Available online at
ScienceDirect
www.sciencedirect.com

Elsevier Masson France
EM|consulte
www.em-consulte.com

General review

Things you wanted to know (but might have been afraid to ask) about how and why to explore and modulate brain plasticity with non-invasive neurostimulation technologies

C. Stengel [a], C. Sanches [a], M.N. Toba [b], A. Valero-Cabré [a,c,d,*]

[a] Causal Dynamics, Plasticity and Rehabilitation Group, FRONTLAB team, office 3.028, Paris Brain Institute (Institut du Cerveau), CNRS UMR 7225, Inserm UMRS 1127 and Sorbonne Université, 47, boulevard de l'Hôpital, 75013 Paris, France
[b] Laboratory of Functional Neurosciences (UR UPJV 4559), University Hospital of Amiens and University of Picardie Jules Verne, Amiens, France
[c] Laboratory for Cerebral Dynamics Plasticity and Rehabilitation, Boston University School of Medicine, 700, Albany Street, Boston, MA W-702A, USA
[d] Cognitive Neuroscience and Information Technology Research Program, Open University of Catalonia (UOC), Barcelona, Spain

INFO ARTICLE

Article history:
Received 20 October 2021
Received in revised form
15 December 2021
Accepted 28 December 2021
Available online 24 May 2022

Keywords:
Brain Plasticity
Neural Elasticity
Non-invasive transcranial magnetic stimulation
Non-invasive transcranial direct current stimulation
Brain behavior associations
Causality
Connectivity
Cognitive Anatomy

ABSTRACT

Brain plasticity can be defined as the ability of local and extended neural systems to organize either the structure and/or the function of their connectivity patterns to better adapt to changes of our inner/outer environment and optimally respond to new challenging behavioral demands. Plasticity has been traditionally conceived as a spontaneous phenomenon naturally occurring during pre and postnatal development, tied to learning and memory processes, or enabled following neural damage and their rehabilitation. Such effects can be easily observed and measured but remain hard to harness or to tame 'at will'. Non-invasive brain stimulation (NIBS) technologies offer the possibility to engage plastic phenomena, and use this ability to characterize the relationship between brain regions, networks and their functional connectivity patterns with cognitive process or disease symptoms, to estimate cortical malleability, and ultimately contribute to neuropsychiatric therapy and rehabilitation. NIBS technologies are unique tools in the field of fundamental and clinical research in humans. Nonetheless, their abilities (and also limitations) remain rather unknown and in the hands of a small community of experts, compared to widely established methods such as functional neuroimaging (fMRI) or electrophysiology (EEG, MEG). In the current review, we first introduce the features, mechanisms of action and operational principles of the two most widely used NIBS methods, Transcranial Magnetic Stimulation (TMS) and Transcranial Current Stimulation (tCS), for exploratory or therapeutic purposes, emphasizing their

* *Corresponding author* at: Causal Dynamics, Plasticity and Rehabilitation Group, FRONTLAB team, office 3.028, Paris Brain Institute (Institut du Cerveau), CNRS UMR 7225, INSERM U 1127 and Sorbonne Université, 47, boulevard de l'Hôpital, 75013 Paris, France.
E-mail addresses: avalerocabre@gmail.com (A. Valero-Cabré).
https://doi.org/10.1016/j.neurol.2021.12.014

Neuromodulation
Oscillations
Rehabilitation

bearings on neural plasticity mechanisms. In a second step, we walk the reader through two examples of recent domains explored by our team to further emphasize the potential and limitations of NIBS to either explore or improve brain function in healthy individuals and neuropsychiatric populations. A final outlook will identify a series of future topics of interest that can foster progress in the field and achieve more effective manipulation of brain plasticity and interventions to explore and improve cognition and treat the symptoms of neuropsychiatric diseases.

1. The background: brain plasticity and non-invasive brain stimulation technologies

Brain plasticity can be defined as the ability of local and extended neural systems to organize either the structure and/or the function of their connectivity patterns to better adapt to changes of our inner/outer environment and optimally respond to new challenging behavioral demands. This ability which is wired in cerebral and cerebrospinal networks integrated by neurons, interneurons and intermediating astrocytes, is particularly active during specific periods of prenatal and postnatal development and, even if it changes dynamically, persists in some form and intensity throughout life. Plasticity remains essential in fully developed brains for processes such as learning, memory acquisition and consolidation. It is also enabled following peripheral lesions disconnecting sensory receptors and motor and autonomic effectors from central control or following cerebral damage, in an attempt to optimize spared resources and remap function on able networks. Plasticity is engaged either spontaneously or enabled and guided via rehabilitation interventions to limit or compensate the cognitive and behavioral impact of brain damage in neuropsychiatric patients. A lesser (or shorter-lasting) form of plasticity, often referred to as 'elasticity', occurs when interventions or perturbations into brain systems induce short-lasting, reversible changes of function unable to endure, a phenomenon particularly useful in cognitive neuroanatomy to establish brain-behavior relationships.

