



ALMA MATER STUDIORUM
UNIVERSITÀ DI BOLOGNA

ARCHIVIO ISTITUZIONALE
DELLA RICERCA

Alma Mater Studiorum Università di Bologna Archivio istituzionale della ricerca

Information-Based Approaches of Noninvasive Transcranial Brain Stimulation

This is the final peer-reviewed author's accepted manuscript (postprint) of the following publication:

Published Version:

Information-Based Approaches of Noninvasive Transcranial Brain Stimulation / Romei, Vincenzo; Thut, Gregor; Silvanto, Juha. - In: TRENDS IN NEUROSCIENCES. - ISSN 0166-2236. - STAMPA. - 39:11(2016), pp. 782-795. [10.1016/j.tins.2016.09.001]

Availability:

This version is available at: <https://hdl.handle.net/11585/611622> since: 2017-11-24

Published:

DOI: <http://doi.org/10.1016/j.tins.2016.09.001>

Terms of use:

Some rights reserved. The terms and conditions for the reuse of this version of the manuscript are specified in the publishing policy. For all terms of use and more information see the publisher's website.

This item was downloaded from IRIS Università di Bologna (<https://cris.unibo.it/>).
When citing, please refer to the published version.

(Article begins on next page)

This is the post peer-review accepted manuscript of:

Romei, V., Thut, G., & Silvanto, J. (2016). Information-based approaches of noninvasive transcranial brain stimulation. *Trends in Neurosciences*, 39(11), 782-795. <https://doi.org/10.1016/j.tins.2016.09.001>

The published version is available online at: <https://doi.org/10.1016/j.tins.2016.09.001>

Rights / License:

The terms and conditions for the reuse of this version of the manuscript are specified in the publishing policy. For all terms of use and more information see the publisher's website.

Information-Based Approaches of Noninvasive Transcranial Brain Stimulation

Vincenzo Romei^{1*}, Gregor Thut^{2*} & Juha Silvanto^{3*}

1. Centre for Brain Science, Department of Psychology, University of Essex, UK

2. Centre for Cognitive Neuroimaging, Institute of Neuroscience and Psychology, University of Glasgow, UK

3. Dept of Psychology, Faculty of Science and Technology, University of Westminster, UK

*All authors contributed equally.

Correspondence: vromei@essex.ac.uk; gregor.thut@glasgow.ac.uk; j.silvanto@westminster.ac.uk

Abstract Progress in cognitive neuroscience relies on methodological developments to increase the specificity of knowledge obtained regarding brain function. For example, in functional neuroimaging the current trend is to study the type of information carried by brain regions rather than simply compare activation levels induced by task manipulations. In this context noninvasive transcranial brain stimulation (NTBS) in the study of cognitive functions may appear coarse and old fashioned in its conventional uses. However, in their multitude of parameters, and by coupling them with behavioral manipulations, NTBS protocols can reach the specificity of imaging techniques. Here we review the different paradigms that have aimed to accomplish this in both basic science and clinical settings and follow the general philosophy of information-based approaches.

Trends

Conventional use of noninvasive transcranial brain stimulation (NTBS) in the study of perception and cognition involves enhancing or disrupting behavior, aiming to map cortical regions to behavioral functions.

Novel NTBS paradigms aim to understand how information related to perceptual and cognitive processes is represented by neural networks, mirroring the general philosophy of the information-based approach in functional neuroimaging.

This is achieved by manipulations of stimulation parameters and prior/concurrent task demands to target specific neural networks or populations.

Glossary

Transcranial magnetic stimulation (TMS), transcranial alternating current stimulation (tACS), transcranial direct-current stimulation (tDCS): established techniques that allow noninvasive (transcranial) stimulation of the brain through externally applied magnetic (TMS) or electric fields (tACS/tDCS).

Information-based brain stimulation: using prior knowledge of functional, physiological, and anatomical properties to enhance the specificity of stimulation effects to target specific neuronal representations/networks.

State-dependent brain stimulation: leveraging neural activation states to enhance the specificity of brain stimulation effects using preconditioning or concurrent paradigms.

Rhythmic TMS or tACS: tailoring stimulation frequencies to specific oscillatory networks.

Cortico-cortical paired associative brain stimulation (ccPAS): repeated application of TMS over two or more brain regions with temporal delays mimicking temporal connectivity patterns to target plasticity in the stimulated network.

Moving forward from a “black box” approach to informed NTBS

In any field of science, continued progress requires the refinement of experimental approaches. This can take the form of developments of hardware (such as moving to higher field strength in fMRI research) or analysis techniques (such as application of machine learning to fMRI data). In the case of studies of noninvasive brain stimulation, there have been various methodological developments, such as new coil designs and combination with neuroimaging techniques. However, independently of such advances, an important source of increased precision in these studies has come from a refined conceptualization of how the stimulation itself interacts with underlying brain activity. This has allowed researchers to use NTBS to target specific neuronal representations, oscillatory frequencies, and neuronal pathways.

A key conceptual shift underlying these developments has come from moving beyond perceiving participants as ‘passive’ subjects whose brains are either suppressed or excited and from viewing brain regions as black boxes to be disrupted or enhanced. By contrast, recently developed approaches are characterized by the use of detailed prior knowledge of the functional, physiological, and anatomical properties of the networks being targeted. Another key issue is the realization that the spatial resolution of NTBS will never be sufficient to physically stimulate a subpopulation of neurons. This is unfortunate, as cortical areas contain a range of neurons with different tuning and functional properties and a key aim in neuroscience is to understand this diversity. Consequently, while the ‘conventional’ approach has been useful for mapping cortical regions to cognitive functions, it lacks the functional resolution to study how these functions are implemented. This limitation can be overcome by considering the findings of several studies that have shown NTBS effects to result from an interaction between stimulation parameters (e.g., intensity, frequency) and brain activity patterns at the time of stimulation [1–5]. This indicates that NTBS outcomes may be tailored by both the manipulation of underlying brain activity (even if keeping NTBS parameters invariant) and the fine-tuning of NTBS parameters [such as intensity (Box 1) or frequency (see below)]. This has led the field to move beyond the idea that NTBS indiscriminately targets all neurons in a stimulated cortical area. Rather, the focus is now on developing protocols that aim to target specific neuronal subpopulations/networks. This is critical as it enables one to examine the neuronal mechanisms underlying cognitive functions.

An influential means of altering NTBS effects through manipulation of underlying brain activity has been to change the balance of activity between neuronal subpopulations within the stimulated cortex (to enhance the specificity of the stimulation). For example, administering concurrent or preceding tasks can be used to induce differential sensitivity in neuronal subpopulations in the target area to the same NTBS intervention [6,7]. In terms of tailoring NTBS parameters to enhance specificity,

frequency-tuned transcranial alternating-current stimulation (tACS) (see Glossary) and rhythmic transcranial magnetic stimulation (TMS) have been introduced, each thought to promote activity in the oscillatory neuronal network resonating at the stimulation frequency but not in networks operating at other frequencies [5,8,9]. Finally, multiple coils can be used to target plasticity in specific pathways (e.g., [10]). Using these approaches for intervention, behavioral NTBS studies can reach new levels of specificity (see Figure 1 for a schematic representation). Here we review these developments in studies of cognition as well as in the clinical domain.

