tissue distribution[95], but further efforts are needed to improve this focality. The electric field induced by TMS rapidly decays with distance, and thus the maximal effect of stimulation is limited to surface cortical, cerebellar and spinal cord structures. Stimulation of deeper structures, such as the cingulate gyrus, which may be of particular clinical promise, may possibly be achieved through the use of novel coil designs[87]. Improving the focality of stimulation is also a challenge for tDCS. One strategy is to reduce the size of the stimulation electrode while concurrently increasing the size of the reference electrode[96]. Another emerging class of innovations has been the use of novel electrode configurations[97]. A high-definition 4 × 1 ring configuration has recently been explored in computational models[64,97], with this design resulting in increased spatial specificity and peak induced electric field magnitudes directly beneath the stimulating electrode (Fig. 4a,b). Addressing the challenge of tDCS focality will enable further advances in the use of tDCS to gain insight into intrinsic and larger scale functional architecture and network dynamics[83,86].

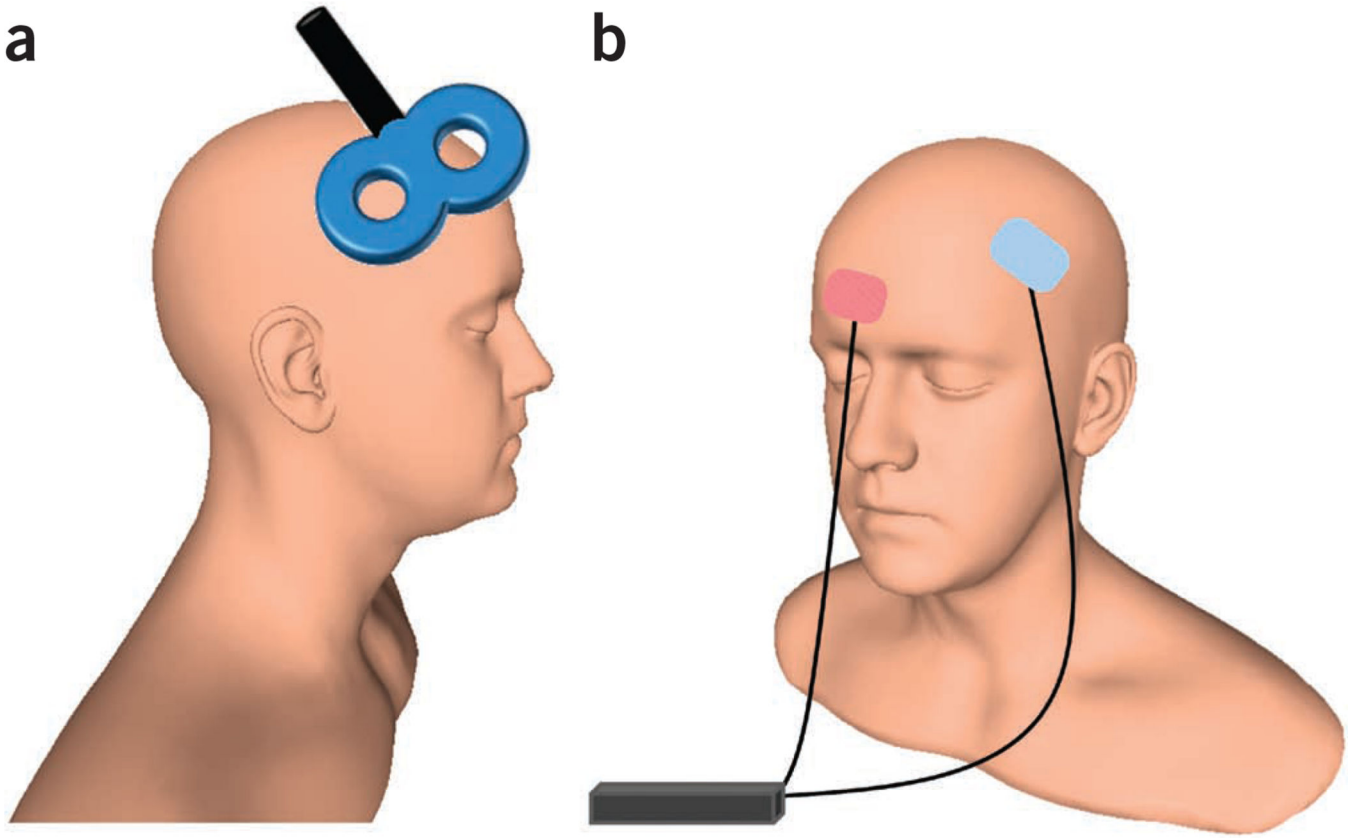

Figure 1.