Plasticity has been conceptualized and studied as naturally-occurring phenomena whose neural and behavioral effects could be observed and measured with mainstream neuroimaging and behavioral methods, and for many decades remained hard to harness 'at will' in healthy humans or patients. In this context, non-invasive brain stimulation (NIBS) approaches born in the late eighties encompass a set of technologies allowing the modulation of neural activity without a need for invasive procedures to access brain systems. Since its inception, NIBS has been closely related to concepts such as neural 'elasticity' and 'plasticity' thanks to its ability in exploratory or clinical settings to short- or long-lastingly manipulate brain activity correlates such as cortical excitability, regional hemodynamic and metabolic signals, brain rhythms, and, as a result, modify behaviors and disease symptoms.

NIBS technologies can be generally conceptualized as the use of a source of energy capable of either inducing action potentials or modifying (enhancing or decreasing) ongoing activity patterns tied to specific cognitive processes. Since their advent and development, the number of studies employing NIBS has increased exponentially, making this type of neurotechnologies and their applications a dynamic and fast-moving field within fundamental and clinical neurosciences [1]. The two most mainstream and widely used NIBS techniques these days are Transcranial Magnetic Stimulation (TMS) and Transcranial Current Stimulation (tCS). TMS is delivered by bulky, heavy non-portable and expensive equipment and characterized by its excellent targeting focality and ability to trigger action potentials and generate intense modulatory effects, which makes it the technique of choice for causal exploratory studies. tCS is characterized by its high portability, ease of use, excellent safety profile and low cost, which comes at the expense of weaker and widely spread modulatory effects unable to trigger action potentials. Both are capable of inducing modulatory effects while they are being delivered (online effects), which outlast the duration of the patterns (offline effects or after-effects) but that are quickly reversible and wear off rapidly, unless booster sessions are applied with some periodicity via a multiday-stimulation regime (see [1,2] for reviews on the subject).

Amongst many potential applications, NIBS technologies remain the sole tool in the domain of fundamental neuroscience allowing the investigation of *causal* brain-behavior relationships by locally perturbing brain activity patterns while recording changes of behavior. Such devices, alone or coupled to neuroimaging or neurophysiological recording methods, can be applied to characterize brain functional connectivity between specific cortical sites and to probe the degree and limits of cerebral plastic capabilities in the healthy or impaired human brain. For this reason, NIBS technologies, and particularly TMS, remain unique, amongst other techniques and methods used to explore the human brain, in allowing a transient or lasting manipulation of firing patterns, with high temporal and spatial precision. Importantly, the notion of causality–which is out of reach of extremely valuable and popular correlation methods (such as fMRI, PET, EEG-MEG etc.) widely used to map or study cognitive anatomy–is intimately associated to uses of NIBS technologies. This is thanks to their unique capacity to directly manipulate brain sites, monitor changes in behavioral performance and effectively verify the two main rules of causality which, applied to cognitive neuroanatomy, can be simplified as follows: (1) any cause (e.g., the manipulation of a brain site)