Enhancing NTBS specificity by manipulating underlying brain activity

Using perceptual and cognitive manipulations prior to NTBS

One approach to improve the specificity of NTBS has been to require subjects to perform a particular task before stimulation. This is thought to control the state of the to-be-stimulated networks. This contrasts with the ‘conventional’ approach, in which the participant is perceived to be ‘passive’ during NTBS administration (e.g., [1]). Ongoing brain activity, unsurprisingly, has been shown to interact with the impact of brain stimulation (e.g., [2,3]) and not controlling for this interaction might explain the large variability in the induced aftereffects of conventional NTBS protocols (e.g., [11]). The utility of modulating brain state before the application of TMS to modulate the direction of aftereffects was initially shown by either enhancing or suppressing activity in the motor cortex before application of repetitive TMS (rTMS) [2,12]. However, the key to enhancing specificity via this technique is to sensitize a subpopulation of neurons within a region, which can be achieved by the use of behavioral adaptation and priming protocols that selectively precondition a specific neuronal population (henceforth referred to as the TMS-adaptation approach) [3,6].

TMS adaptation has been used to study neural properties in various perceptual and cognitive domains, such as number processing [13], letter selectivity and language processing [14,15], motion perception [16,17], and category selectivity [18]. A good example of the usefulness of this approach is a line of research (e.g., [19,20]) that aims to investigate neural tuning properties in the motor network associated with action observation. This work has used the combination of adaptation and TMS to demonstrate that actions are encoded in an abstract manner, by adapting participants to conjunctions of actions and effectors and examining whether subsequent application of TMS selectively enhances the adapted actions independently of the effector. More recently [21] this approach has been used to examine the properties of the action observation network during perception and categorization of actions’ goals. Specifically, the study examined where in this network high-level (end goals) and low-level (grip type) action components are represented. Participants were adapted to movies displaying an actor performing goal-directed actions with a tool using either a power or a precision grip. After

adaptation, participants were asked to match the end goal (goal-recognition task) or the grip (grip-recognition task) of the actions shown in test images from the adapting movies. TMS over the inferior frontal cortex (IFC) and primary sensory cortex (S1) differentially modulated adapted versus nonadapted goals, indicating that these regions contain representations of actions' goals. These studies are good demonstrations of how preconditioning by adaptation allows TMS to tease apart neural tuning properties – results that would not be possible with the conventional ‘virtual lesion’ approach.

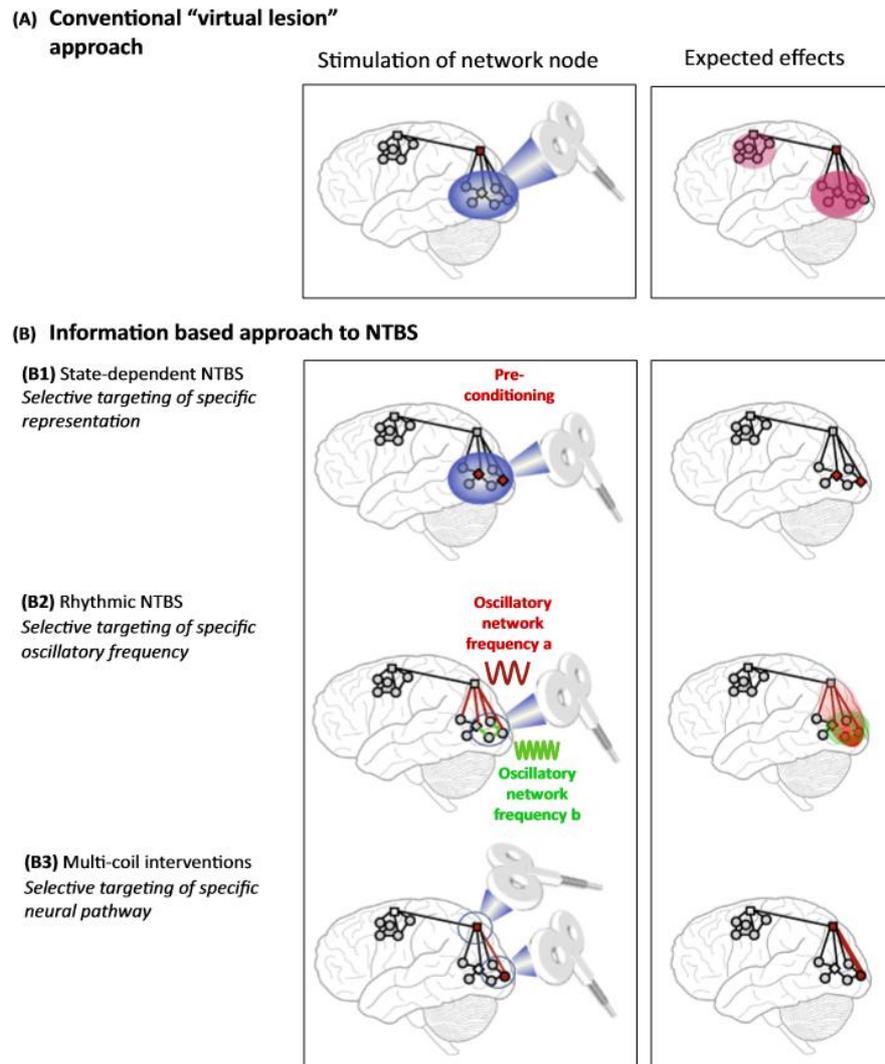


Figure 1. Novel Behavioral Approaches to Enhance Noninvasive Transcranial Brain Stimulation (NTBS) Effects.

(A) In the conventional ‘virtual-lesion’ approach, stimulation is applied over a region of the cortex and all neuronal representations regardless of tuning and oscillation frequency are expected to be similarly affected. The effects also spread to interconnected regions. (B) (1) In the state-dependent NTBS approach, either preconditioning or concurrent task manipulation is used to make a specific neuronal representation differentially susceptible to the stimulation so that the expected neural effects become specific to this representation. (2) In the rhythmic NTBS approach, stimulation is tailored to target a specific oscillatory frequency (in the schematic examples, frequency a or b) promoting the respective oscillatory network (red or green). (3) In the multicoil-intervention approach, the use of two (or more) coils enables selective stimulation of connectivity between two (or more) brain regions.

This preconditioning approach is currently also being tested in the clinical domain. In depression, for instance, NTBS has a long history but the results of stimulation are highly variable. A recent study [22] made use of the finding that positive antidepressant effects of rTMS were present in subjects with higher rostral anterior cingulate cortex (rACC) activity, which correlated with enhanced frontal theta power (frontalu). The authors then used a cognitive task to manipulate frontalu before rTMS treatment, to examine whether this preconditioning could enhance the ability of TMS to induce antidepressant responses (Figure 2). The patient group undergoing this cognitive task before active TMS exhibited a significantly greater reduction in depression scores compared with groups who underwent sham TMS coupled with the cognitive task or active TMS coupled with a sham cognitive task. This indicates that preconditioning of brain regions associated with depression has a major impact in enhancing the efficacy of TMS in treatment.