Typical NIBS setups. (**a**) A standard figure-eight TMS coil placed on the scalp; here, over dorsolateral prefrontal cortex. (**b**) Bipolar tDCS electrode configuration, with one electrode over left dorsolateral prefrontal cortex and a reference electrode over the contralateral supraorbital region. Human head model from http://www.ir-ltd.net/. Used by Creative Commons license.

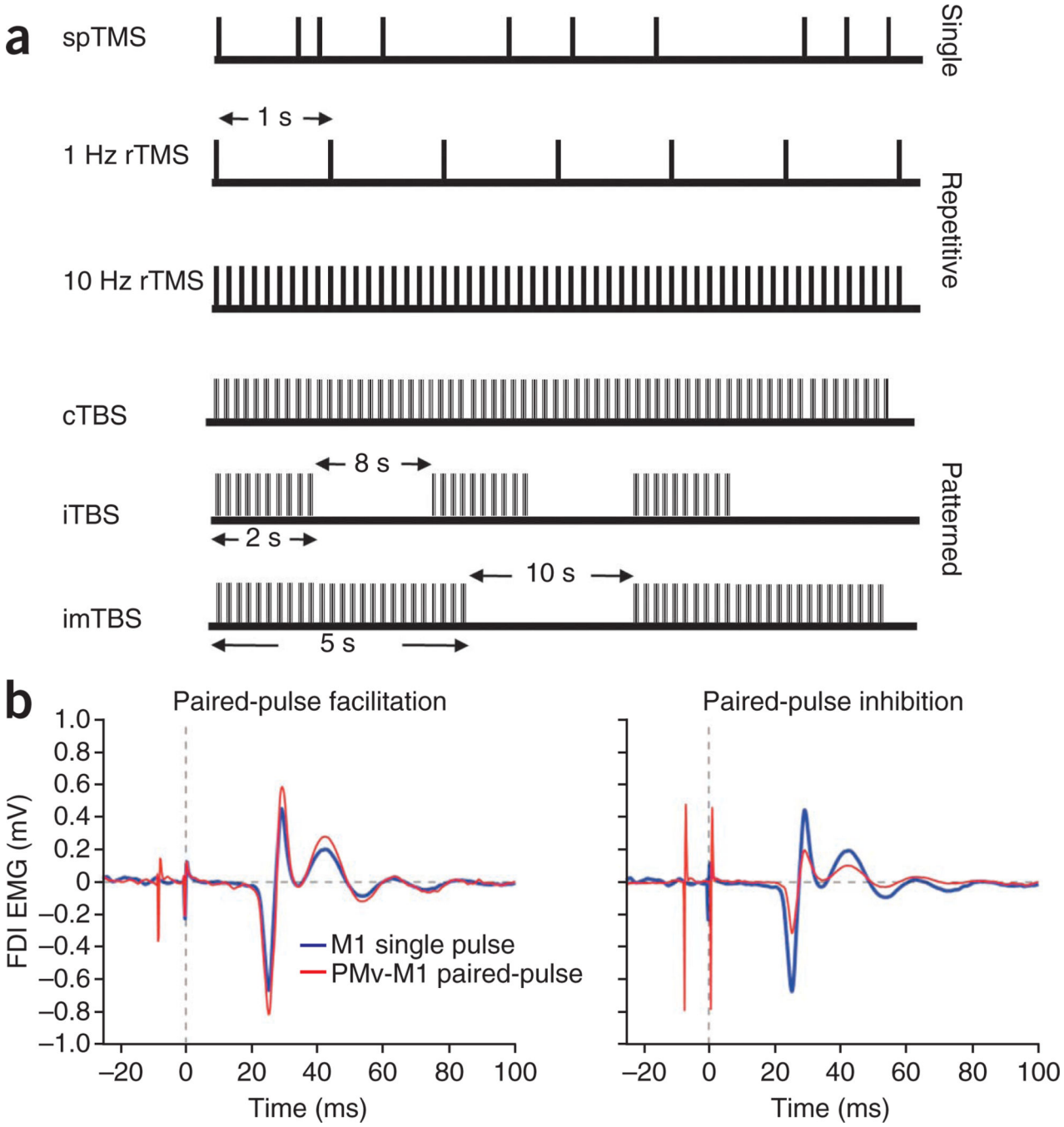

Figure 2.