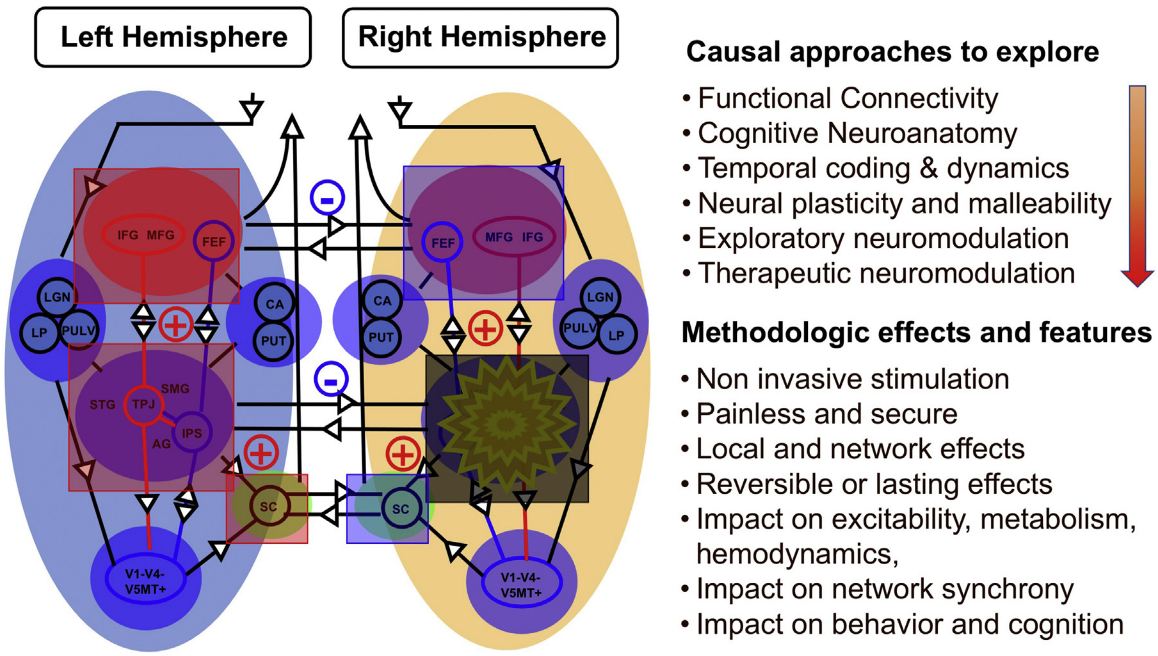

Fig. 1 – Influence of NIBS on brain activity, networks and function. The emergence of cognitive functions requires the integration and precise synchronization in time of neural activity in multiple brain regions organized in complex networks. For example, orienting visuospatial attention relies on contributions from frontal, parietal and occipital cortical areas in both hemispheres and their interactions with subcortical regions (left panel). NIBS allows to modulate, transiently or long-lastingly by engaging brain plasticity mechanisms, patterns of neural activity in specific cortical regions, or nodes of networks, in order to characterize the brain regions causally involved in the emergence of varied cognitive functions. Beyond a local and unspecific 'perturbation' effect of NIBS, the fine-tuning of stimulation parameters, strategies and modalities offer the possibility to manipulate very fine and specific features of brain activity and connectivity, ranging from the precise temporal dynamics of cortical activity and their contribution to neural coding to whole-brain patterns of functional connectivity (right panel). Furthermore, NIBS effects are not restricted to the circumscribed cortical regions initially targeted for stimulation but spread to entire networks through anatomical intra- and inter-hemispheric connections. As illustrated in the left panel, focal stimulation of the right parietal node of the attentional network (marked in yellow) has repercussions on the activity of multiple, dispersed network nodes, located ipsi- and contralaterally (highlighted by colored boxes). IFG: inferior frontal gyrus; MFG: middle frontal gyrus; FEF: frontal eye field; LGN: lateral geniculate nucleus; LP: lateral dorsal nucleus of the thalamus; PULV: pulvinar; CA: caudate nucleus; PUT: putamen; STG: superior temporal gyrus; TPJ: temporoparietal junction; SMG: supramarginal gyrus; AG: angular gyrus; IPS: intraparietal sulcus; SC: superior colliculus; V1-V4-V5/MT: visual cortex.

should precede its consequences (e.g., a change in cognitive performance); (2) increases or decreases of the magnitude of the cause (brain modulation) should also modify the magnitude of the consequence (cognitive performance). Most importantly, NIBS sources are directed to initially affect specific cortical locations, restricted for TMS and large for tCS, nonetheless such effects travel through structural connectivity patterns and eventually induce network effects in interconnected sites of the hemisphere ipsi- and contralateral to the stimulation target (see [2] for a review on the subject).

Nonetheless, beyond evaluation using a perturbation strategy of which areas and their associated networks could be involved in a given process, specific strategies and stimulation parameters (some of them quite novel) allow to influence in further detail finer anatomical and neurophysiological features, such as specific coding strategies based on oscillatory rhythms and their phase [3–6], the dissection of the time course of cortical contributions to several aspects of cognition [7,8] or the localization, extent and interaction patterns of neural networks [9–11]. The flexibility of NIBS, achieved with the fine-tuning of stimulation parameters, opens opportunities to influence and characterize a large variety of brain networks and their associated functions such as, to mention only a few, sensory processing, motor planning and execution, selective and sustained attention, decision making, memory, number processing, language and decision making (see [1,2] for reviews on the subject) (Fig. 1).

Importantly, knowledge about brain function provided by causal studies has historically proven crucial to translate NIBS applications to clinical settings such as the rehabilitation of cognitive disorders. This is possible because NIBS unites in the same technology the rare ability to causally explore brain systems via short-lasting reversible perturbations (inducing elastic processes) and, on such basis, to operate in the same systems longer-lasting functional improvements by means of periodical perturbations that enable durable plasticity. For this reason, anatomically and physiologically inspired successful projects in the field of NIBS modulation are usually planned as three step processes. First, a thorough exploration of possible causal links between specific brain activity patterns and cognitive processes using NIBS approaches (alone or combined with neuroimaging or neurophysiological recordings) are used to generate causal understanding of anatomical networks and neurophysiological coding features involved in cognition and/or in associated diseases. Second, the ability to modulate correlates of brain activity and behavior transiently beyond the time that NIBS is being applied is used, during a unique stimulation session, to test the plastic malleability of a given neural system and its associated behaviors, providing proof of concept for potential longer-lasting enduring effects. Third and last, repeated stimulation sessions are used to pave the way for the development of therapeutic strategies that might allow a durable restoration of impaired cognition in neuropsychiatric populations (modulation therapy) or boosting of brain function in healthy populations (neuroenhancement).

For the success of such a three-step process, two conditions have been proven particularly paramount: first, any short-lasting or long NIBS intervention should be planned on the basis of well-established anatomical and neurophysiological frameworks (or the best available one we can make use of at the time of the intervention), informing on a location or set of brain locations organized as a network (*Where*), a specific window or windows of time for the contribution of such regions (*When*) and the most likely coding strategies (*How*) used by them to enable the engagement of a brain process resulting in a measurable behavior. Second, the efficacy of long-term interventions or treatments based on the use of NIBS is optimized when targeted regions and behavioral processes or pathological conditions were not simply correlated but were previously probed as causally related and malleable.