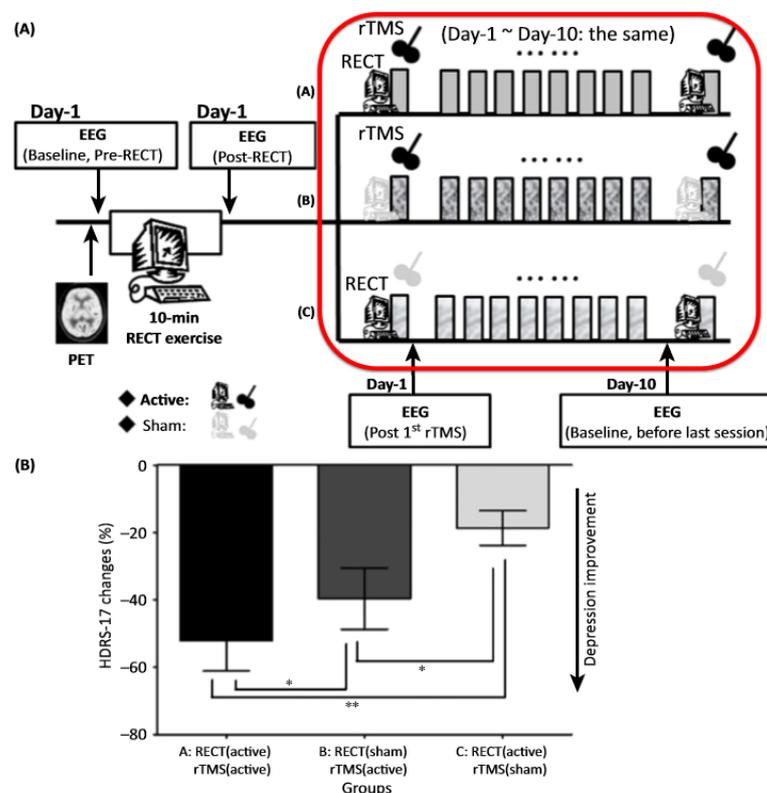


Figure 2. Enhancing Transcranial Magnetic Stimulation (TMS) Specificity by Behavioral Preconditioning (TMS Adaptation). (A) A recent study [22] used a computerized cognitive task (RECT) engaging the rostral anterior cingulate cortex for preconditioning before application of TMS. In group A, a 10-min RECT was re-presented every day immediately before the active repetitive TMS (rTMS) treatment. In group B, a 10-min sham RECT was presented every day immediately before the active rTMS treatment. In group C, a 10-min active RECT was re-presented but was followed by a sham rTMS treatment every day for 10 days. (B) Mean (SD) changes of total depression scores on the 17-item Hamilton Rating Scale for Depression (HDRS-17) in the three groups indicating that RECT-modulated rTMS (group A) had better clinical effects. Group A exhibited significantly better antidepressant effects than group B and group C. Adapted from [22].

Using concurrent task manipulations

There have been numerous successful attempts to engage participants concurrently in behavioral tasks while administering NTBS, to make its aftereffects more specific. Perhaps the earliest use of this approach is the combination of a modified theta-burst TMS paradigm with presentation of visual information during TMS. In this study participants were asked to view visual stimuli moving in a specific direction while being stimulated with TMS [7]. The results showed that the aftereffects of TMS on subsequent motion-direction discrimination depended on the direction of motion viewed during the TMS application. More recently, modulation of NTBS effects by concurrent tasks has been successfully extended to research using transcranial electrical stimulation (tES).

One such study [23] investigated whether engagement in motor imagery modulates the aftereffect induced by tACS, which was applied at different frequencies (theta, alpha, beta, and gamma), to the primary motor cortex. Aftereffects were measured in terms of changes to the excitability of the motor cortex, assessed by measuring TMS-induced motor-evoked potentials (MEPs). With concurrent motor imagery, the tACS-induced increase in corticospinal excitability was maximal with theta-tACS. This was interpreted as tACS enhancing the excitability increase in the motor cortex that results from engaging in motor imagery. By contrast, the maximal tACS-induced increase in MEPs in subjects at rest was obtained with beta-tACS. This dissociation demonstrates the ability of the concurrent approach on the one hand to influence NTBS outcome and on the other hand to tap into the functional role of different oscillatory frequencies within a brain region (see also the next section).

How concurrent task demands interact with the aftereffects of transcranial direct-current stimulation (tDCS) has also been investigated [24]. This was done by combining anodal tDCS (a-tDCS) with different types of motor tasks that selectively induced either an increase or a decrease in cortical excitability. The aftereffects of concurrent stimulation were examined by using TMS to induce MEPs as well as by measuring performance in the trained tasks before and after the a-tDCS protocol. The results showed that, when combined with a motor task that increased cortical excitability, a-tDCS reduced learning. By contrast, a-tDCS facilitated learning for the motor task that decreased cortical excitability. These effects were mirrored in the MEPs. Thus, modifying cortical excitability concurrently with tDCS induces a qualitative shift in the direction of the aftereffect induced by tDCS, highlighting the potential of concurrent task demands to modulate NTBS effects. Such work is important, given the recent critiques on the strength and consistency of tDCS effects [25,26].

The concurrent-task approach offers great promise for clinical use and exciting work has been done already in the field of visual rehabilitation after stroke (e.g., [27,28]). For example, a new approach to facilitate recovery in hemianopia has been to use NTBS to enhance the level of suboptimal activity

of visual cortical neurons in the damaged brain. In one study [29] this was done by concurrently applying tDCS while patients were engaged in a training protocol; specifically, the researchers studied groups in which participants engaged in Visual Rehabilitation Therapy (VRT) with either sham or active tDCS. The study involved 1-h training sessions three times per week, conducted for 3 months. Outcome measures included objective and subjective changes in the visual fields, visual fixation performance, and vision-related activities of daily living (ADLs) and quality of life (QOL). At the end of training, the group receiving combined VRT and active tDCS displayed significantly larger expansion of the visual field than the VRT + sham group. Furthermore, eye-movement monitoring enabled the authors to exclude an explanation of these effects in terms of compensatory eye movements. While studies with larger patient groups are required to conclusively demonstrate the benefit of this therapy, this work indicates that concurrent occipital tDCS with visual field rehabilitation offers great promise in recovering some visual function.

Enhancing stimulation specificity by physiologically informed fine-tuning of NTBS stimulation parameters:

Rhythmic NTBS interventions (and the role of stimulation frequency)

Another approach to fine-tune the specificity of NTBS is tuning the frequency of stimulation to target underlying oscillatory brain activity. This can be done by rhythmic stimulation techniques including rhythmic TMS, tACS, or oscillatory tDCS (o-tDCS). The general idea behind the method is to interact with endogenous oscillatory neural activity through either entrainment or phase cancellation (by means of the rhythmic electromagnetic forces associated with rhythmic TMS/tACS/o-tDCS; e.g., [5,8,9]). The overarching aim is to drive network activity (and associated functions) through interaction with brain oscillations, an idea grounded in the evidence that brain oscillations reflect the synchronization of disparate network elements into functional assemblies (e.g., [30]). Thus, enhanced specificity is thought to be brought about by effects on those networks linking to the targeted area via coupling of activity at the stimulation frequency.

There is electrophysiological and behavioral support for entrainment of neural activity through frequency-tuned NTBS, and support for enhanced specificity. In terms of electrophysiology, several studies have shown upregulation of oscillatory activity at the target frequency; this is the case for interventions with both frequency-tuned rhythmic TMS [31–33] and tACS (for electroencephalography (EEG) see [34], for magnetoencephalography (MEG) see [35–37]; see also [38] for tDCS) despite the mechanisms of interaction between a particular stimulation type and the underlying neurons most likely being fundamentally different. Specifically, while frequency-tuned rhythmic TMS is likely to entrain oscillatory activity by phase resetting ongoing oscillations through its depolarizing action [39,40], tACS/o-TDCS will affect brain oscillations by its modulatory

influences at the level of membrane potentials (e.g., [41]). Importantly, some studies have shown that the upregulation of brain oscillations at target frequencies is more effective when the frequency of stimulation matches the natural rhythms than when it is offset (e.g., see [32] for results in the human brain), which is in line with models of entrainment [42].

In addition to electrophysiological evidence, there is also good (albeit indirect) behavioral evidence for entrainment. Many NTBS studies have shown frequency-specific effects on behavioral performances measures, in line with known correlative relationships between oscillatory activity and task performance (as inferred from EEG/MEG). For instance, tuning NTBS to brain areas and frequencies that have been identified via EEG/MEG to be relevant for perception induces changes in perception when using both rhythmic TMS (e.g., [43–48]) and tACS (e.g., [49–51]). Analogous results have been reported for cognitive and motor performance when stimulation is tuned to respective rhythms and areas (e.g., [33,52–54]).