TMS protocols. (**a**) TMS is commonly applied in single pulses (spTMS), multiple pulses or repetitively (rTMS, applied in low or high frequencies). An emerging form of rTMS is theta-burst stimulation (TBS), in which three 50-Hz pulses are applied at 5 Hz for 20–40 s (continuous TBS, cTBS) or each burst is applied for 2 s and repeated every 10 s for 190 s (intermittent TBS, iTBS). In a third variant, intermediate TBS (imTBS), 5-s burst trains are repeated every 15 s for a total of 110 s (ref. 31). (**b**) MEPs recorded from the first dorsal

interosseous (FDI) muscle using surface electromyography (EMG) after spTMS to M1 and paired-pulse TMS to ventral premotor cortex (PMv) and M1.

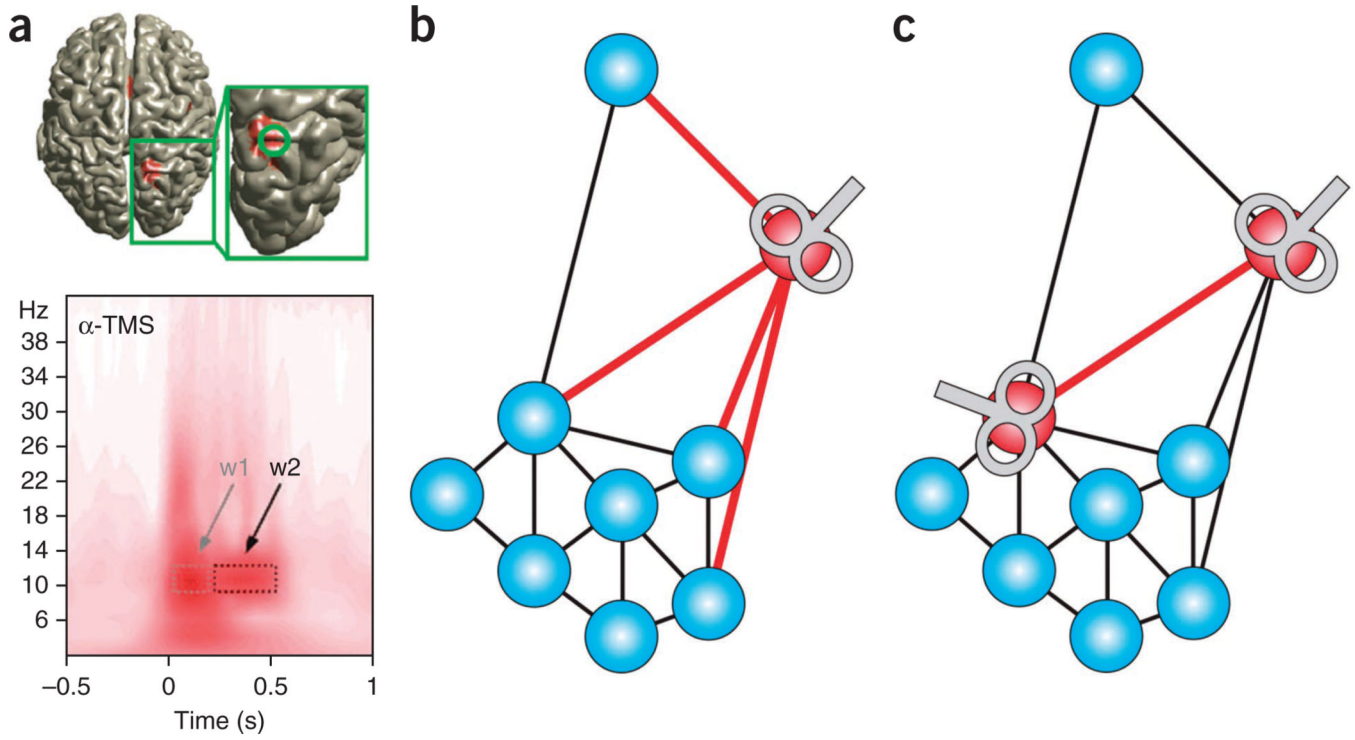

Figure 3.

Probing cortical network dynamics with NIBS. (**a**) Alpha-frequency rhythmic TMS applied to presumed generators of endogenous alpha oscillations in the posterior parietal cortex (inset, top; shown in red) entrains local endogenous oscillations that are specific to that frequency. This results in progressive increase in alpha power in early (w1) and late (w2) time windows (bottom). Modified from ref. 67 with permission. (**b,c**) rTMS protocols for investigating the role of nodes and connections in brain network dynamics. (**b**) A conventional rTMS protocol application that targets a specific brain region, or network node. In combination with functional neuroimaging, the effects of this stimulation on overall network dynamics can be assessed. (**c**) A recently developed repetitive paired-pulse TMS that seems to be capable of targeting a specific functional connectivity pathway (red). This will enable investigation of the roles of connections in network dynamics[44].