In many regards, NIBS is part of a larger family of exploratory and sometimes therapeutic perturbational methods which include invasive intracranial electrical stimulation methods such as those used in awake tumoral neurosurgery per-operative stimulation [12], deep brain stimulation [13] or intracranial stimulation of implanted epileptic patients [14]. These methods are effectively used to modulate brain function and cognition, such as Parkinson's disease tremor and akinesia, chronic pain and obsessive compulsive disorder symptoms also by interfering or modulating 'deleterious' activity which contributes to impaired functions [13,15]. However, since invasive methods can only inform on the features of healthy brain areas embedded in impaired brains, their use is highly constrained to very specific clinical diagnostic or therapeutic applications on a highly differing patient-by-patient basis, and given the risks of heavy surgery, cannot be freely or easily extended to the study of any brain area or any type of patient populations. In contrast, NIBS technologies, which are in turn affected by limitations invasive methods lack such as limited focality, intensity and mechanisms of actions, have been opening opportunities for exploratory and therapeutic brain stimulation strategies in healthy human participants for whom invasive methods are simply not applicable, and in wider patient populations other than the few mentioned above.

The current review will first highlight the key technical characteristics of the two most widely used NIBS techniques, TMS and tCS, in order to provide a basic understanding of how these techniques operate on brain regions and systems. We will then describe their ability to manipulate brain elasticity and plasticity. Both transient and reversible effects of NIBS, observed during stimulation sessions or shortly thereafter, and long-lasting NIBS effects used for treatment strategies for cognitive disorders will be developed.

2. The technologies: transcranial magnetic stimulation and transcranial current stimulation

The domain of non-invasive brain stimulation encompasses technologies and associated strategies able to modulate transcranially brain activity in humans without the need of invasive surgery which, via a large or small craniotomy, allows to put in contact the stimulation source with the cortical surface or any deeper brain white or gray matter structure. They are characterized by their ability to painlessly convey through layers of tissue protecting the brain's gray matter – skin, skull, epidural, subdural spaces filled with cerebrospinal fluid (CSF) – electrical current which has the ability to generate effects that directly influence the firing patterns of cortical neurons. Importantly, well-documented international guidelines ensure a very safe use of the two most popular and widely used NIBS techniques in healthy and patient populations, which to this day remain tCS and TMS [16–18]. Nonetheless, the field of NIBS is very dynamic and innovative, and novel brain stimulation methods based on magnetic/electrical sources or more recently even non-electrical sources of energy, such as for example low-intensity Focused Ultrasound Pulsation (FUP) [19] or Near-Infrared Stimulation (NIRS) [20], are emerging and mainly under evaluation in animal models, although they might become mainstream and used in humans.

TMS is the most classical stimulation technique developed in the mid-eighties by Anthony Barker as a painless diagnostic tool to estimate corticospinal conduction in plexus- and spinal cord-damaged patients [21]. It employs a strong but brief magnetic field able to induce non-invasively an electrical current in the cortex. It is delivered through a stimulation coil – most commonly a figure-of-8 or 'butterfly' shaped coil – placed on the subject's scalp directly above the cortical stimulation target (Fig. 2). Electrical current is stored in a series of capacitors, placed inside a rather bulky and heavy device, and then briefly circulated through the copper wire coil to generate an intense (~1.5 to 2 Tesla depending in the TMS device) short-lasting (100-250 μs) monophasic or bi-phasic magnetic field, referred to as a 'TMS pulse', able to penetrate throughout outer layers of the skull, including bone, epidural and subdural spaces and CSF, without major distortion before reaching the brain [2,22,23]. In the cortical gray matter, the pulsed magnetic field generates an electric current perpendicular to the primary magnetic field (so more or less parallel to interneuron layers) within a circumscribed cortical region (12-15 mm radius) [24], able to transiently activate (i.e., depolarize)