The above-reported frequency-specific effects support the claim that frequency-tuned NTBS may enhance the specificity of interventions relative to conventional approaches. For instance, it is well known that stimulation of the intraparietal sulcus (IPs) by conventional TMS affects attention and perception: TMS over the IPs has been shown to impair target detection in the visual field contralateral to the TMS and enhance it ipsilaterally (e.g., [55]). This push–pull effect on perception is in line with the interpretation of TMS interference in an attentional node. Using rhythmic TMS, a more recent report [45] replicated this push–pull effect but showed in addition that the perceptual outcome depends on the frequency of stimulation. Contralateral suppression and ipsilateral enhancement of target detection was limited to stimulation of the IPs at alpha frequency, a posterior brain rhythm known to be associated with attentional functions [56]. Thus, frequency tuning enhanced specificity in this case. Moreover, recent evidence suggests that tACS can bring the individual alpha oscillator to cycle at the input frequency when slightly offset [50] and this in turn can impact perceptual processing associated with the speed of alpha oscillations [51] (Figure 3).

Interestingly, effects of frequency tuning have been reported to depend on the activity patterns at the time of stimulation, suggesting that the internal state also needs to be considered when attempting to enhance specificity by fine-tuning NTBS parameters. For instance, a TMS–EEG study [31] showed that the strength of entrainment of EEG alpha oscillations by a parietal TMS pulse train at alpha frequency depends on the phase angle at which the TMS train catches the ongoing oscillations. Others have shown that alpha-power enhancement/entrainment with occipital tACS at alpha frequency depends on pre-tACS alpha power or eyes-open versus -closed conditions [37,57]. Similarly, the effects of frequency-tuned tACS on behavior have been shown to depend on concurrent task

execution (with the task presumably driving a particular activity pattern at the time of stimulation) [23].

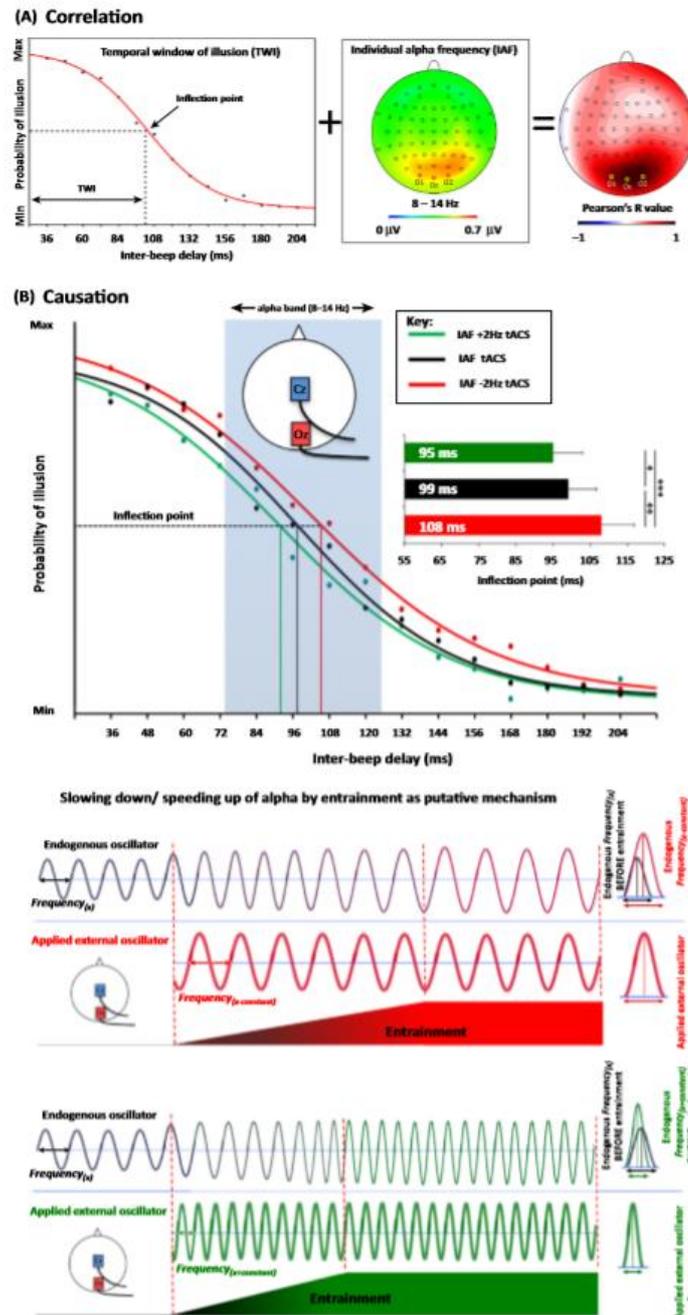


Figure 3. Interacting with Functional Network Rhythms by Rhythmic Noninvasive Transcranial Brain Stimulation (NTBS). (A) Correlation. In the flash–beep illusion [78], a second illusory flash is often perceived when one flash is paired with two sounds whose temporal delay [temporal window of illusion (TWI)] does not exceed 100 ms (a full alpha cycle) (left). The TWI shows interindividual variability, as does individual alpha frequency (IAF) (8–14 Hz) (center). A recent study [51] showed an inverse relationship between these two measures such that faster IAFs account for shorter TWIs and vice versa (right). (B) Causation. If IAF determines TWI, slowing down or speeding up IAF should enlarge or shrink the TWI, respectively. Accordingly, IAF - 2 Hz transcranial alternating-current stimulation (tACS) (red bars and curves) enlarged the TWI while IAF + 2 Hz tACS (green bars and curves) shrunk the TWI compared with IAF tACS (black bars and curves). The putative mechanism that best explains these results is a slowing down and speeding up of alpha by tACS entrainment [34] (lower panels). Adapted from [51].

Finally, frequency-tuned interventions may be of interest for clinical purposes. One showcase example is the reduction of tremor in patients with Parkinson's disease (PD) during tACS of the motor cortex at tremor frequency. One study [58] showed that tremor can be reduced significantly when such motor cortex tACS is applied at specific phase delays to the ongoing tremor. The idea is that tACS has suppressed the tremor by phase cancellation through out-of-phase stimulation. The ability of rhythmic NTBS to potentially enhance (by entrainment) or suppress (by phase cancellation) oscillations represents an attractive characteristic for interventions in oscillopathies (for examples of other applications, see [59]).

Using a multi-coil approach to induce pathway-specific Hebbian plasticity

A further development in refining the effects of NTBS involves the concurrent use of two or more stimulation coils. In dual-coil TMS paradigms [60], engagement of network connections can be tested by studying the influence that a first conditioning stimulus delivered over one node of the network exerts on a second test stimulus delivered at the other end of the network. This approach has been applied, for example, to test models of interhemispheric or interareal communication in specific populations (e.g., [61,62]) or functions (e.g., [63,64]). Dual-coil TMS has also been used to examine whether cognitive operations require bilateral involvement of given brain regions [65] and triple-coil paradigms have been developed to assess interactions between three brain regions [66]. Multicoil TMS can also be used to combine offline and online TMS paradigms to assess the functional changes to the rest of the network resulting from disruption to one of its nodes [67,68]. The strength of multicoil TMS lies in its capacity to precisely fine-tune stimulation to the chronometry of brain connectivity; that is, to implement stimulation parameters that best mimic network interactions. When the site of network nodes and the directionality and timing of information processing between the nodes are appropriately matched, NTBS can influence the ongoing network activity in expected directions and inform on functional network properties.