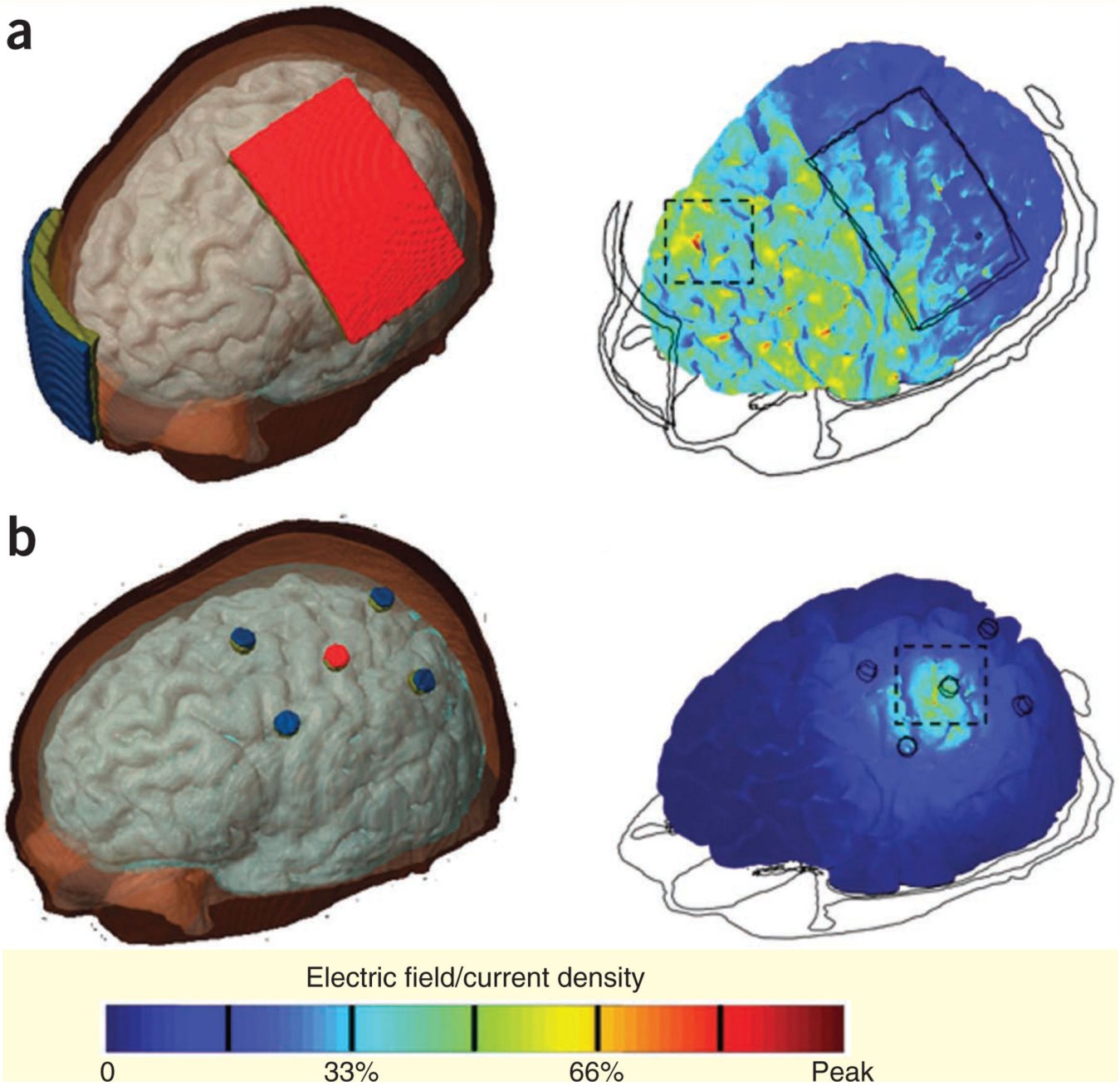

Figure 4.

Stimulation focality of tDCS. (**a**) Cortical electric fields induced by a conventional tDCS electrode configuration. (**b**) Cortical electric fields induced by a 4 × 1 ring electrode configuration. Modified from ref. 97 with permission.