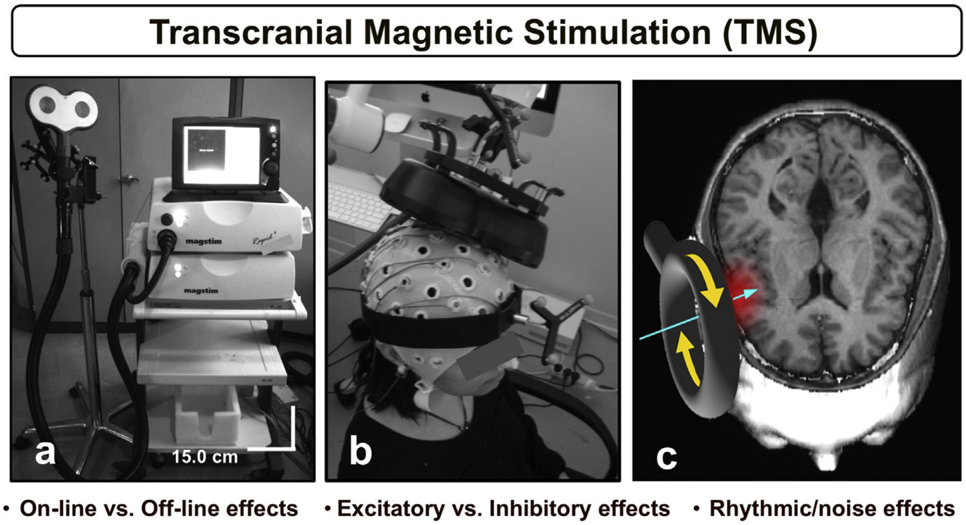

Fig. 2 – Transcranial Magnetic Stimulation (TMS) equipment and subject preparation. (a) TMS requires a bulky, non-portable equipment. To deliver a TMS pulse, current is first charged in a series of capacitors contained in the central unit. The current is then briefly circulated through a stimulation coil–here a "butterfly" or figure-of-8 coil–attached to the central unit by a flexible electrical cord. This generates a brief magnetic field, called a pulse, capable of penetrating through skull and tissue layers to depolarize neurons. (b) The TMS coil is positioned lying flat over the subject's head directly above the cortical regions targeted for stimulation, as the direction of the induced magnetic field is perpendicular to the coil surface. (c) The TMS coil is placed and angled such as to minimize the distance between the center of the coil and the cortical stimulation target. The intensity of the induced magnetic field is attenuated as a function of distance, minimizing the distance to the cortical target ensures maximal stimulation intensity reaches the cortex. TMS can be delivered as single isolated pulses, short bursts (4 or 5 pulses) or longer patterns of repetitive stimulation, to generate either 'online' effects during the stimulation or 'offline' effects which persist after the stimulation period.

neuronal clusters. This effect can be easily demonstrated by the objective induction of muscle twitches (motor evoked potentials) recorded following single TMS pulses to the primary motor cortex [21] or via subjective reports of visual percepts, known as 'phosphenes', in response to stimulation of early visual areas [25]. In regions that are neither motor not visual (hence unable to generate visible or reportable physiological effects) the perturbation of TMS pulses can be recorded as interferences in their ability to contribute to specific cognitive functions, hence inducing changes in behavior which manifest as longer reaction times or performance decreases in titrated computer-based tasks. According to the specific brain process and the region that is targeted for stimulation, TMS parameters such as stimulation intensity, duration and temporal organization of the pulses have to be adjusted. Indeed, while single, isolated pulses can be used to transiently disturb cortical activity, bursts of TMS pulses can also be delivered in close succession to create a wide variety of stimulation patterns such as paired-pulse TMS, rhythmic TMS or repetitive TMS. These are tailored to either boost or perturb intracortical interactions, local neural oscillators and rhythms, or generate lasting modulatory effects (offline or after-effects), respectively. Although, its uses are currently highly regulated via international guidelines and severe side effects are rare, repetitive TMS patterns (generally high frequencies) are potentially epileptogenic hence have to be administered carefully.

Another NIBS technique that has gained great popularity thanks to its ease of use, excellent safety profile, portability and low cost, is tCS. This technology, first tested in the late sixties in animals then abandoned for nearly four decades and recently rediscovered, is based on the delivery of a weak current (1–2 mA or ~0.06 mA/cm^2) between at least two electrodes (an anode and cathode acting either as 'active' or 'return' leads, between 25 to 35 cm^2 in size) placed directly on the subject's scalp [26]. Because of the conductive properties of the outer-brain layers, an important part of the circulated current will be shunted through the scalp [27] and be unable to induce any neural effect; however a small portion will penetrate through the tissue layers to reach the cortical surface, spreading over large cortical areas located beneath the electrodes [28]. The electrical field generated in the cortex will attract and distribute electrical charges in the extracellular space and shift the resting membrane potential either closer to the firing threshold for neurons located below the anodes (i.e. electrodes receiving current), therefore increasing the likelihood to generate action potentials, or away from the firing threshold for neurons located below the cathodes (i.e. electrodes emitting current), making those neurons less likely to depolarize [26,29,30]. Depending on the shape of current circulated between electrodes, tCS can be subdivided in three main submodalities: transcranial direct current stimulation (tDCS) based on a constant current able to increase or decrease regional excitability, transcranial alternating current stimula-