A fundamental new level of investigation in the study of brain networks through dual-coil protocols was recently implemented, aiming for the plastic adaptation of functional networks using a novel cortico-cortical paired associative stimulation (ccPAS) paradigm. This new approach moves away from the conception of a neural network as merely reflecting preestablished structures. It is based instead on the view that neural networks are amenable to changes; for example, through the balance between statistical regularities in, and the everchanging characteristics of, external input. There is ample evidence that repetitive activation of neuronal circuits by sensory input can induce long-term changes in neural network responses, a phenomenon known as associative long-term potentiation (LTP). According to the Hebbian rule, when presynaptic nodes repeatedly facilitate action potential generation in the postsynaptic node, the synaptic connection will strengthen, a phenomenon referred

to as spike-timing-dependent plasticity (STDP), forming the cellular basis of learning-related plastic adaptation in the brain [69]. In the context of information-based approaches to NTBS, Hebbian associative plasticity can be instantiated by repeated sequential associative stimulation of pre- and postsynaptic subpopulations through ccPAS (Figure 4B) and induced plastic changes in the targeted network can be assessed at the physiological and behavioral level.

Research using ccPAS has focused almost exclusively on the study of functional plasticity in the motor system. These studies overall demonstrate that ccPAS can induce LTP- [but also longterm depression (LTD)]-like effects [70], which are timing, direction, and state dependent. In addition, the recent use of ccPAS in combination with EEG [70,71] and neuroimaging techniques [72] has provided further evidence for induced STDP mechanisms by showing causal and directional impact of the presynaptic over the postsynaptic target region, following the temporal profile of Hebbian plasticity [10]. Moreover, these studies have provided information about the impact of ccPAS on oscillatory coherence across the network [71] and on the spatial properties of the NTBS manipulation, confirming the specificity of enhanced connectivity between the stimulated nodes. They also show parallel weakening effects in other, related areas of the network [72].

Beyond the motor system, ccPAS has recently been applied to study the malleability of V5–V1 back projections and their function in the perception of coherent visual motion stimuli [73]. The V5–V1 neural pathway was repeatedly activated by manipulating design parameters in four different groups (Figure 4B). In the experimental group, ccPAS specifically aimed at strengthening reentrant V5–V1 connectivity enhanced perception of coherent visual motion for at least 60 min. This behavioral time course resembled that of the Hebbian-like physiological effects observed in previous studies using ccPAS over the human motor system. This effect was selective for the experimental group as none of the control groups experienced significant changes in motion perception. Therefore, plastic changes can occur only when the external manipulation closely mimics the spatiotemporal dynamics of the stimulated network. If only one of these constraints is not met, Hebbian associative plasticity cannot occur despite the same overall amount of TMS energy being injected, resulting in no net impact on behavior. These results highlight for the first time the behavioral impact of ccPAS on the perceptual involvement of V5–V1 back projections, a connection known to be instrumental for motion perception and shown now to be functionally malleable.

The above-reported state-dependent and timing- and direction-specific effects suggest that ccPAS NTBS can enhance the specificity of therapeutic interventions. This new paradigm may offer countless applications in future research and may have fundamental, important consequences on the way we conceive NTBS approaches in rehabilitation. Models of the functional malleability of brain networks can be tested in a healthy population before being applied in clinical settings to recover

functional loss. Importantly, a full understanding of spatiotemporal network dynamics, as well as their state dependency, will be fundamental to fine-tuning the efficacy of this approach and exploring the extent to which it is possible to best tailor interventions. This could be done via directly testing for the optimal parameters that best explain both the functional connectivity and the malleability of the network under investigation (e.g., the physiological and behavioral impact of ccPAS NTBS). Finally, it is exciting that this paradigm may provide unique information – for example, about functional asymmetries in brain connections – that no other neuroimaging technique or protocol, in isolation, has been readily able to test.

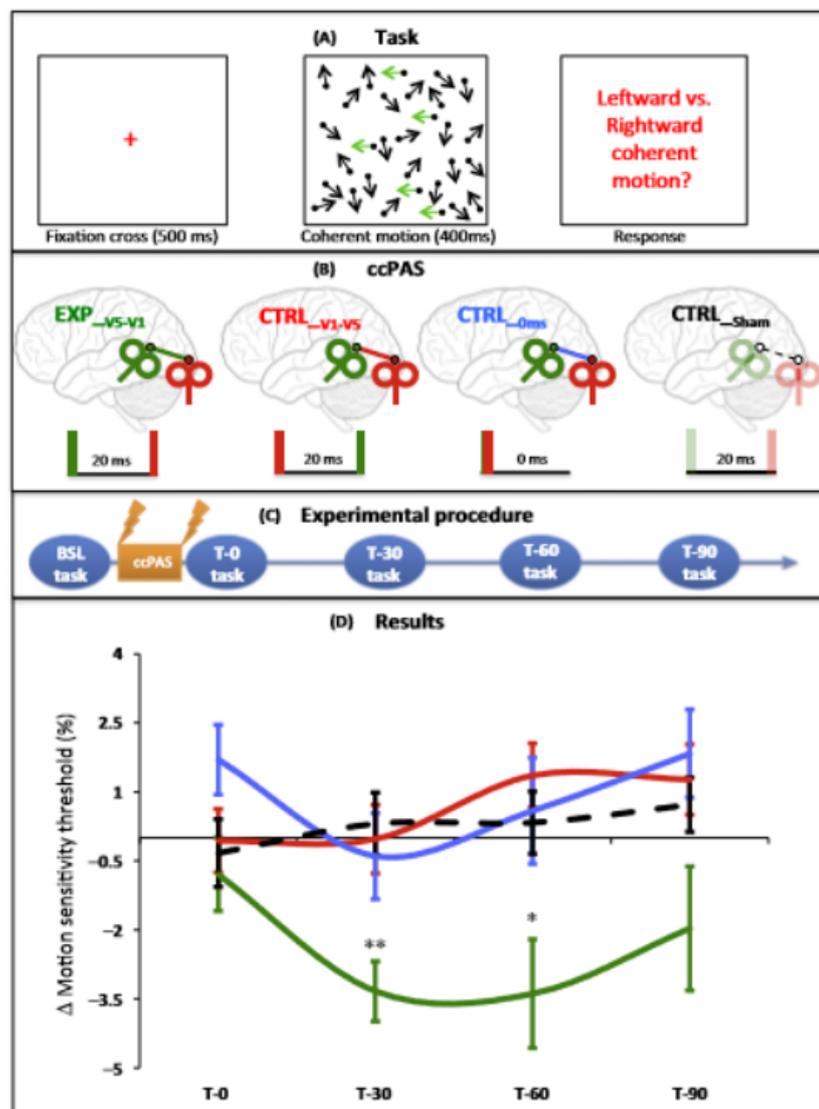


Figure 4. Influencing Functional Connectivity by Cortico-cortical Paired Associative Stimulation (ccPAS). (A) Task and stimuli. Each trial comprised a central fixation cross followed by 400 moving dots with different degrees of motion coherence toward left or right across trials. Participants indicated on each trial whether left or right coherent motion was perceived. The coherence threshold was defined as the minimum number of dots moving in the same direction needed for the participant to perceive the predominant motion direction in 75% of cases. The arrows in the central display represent the motion direction of each dot. Green arrows depict dots moving in the same, coherent direction while black arrows depict dots moving in different, random directions. (B) ccPAS protocol. Transcranial magnetic stimulation (TMS)

pulses were delivered over V1 and V5 every 10 s (0.1 Hz) using 90 pairs of pulses. Depending on the group, stimulation parameters (directionality and timing of interpulse interval) were varied as follows. In the experimental group (ExpV5–V1), V5 stimulation preceded V1 stimulation by 20 ms (as maximal interaction between V5 and V1 back projections were observed at this short timing [63,64]). In control group 1 (CTRLV1–V5), V1 stimulation preceded V5 stimulation by 20 ms, controlling for directionality (feedforward connections). Control group 2 (CTRL0ms) underwent simultaneous V5 and V1 stimulation, controlling for pre- and postsynaptic activation necessary to induce Hebbian-like plasticity (testing for both the timing and the plausibility of Hebbian-like effects). Control group 3 (CTRLsham) underwent sham stimulation with no effective magnetic pulses delivered over the targeted areas. (C) Experimental procedure. Thirty-two participants were randomly assigned to one of the four groups and performed the same task before (BSL), immediately after (T0), and 30 (T30), 60 (T60), and 90 (T90) min following the ccPAS protocol. (D) Results. Participants in ExpV5–V1 (green line) became more sensitive to visual motion 30 and 60 min after ccPAS compared with their baseline performance as well as with the performance of participants in the control groups (CTRLV1–V5, red line; CTRL0ms, blue line; CTRLsham, black broken line). None of the control groups showed a reduction in motion coherence threshold after ccPAS, suggesting that perceptual boosting was specifically determined by the ccPAS manipulation when stimulation directionality (from V5 to V1) and timing (20 ms) met the physiological constraints of reentrant connectivity. Adapted from [73].

Concluding remarks

The studies reviewed above are part of a new era of noninvasive human brain stimulation that follows the general philosophy of information-based approaches emerging in other tools of cognitive neuroscience. In NTBS, this era is defined by protocols that use detailed prior knowledge of the functional, physiological, and anatomical properties of the networks being targeted. More specifically, the aim is to increasingly move away from the notion of merely enhancing or impairing perceptual and cognitive functions toward leveraging understanding of neural tuning, underlying oscillatory networks, and connectivity between brain areas. One can argue that these manipulations have turned NTBS from a coarse tool for disrupting large regions of cortex indiscriminately to a subtle technique for targeting subpopulations of neurons. While one way to increase the amount of information available from NTBS studies is to combine it with neuroimaging, the unique feature of the paradigms reviewed here is their aim of making the stimulation effects more specific (Figure 1) – something that the NTBS–neuroimaging combination on its own does not achieve. However, the combination of these novel approaches, together with development of behavioral measures (Box 2) and neuroimaging, may be used to extend this specificity further (see Outstanding Questions).

Acknowledgments

V.R. is supported by the Ministero della Salute (Bando Ricerca Finalizzata Giovani Ricercatori 2010, GR-2010-2319335). G.T. is supported by the Wellcome Trust (grant number 098434). J.S. is supported by the European Research Council (336152).

Outstanding Questions

Combining physical parameters and task demands to enhance specificity. NTBS studies generally use either parameter manipulations (e.g., stimulation frequency, paired stimulation) or brain state manipulations (e.g., preconditioning by sensory stimulation or concurrent task demands) to enhance functional resolution. Combining these approaches may be a promising avenue with the aim of enhancing the specificity of effects even further. For example, ccPAS combined: (i) with visual stimulation might be used to target Hebbian plasticity in the networks involved in encoding a particular stimulus feature; or (ii) with rhythmic stimulation might target frequency-tuned Hebbian plasticity.

Understanding the mechanisms of NTBS: characterizing the relationship between stimulation intensity, frequency, and task demands. The field of NTBS has suffered from a lack of models explaining the behavioral effects of stimulation; this is particularly important given that interactions involving NTBS effects are often nonlinear (e.g., with respect to stimulation intensity). Furthermore, interpretation of null effects may be complex in certain situations as it leaves open the possibility that effects might have been obtained with other stimulation parameters. Thus, the development of comprehensive models is important for progress of the field.

Replicability and magnitude of effects. Especially with respect to tES, there has been much debate regarding whether the effects are robust and replicable. This issue may partly reflect interindividual variability at baseline and differences in stimulation parameters. Developing manipulations that can maximize the obtained effects is therefore important.

Developing behavioral measures. As discussed in Box 2, moving beyond simple accuracy and reaction time measures for assessment of behavior may enhance the amount of information that can be gained from NTBS studies, with respect to specifying distinct processing stages between initial stimulus encoding and behavioral output.

BOX 1: Role of stimulation intensity in TMS studies

A further important variable in NTBS studies, and particularly in TMS, is the intensity of stimulation. The ‘virtual-lesion’ effects of TMS in studies of perception and cognition have been conventionally explained in terms of noise induction. Specifically, a widespread notion held that TMS indiscriminately activates neurons in a targeted region and in this manner adds noise to neural processing. This noise reduces the signal-to-noise ratio of signals relevant to the cognitive task under investigation and thus impairs performance [74]. In this view TMS intensity is equated to the amount of noise added to neural processing. A key realization in recent years is that the effect of TMS may be neither simply additive nor homogenous across neuron types. Rather, it appears to differentially affect neurons depending on their ongoing level of activity. Neurons already firing in response to visual stimulation are less likely to be susceptible to additional activation by TMS and the behavioral effect may therefore result from the disproportional activation of task-irrelevant neurons; that is, those not being activated by current stimuli or task demands [75]. This has been proposed as a mechanism for how TMS reduces the signal-to-noise ratio in perceptual and cognitive tasks: by selectively enhancing the activity of non-active neurons (i.e., those not involved in the cognitive task) [1,3,76]. This opens the possibility for selectively targeting active versus non-active neurons. Indeed, this selective targeting may be what users have always been doing, unbeknownst to them.

An intriguing aspect of noise is that it is not always detrimental to behavior; this depends on the amount of noise and the initial signal strength. In systems with measurement thresholds, the addition of noise can push weak subthreshold signals across the threshold, improving information transfer. This is known as stochastic resonance [77]. The key issue is the level of noise: when the level is too high, the signal is weakened too much. However, a moderate amount of noise can be beneficial to task performance. There is evidence of such stochastic resonance effects in TMS; in one case, low-intensity TMS facilitated performance when initial task performance was low [4]. This is consistent with the idea that low (but not high) levels of noise can aid in the detection of a weak stimulus.

BOX 2: Enhancing behavioral measures in brain stimulation studies

Conventionally, behavioral TMS studies make use of performance accuracy and reaction times. While some studies find effects on accuracy, others find effects on reaction times. This may depend on task demands; for example, whether participants are encouraged to respond fast or accurately. An important issue here is the amount of evidence that subjects must accumulate before making a response [79]. Participants generally vary with respect to the criterion level of evidence required to trigger a response. Naturally, a liberal criterion leads to fast responses but also increases error rates; by contrast, a conservative criterion leads to higher accuracy but tends to be associated with slower response times (RTs) [79]. Attempts have been made to take into account the tradeoff between the two. One approach has been the so-called inverse-efficiency measure, in which RTs are divided by accuracy [44,46]. Another fruitful approach is the use of diffusion models [which have a similar approach to signal detection theory (SDT)] [80]. Taking into account accuracy, mean RT, and RT variance, this model yields three different parameters: (i) drift rate, which combines response speed and response accuracy to quantify subject sensitivity (and can be viewed as an index for the signal-to-noise ratio); (ii) boundary separation, which indicates response conservativeness (the equivalent of criterion in SDT models); and (iii) mean non-decision time, which refers to the duration of information processing before the decision process and the time taken to execute the motor command. These parameters allow one to determine the source of patterns of behavioral results and thus offer more precise insights into the source of TMS effects (see [81] for discussion of this issue and [13,82] for examples of NTBS studies using this approach).