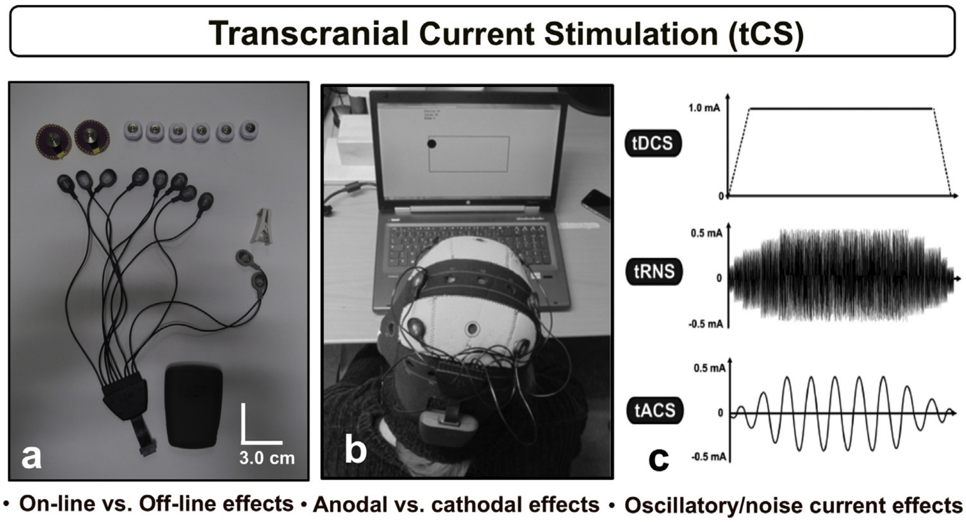

Fig. 3 – Transcranial Current Stimulation (tCS) equipment and modalities. (a) tCS is delivered with a light and portable rechargeable battery (black unit) connected and controlled wirelessly by a computer. Current is circulated through thin electrical wires connected to a montage of several electrodes (at least two, an anode and a cathode). The electrodes can be either large sponge contacts (upper left corner) or ferromagnetic leads (upper right). (b) Electrodes are mounted on a *lycra* cap worn by participants while performing a task on a computer screen. A low-intensity current is circulated between the electrodes placed on specific locations on the subject's scalp in order to generate a current gradient able to reach the cortical regions of interest. (c) tCS modalities. Transcranial Direct Current Stimulation (tDCS) consist in circulating a current of fixed amplitude between the electrodes in the montage. Current amplitude can also be changed over time, either to deliver a current that randomly fluctuates between current amplitudes, akin to a "white noise" signal, in a modality called Transcranial Random Noise Stimulation (tRNS), or oscillated at a constant frequency to deliver Transcranial Alternating Current Stimulation (tACS). Different tCS modalities produce different effects on brain activity. tDCS will modulate cortical excitability, with opposite effects under anodal and cathodal stimulation, while tACS allows the modulation of oscillatory activity and tRNS has been postulated to introduce noise in cortical activity.

tion (tACS) delivering frequency-constant oscillated current able to entrain or modulate ongoing rhythmic activity, and transcranial random noise stimulation (tRNS) relying on a randomly fluctuating current (akin to a "white noise" signal) used to desynchronize ongoing oscillations or to add extrinsic noise to neural systems [31] (Fig. 3). As for TMS, all tCS modalities induce modulatory effects on neural signals and behavioral correlates when being delivered (online effects), whereas only one of them, tDCS has shown thus far to induce after-effects. Although the simplest tCS montage involves current passed from an anode to a cathode, for some projects, more sophisticated scalp montages involving a single active electrode but several return electrodes (high-density tCS via 4×1 electrode montages or ring electrodes) can help focalize currents in more circumscribed areas at the expense of intensity loss [32]. In parallel, MRI-based biophysical FEM (Finite Element Models) computational models of tCS current distribution taking into account permittivity of tissue layers are quite often used to simulate current peaks and spread according to each subject's head anatomy and optimize electrode montages [33].

Both TMS and tCS are currently highly complementary and used in different scenarios or for different purposes. Capitalizing on its affordability, portability and excellent safety profile, tCS has been widely used either to assess plastic malleability of large cortical regions in healthy individuals or to deliver modulatory treatments in neuropsychiatric patients affected by large areas of damage often combined with neurorehabilitation. In contrast, owing to its high focality, excellent temporal resolution and power to trigger action potentials, TMS remains the technology of choice for research studies exploring brain-behavior relationships, characterizing interregional connectivity, or the oscillatory coding involved in cognitive processes. It is also used in therapeutic schemes for neuropsychiatric conditions, for which a circumscribed target can be identified.

3. The mechanisms: from virtual lesions and excitability modulation to oscillatory entrainment

Historically, from the late eighties to early 2000, TMS effects were conceptualized with the misnomer '*virtual lesions*', defined as transient (i.e. reversible) perturbation of neural excitability, metabolism or cortical coding patterns [34,35] during or outlasting their delivery, manifesting as slightly impaired behaviors [36,37]. Ten years ago, this confusing and controversial term was definitively abandoned, and a more thorough understanding of NIBS effects on short- and longer-term plasticity obtained first with TMS coupled with PET, fMRI and EEG recordings has revealed a variety of NIBS-driven effects on cortical activity, depending on the stimulation site and parameters such as intensity, pulse number, frequency, session duration and regime periodicity for TMS or electrode montage, current pattern, modality, intensity, session duration and regime periodicity for tCS.