References:

- [1] Silvanto, J. and Muggleton, N.G. (2008) New light through old windows: moving beyond the "virtual lesion" approach to transcranial magnetic stimulation. *NeuroImage* 39, 549–552
- [2] Siebner, H.R. et al. (2004) Preconditioning of low-frequency repetitive transcranial magnetic stimulation with transcranial direct current stimulation: evidence for homeostatic plasticity in the human motor cortex. *J. Neurosci.* 24: 3379–3385
- [3] Silvanto, J. et al. (2008) State dependency in brain stimulation studies of perception and cognition. *Trends Cogn. Sci.* 12, 447–454
- [4] Schwarzkopf, D.S. et al. (2011) Stochastic resonance effects reveal the neural mechanisms of transcranial magnetic stimulation. *J. Neurosci.* 31, 3143–3147
- [5] Thut, G. et al. (2011) Entrainment of perceptually relevant brain oscillations by non-invasive rhythmic stimulation of the human brain. *Front. Psychol.* 2, 170
- [6] Silvanto, J. et al. (2007) Neural adaptation reveals statedependent effects of transcranial magnetic stimulation. *European Journal of Neuroscience* 25(6):1874–1881
- [7] Silvanto, J. et al. (2007) Neural activation state determines behavioral susceptibility to modified theta burst transcranial magnetic stimulation. *Eur. J. Neurosci.* 26, 523–528
- [8] Herrmann, C.S. et al. (2016) EEG oscillations: From correlation to causality. *Int. J. Psychophysiol.* 103, 12–21
- [9] Fröhlich, F. (2015) Experiments and models of cortical oscillations as a target for noninvasive brain stimulation. *Prog. Brain Res.* 222, 41–73
- [10] Buch, E.R. et al. (2011) Noninvasive associative plasticity induction in a corticocortical pathway of the human brain. *J. Neurosci.* 31, 17669–17679
- [11] Ziemann, U. and Siebner, H.R. (2015) Inter-subject and Inter-session Variability of Plasticity Induction by Non-invasive Brain Stimulation: Boon or Bane? *Brain Stim.* 8, 662–663
- [12] Lang, N. et al. (2004) Preconditioning with transcranial direct current stimulation sensitizes the motor cortex to rapid-rate transcranial magnetic stimulation and controls the direction of after-effects. *Biol. Psychiatry* 56, 634–639

- [13] Cohen Kadosh, R. et al. (2010). Double dissociation of format-dependent and number-specific neurons in human parietal cortex. *Cereb. Cortex* 20, 2166–2171
- [14] Cattaneo, Z. et al. (2009) TMS-adaptation reveals abstract letter selectivity in the left posterior parietal cortex. *Cereb. Cortex* 19, 2321–2325
- [15] Hoffman, P., et al. (2010) Ventrolateral prefrontal cortex plays an executive regulation role in comprehension of abstract words: convergent neuropsychological and repetitive TMS evidence. *J. Neurosci.* 30, 15450–15456
- [16] Guzman-Lopez, J. et al. (2011) Visual motion adaptation increases the susceptibility of area V5/MT to phosphene induction by transcranial magnetic stimulation. *Clin. Neurophysiol.* 122, 1951–1955
- [17] Perini, F et al. (2012) Occipital transcranial magnetic stimulation has an activity-dependent suppressive effect. *J. Neurosci.* 32, 12361–12365
- [18] Cattaneo, Z. et al. (2010) The causal role of category-specific neuronal representations in the left ventral premotor cortex (PMv) in semantic processing. *NeuroImage* 49, 2728–2734
- [19] Cattaneo, L. et al. (2010) State-dependent TMS reveals a hierarchical representation of observed acts in the temporal, parietal, and premotor cortices. *Cereb. Cortex* 20, 2252–2258
- [20] Cattaneo, L. et al. (2011) One's motor performance predictably modulates the understanding of others' actions through adaptation of premotor visuo-motor neurons. *Soc. Cogn. Affect. Neurosci.* 6, 301–310
- [21] Jacquet, P.O. and Avenanti, A. (2015) Perturbing the action observation network during perception and categorization of actions' goals and grips: state-dependency and virtual lesion TMS effects. *Cereb. Cortex* 25, 598–608
- [22] Li, C.T. et al. (2016) Cognition-Modulated Frontal Activity in Prediction and Augmentation of Antidepressant Efficacy: A Randomized Controlled Pilot Study. *Cereb. Cortex* 26, 202–210
- [23] Feurra, M. et al. (2013) State-dependent effects of transcranial oscillatory currents on the motor system: what you think matters. *J. Neurosci.* 33, 17483–17489
- [24] Bortoletto, M. et al. (2015) The interaction with task-induced activity is more important than polarization: a tDCS study. *Brain Stimul.* 8, 269–276

- [25] Horvath, J.C. et al. (2015) Quantitative Review Finds No Evidence of Cognitive Effects in Healthy Populations From Single-session Transcranial Direct Current Stimulation (tDCS). *Brain Stimul.* 8, 535–550
- [26] Horvath, J.C. et al. (2015) Evidence that transcranial direct current stimulation (tDCS) generates little-to-no reliable neurophysiologic effect beyond MEP amplitude modulation in healthy human subjects: A systematic review. *Neuropsychologia* 66, 213–236
- [27] Calzolari, E. et al. (2015) Restoring abnormal aftereffects of prismatic adaptation through neuromodulation. *Neuropsychologia* 74, 162–169
- [28] Làdavas, E. et al. (2015) a-tDCS on the ipsilesional parietal cortex boosts the effects of prism adaptation treatment in neglect. *Restor. Neurol. Neurosci.* 33, 647–692
- [29] Plow, E.B. et al. (2011) Combining visual rehabilitative training and noninvasive brain stimulation to enhance visual function in patients with hemianopia: a comparative case study. *PM R.* 3, 825–835
- [30] Buzsaki, G. (2006) Rhythms of the brain. *New York: Oxford University Press*
- [31] Thut, G. et al. (2011) Rhythmic TMS causes local entrainment of natural oscillatory signatures. *Curr. Biol.* 21, 1176–1185
- [32] Romei, V. et al. (2016) Causal evidence that intrinsic beta-frequency is relevant for enhanced signal propagation in the motor system as shown through rhythmic TMS. *NeuroImage* 126, 120–130
- [33] Hanslmay, S. et al. (2014) Entrainment of prefrontal beta oscillations induces an endogenous echo and impairs memory formation. *Curr. Biol.* 24, 904–909
- [34] Helfrich, R.F. et al. (2014) Entrainment of brain oscillations by transcranial alternating current stimulation. *Curr. Biol.* 24, 333–339
- [35] Witkowski, M. et al. (2015) Mapping entrained brain oscillations during transcranial alternating current stimulation (tACS). *NeuroImage* doi.: 10.1016/j.neuroimage.2015.10.024
- [36] Neuling, T. et al. (2015) Friends, not foes: Magnetoencephalography as a tool to uncover brain dynamics during transcranial alternating current stimulation. *NeuroImage* 118, 406–413
- [37] Ruhnau, P. et al. (2016) Eyes wide shut: Transcranial alternating current stimulation drives alpha rhythm in a state dependent manner. *Scientific Reports* 6, 27138.S

- [38] Soekadar, S.R. et al. (2013) In vivo assessment of human brain oscillations during application of transcranial electric currents. *Nat. Commun.* 4, 2032
- [39] Herring, J.D. et al. (2015) Attention modulates TMS-locked alpha oscillations in the visual cortex. *J. Neurosci.* 35, 14435–14447
- [40] Rosanova, M. et al. (2009) Natural frequencies of human corticothalamic circuits. *J. Neurosci.* 29, 7679–7685
- [41] Antal, A. et al. (2011) Electrical stimulation and visual network plasticity. *Restor. Neurol. Neurosci.* 29, 365–374
- [42] Herrmann, C.S. et al. (2016) Shaping Intrinsic Neural Oscillations with Periodic Stimulation. *J. Neurosci.* 36, 5328–5337
- [43] Quentin, R. et al. (2015) Fronto-Parietal Anatomical Connections Influence the Modulation of Conscious Visual Perception by High-Beta Frontal Oscillatory Activity. *Cereb. Cortex* 25, 2095–2101
- [44] Romei, V. et al. (2011) Rhythmic TMS over parietal cortex links distinct brain frequencies to global versus local visual processing. *Curr. Biol.* 21, 334–337
- [45] Romei, V. et al. (2010) On the role of prestimulus alpha rhythms over occipito-parietal areas in visual input regulation: correlation or causation? *J. Neurosci.* 30, 8692–8697
- [46] Romei, V. et al. (2012) Causal implication by rhythmic transcranial magnetic stimulation of alpha frequency in feature-based local vs. global attention. *Eur. J. Neurosci.* 35, 968–974
- [47] Chanes, L. et al. (2013) Causal frequency-specific contributions of frontal spatiotemporal patterns induced by non-invasive neurostimulation to human visual performance. *J. Neurosci.* 33, 5000–5005
- [48] Ruzzoli, M. and Soto-Faraco, S. (2014) Alpha stimulation of the human parietal cortex attunes tactile perception to external space. *Curr. Biol.* 24, 329–332
- [49] Feurra, M. et al. (2011) Frequency specific modulation of human somatosensory cortex. *Front. Psychol.* 2, 13
- [50] Helfrich, R.F. et al. (2014) Selective modulation of interhemispheric functional connectivity by HD-tACS shapes perception. *PLoS Biol.* 12, e1002031

- [51] Cecere, R. et al.. (2015) Individual differences in alpha frequency drive crossmodal illusory perception. *Curr. Biol.* 25, 231–235
- [52] Joundi, R.A. et al. (2012) Driving oscillatory activity in the human cortex enhances motor performance. *Curr. Biol.* 22, 403–407
- [53] Pogosyan, A. et al. (2009) Boosting cortical activity at Beta-band frequencies slows movement in humans. *Curr. Biol.* 19, 1637–1641
- [54] Santarnecchi, E. et al. (2013). Frequency-dependent enhancement of fluid intelligence induced by transcranial oscillatory potentials. *Curr. Biol.* 23, 1449–1453
- [55] Hilgetag, C.C. et al. (2001) Enhanced visual spatial attention ipsilateral to rTMS-induced 'virtual lesions' of human parietal cortex. *Nat. Neurosci.* 4, 953–957
- [56] Foxe, J.J. and Snyder, A.C. (2011) The Role of Alpha-Band Brain Oscillations as a Sensory Suppression Mechanism during Selective Attention. *Front. Psychol.* 2, 154
- [57] Ruhnau, P. et al. (2016) Eyes wide shut: Transcranial alternating current stimulation drives alpha rhythm in a state dependent manner. *Sci. Reports* 6, 27138
- [58] Neuling, T. et al. (2013) Orchestrating neuronal networks: sustained after-effects of transcranial alternating current stimulation depend upon brain states. *Front. Hum. Neurosci.* 7, 161
- [59] Brittain, J.S. et al. (2013) Tremor suppression by rhythmic transcranial current stimulation. *Curr. Biol.* 23, 436–440
- [60] Krause, V. et al. (2013) Cortico-muscular coupling and motor performance are modulated by 20 Hz transcranial alternating current stimulation (tACS) in Parkinson's disease. *Front. Hum. Neurosci.* 7, 928
- [61] De Gennaro, L. et al. (2003) Reproducibility of callosal effects of transcranial magnetic stimulation (TMS) with interhemispheric paired pulses. *Neurosci. Res.* 46, 219–227
- [62] Romei, V. et al. (2008) Interhemispheric transfer deficit in alexithymia: a transcranial magnetic stimulation study. *Psychother. Psychosom.* 77, 175–181
- [63] Silvanto, J. et al. (2006) Stimulation of the human frontal eye fields modulates sensitivity of extrastriate visual cortex. *J. Neurophysiol.* 96, 941–945

- [64] Pascual-Leone, A. and Walsh, V. (2001) Fast backprojections from the motion to the primary visual area necessary for visual awareness. *Science* 292, 510–512
- [65] Silvanto, J. et al. (2005) Striate cortex (V1) activity gates awareness of motion. *Nat. Neurosci.* 8, 143–144
- [66] Hartwigsen, G. et al. (2010) The right posterior inferior frontal gyrus contributes to phonological word decisions in the healthy brain: evidence from dual-site TMS. *Neuropsychologia* 48, 3155–3163
- [67] Silvanto, J. et al. (2008) The Perceptual and Functional Consequences of Parietal Top-Down Modulation on the Visual Cortex. *Cereb. Cortex* 19, 327–330
- [68] Hartwigsen, G. et al (2016) Dissociating Parieto-Frontal Networks for Phonological and Semantic Word Decisions: A Condition-and-Perturb TMS Study. *Cereb. Cortex* 26, 2590–2601
- [69] Sack, A.T. et al. (2005) The dynamics of interhemispheric compensatory processes in mental imagery. *Science* 308, 702–704
- [70] Hebb, D. (1949) *The Organization of Behavior*. Wiley, New York
- [71] Koch, G. et al. (2013) Hebbian and anti-Hebbian spike-timing-dependent plasticity of human cortico-cortical connections. *J. Neurosci.* 33, 9725–9733
- [72] Veniero, D. et al. (2013) Paired associative stimulation enforces the communication between interconnected areas. *J. Neurosci.* 33, 13773–13783
- [73] Johnen, V.M. et al. (2015) Causal manipulation of functional connectivity in a specific neural pathway during behaviour and at rest. *Elife* 9, 4
- [74] Romei, V. et al. (2016) Empowering Reentrant Projections from V5 to V1 Boosts Sensitivity to Motion. *Curr. Biol.* 26, 2155–2160
- [75] Walsh, V. and Pascual-Leone, A. (2003) *Transcranial Magnetic Stimulation: A Neurochronometrics of Mind*. MIT Press, Cambridge, MA
- [76] Siebner, H.R. et al. (2009) How does transcranial magnetic stimulation modify neuronal activity in the brain? Implications for studies of cognition. *Cortex* 45, 1035–1042
- [77] Ruzzoli, M. et al. (2010) The neural mechanisms of the effects of transcranial magnetic stimulation on perception. *J. Neurophysiol.* 103, 2982–2989

- [78] Stocks, N.G. (2000) Suprathreshold stochastic resonance in multilevel threshold systems. *Phys. Rev. Lett.* 84, 2310–2313
- [79] Schwarzkopf, D.S. et al. (2011) Stochastic resonance effects reveal the neural mechanisms of transcranial magnetic stimulation. *J. Neurosci.* 31, 3143–3147
- [80] Pachella, R.G. (1974) The interpretation of reaction time in information-processing research, in, Kantowitz, B. (ed) *Human Information Processing: Tutorial in Performance and Recognition*, Erlbaum 41–82
- [81] Wagenmakers, E.J. et al. (2007) An EZ-diffusion model for response time and accuracy. *Psychon. Bull. Rev.* 14, 3–22
- [82] Hartwigsen, G. et al. (2015) Modeling the effects of noninvasive transcranial brain stimulation at the biophysical, network, and cognitive level. *Prog. Brain Res.* 222, 261–287
- [83] Soto, D. et al. (2012) Distinct causal mechanisms of attentional guidance by working memory and repetition priming in early visual cortex. *J. Neurosci.* 32, 3447–3452
- [84] Shams, L. et al. (2000) Illusions. What you see is what you hear. *Nature* 408, 788.