Highlighting the importance of precise stimulation parameters to control the direction of the stimulation effects, double TMS pulses delivered in close succession (within 1 to 12 ms interval) showed early on an ability to induce short-lasting modulations of cortical outputs, by producing either inhibitory (GABA dependent) or excitatory (glutamate-related) effects on cortical excitability, depending on the time interval between two consecutively delivered pulses [38,39]. Likewise, repetitive TMS (abbreviated rTMS), a modality consisting in long trains of TMS pulses repeated at a fixed rate delivered over long periods of time (15 to 30 min), either continuously or with short interruptions, showed more than 25 years ago opposite effects depending, amongst other co-variates (e.g. targeted site, pattern duration or TMS intensity), on stimulation frequency [24,40–42]. To this regard, so called 'conventional' low frequency rTMS patterns (at 1 Hz) showed in the motor cortex a tendency to transiently suppress excitability, i.e. lowering intrinsic activity levels and silencing the contribution of several stimulated regions to their associated cognitive processes [43,44]. Conversely, conventional high frequency rTMS patterns (>5 Hz) yielded increases of motor cortical excitability which outlasted the duration of the stimulation, whereas similar frequencies yielded performance improvements in several cognitive domains. In addition to frequency, it has been shown that TMS-free intervals during pulsed repetitive patterns may also have a bearing on the direction and magnitude of excitability modulations. To this regard, for example, so-called theta burst stimulation (TBS) patterns, classified as 'patterned TMS', made of 50 Hz pulse triplets repeated at 5 Hz during 2.5 to 4 minutes, have shown to transiently decrease excitability when delivered continuously, and to increase excitability for periods of up to 45 minutes when delivered with 8-second interruptions [45]. Interestingly, similar effects on cortical excitability levels, hence reversible plasticity (or elasticity) have been achieved with tCS. Indeed, current circulated between the electrodes during tDCS hyperpolarizes and depolarizes resting membrane potentials differentially for neurons below the anode and the cathode, respectively, an effect that manifests as a modulation of neuronal excitability and influences firing probability rates [26,29] during online and offline effects. Such modulations of excitability, which can also be achieved with tRNS [31], have been applied in proof-of-concept studies to assess brain-behavior relationships for large cortical areas, and the ability to malleably modulate regional plasticity and behavioral outputs (either to improve or degrade them) in healthy individuals or patients.

Such immediate offline effects (or after-effects) of rTMS and tDCS were among the first to reveal that, indeed, the modulatory impact derived from single isolated stimulation sessions engaged mechanisms of short-term and reversible plasticity (i.e., elasticity) similar to those induced by training. Such impact was measured in the motor cortex via motor evoked potentials, in the visual cortex via changes in reported phosphene excitability, and in non-visual or motor regions by changes in performance in a combination of computer-based tasks titrated to be sensitive to slight variations in cognitive abilities, as well as concurrent modulations of neuroimaging (PET, fMRI) or neurophysiological (EEG, MEG) signals when available.

Moreover, these same observations anticipated the idea that periodical short-term and reversible modulatory changes, either excitatory or inhibitory, could be perpetuated via the engagement of longer-term plasticity, by delivering consecutive daily sessions of stimulation as part of a multiday stimulation regime, and opened the door to therapeutics.

Importantly, beyond the modulation of excitability levels, both of these highly popular NIBS techniques have recently shown the ability to either boost ongoing or entrain de novo periodical patterns of neural activity, namely modulate the amplitude and synchronization of neural oscillations. This is extremely relevant, since local oscillations and network synchronizations are ubiquitous in cortical and subcortical systems and their activation has been shown to subtend the engagement of a large variety of cognitive functions or subprocesses, many of them of higher complexity and integrative nature (see [46] for a review) such as sustained and selective attention, conscious access or self-consciousness. To this specific regard, the first evidence came from TMS single-pulse experiments that provided evidence for the possibility to boost the so-called predominant, or 'natural', oscillation frequencies characterizing the stimulated brain region [47] and defined as the depolarization-repolarization rhythmic frequency at which local neuron assemblies (oscillators) tend to cycle spontaneously. Such an effect occurred because TMS leads to a phase-resetting of cortical oscillators, hence aligning their temporal dynamics and giving rise to synchronized cortical oscillations.

A TMS-driven increase of natural cortical oscillations can be maximized by repeating TMS pulses in short bursts of 4 or 5 pulses delivered at a fixed frequency which reproduces the natural oscillating frequency of the stimulated region [48]. This particular TMS pattern, referred to as rhythmic TMS, has been used during the last decade to boost or entrain frequency-specific cortical oscillations either on local regions [6,49] or traveling across networks towards other cortical sites [5], and by virtue of such effect, enabling information processing or the modulation of cognition and behavior [3,50–53] (Fig. 4). It provides a unique tool to probe the potential causal role of an episodic frequency-specific local rhythm on a specific cortical location likely responsible for a specific cognitive operation or behavior, by comparing it with the impact of a control equally-long pattern of jittered or non-frequency specific pulses. Unfortunately, oscillatory TMS entrainment seems to be highly restricted and dependent on the presence of an external rhythm (online phase), and does not outlast rhythmic stimulation for more than a cycle and a half.

Likewise, alternating current patterns, a tCS submodality referred to as tACS, has been also hypothesized to give rise to oscillatory activity [54–56] and improve synchrony across large brain networks [57,58]. However, the ability of tACS to entrain oscillatory activity still remains rather controversial. This is because evidence on the modulation or de novo entrainment of neural oscillations by tACS during stimulation period is hard to achieve given that, unlike rhythmic TMS-EEG

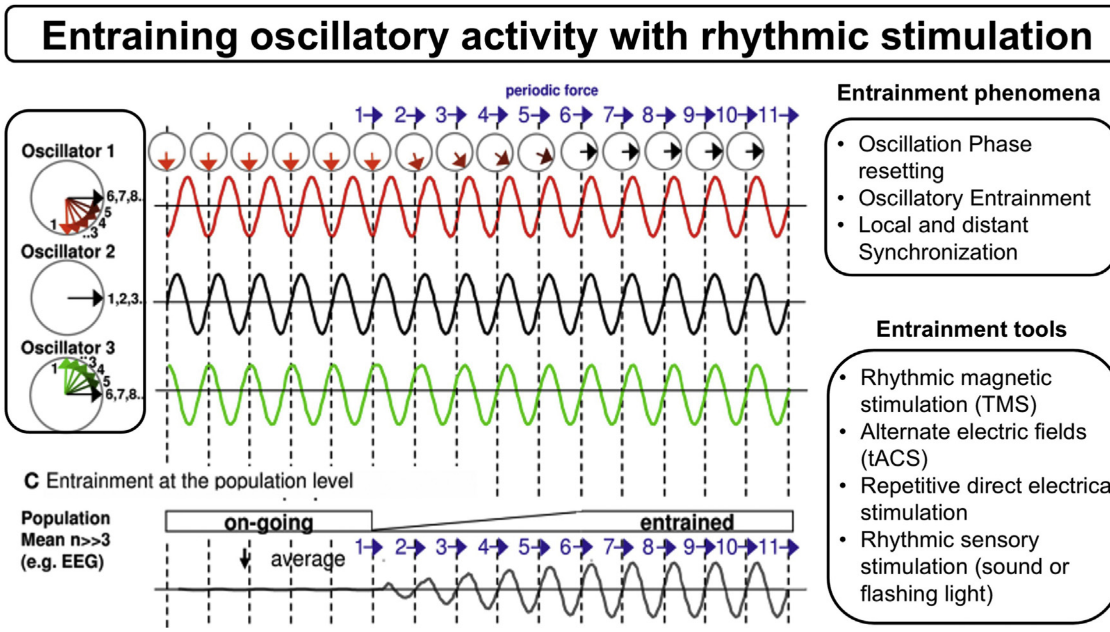

Fig. 4 – Descriptive model of how oscillatory entrainment by NIBS is enabled. Independent neural oscillators (drawn in red, black and green) are naturally oscillating at the same frequency but different phases. When a periodic external force, for instance in the form of single TMS pulses repeated periodically during rhythmic TMS or an oscillating current during tACS, is applied to these neural oscillators, they progressively synchronize the phase of their oscillatory activity, i.e. their activity is progressively phase-locked to the phase of the external periodic force. At the level of the neural population (bottom panel), when oscillators are phase-locked, their summed activity manifests as an oscillating signal which can be recorded by electrophysiological recording techniques such as EEG or MEG. Fig. adapted with permission from Thut et al., 2011 [49].

recordings, EEG signals acquired under tACS are constantly artifacted by the fluctuating ongoing electrical field, and tACS offline effects on oscillatory activity seem, as for TMS, rather scarce [59]. Regardless, the field of exploratory or therapeutic rhythmic neuromodulation with rhythmic compared to irregular TMS bursts and with tACS compared to tRNS patterns is currently booming due to their high promise to correct oscillopathies, i.e., abnormal patterns of oscillatory activity deemed to subtend pathological symptoms [60], and restore normal rhythms.

4. The consequences: network effects and coupling with mapping methods to study plasticity

When considering NIBS effects on the brain, it is important to acknowledge that any effect induced in a circumscribed region targeted for stimulation will spread via white matter projections throughout the interconnected brain networks. Such distributed effects are dependent on the specificity, richness and overall net inhibitory or excitatory influences of white matter connections linking the stimulated regions with other cortical and subcortical regions [24]. In humans, the specific coupling of NIBS with PET or fMRI neuroimaging has traditionally enabled whole-brain recordings of stimulation effects and allowed for a local and network-wide characterization of changes in cortical activity in response to focal stimulation [11,61]. Indeed, in parallel with high resolution metabolic recordings on feline models [24,42], combined TMS-PET studies followed by TMS-fMRI and tDCS-fMRI were used to highlight, in whole-brain recordings, the activation or modulation of widespread networks of brain regions activated during (*online* effects) or directly following (*offline* effects) stimulation [62–64] with a quite acceptable spatial resolution. Importantly, these same neuroimaging approaches served to identify, characterize and track over time the elastic (reversible) and plastic (durable) changes induced by NIBS perturbations on brain systems, following single sessions or multiday regimes treatments respectively. Early TMS-PET work in animals [42] and humans [65], showed that during the *offline* period, functioning neighboring areas react to the stimulation patterns and tend to compensate via acute remapping the effects caused by the initial perturbation in order to maintain within homeostatic levels a '*status quo*' of cortical activity and prevent maladaptive plasticity. Such reactive phenomena would be responsible for canceling out lasting neural and behavioral effects generated by perturbations explaining the elastic nature and short duration of TMS effects. Importantly, focally injured brains treated with NIBS neuromodulation in periodical regimes exert lesser reaction to stimulation and prove more prone to perpetuate reversible session-by-session changes into long-lasting plasticity yielding a recovery of lost function.

Whereas the combination of TMS-PET or tDCS-PET is free of electromagnetic interferences, but acquisitions lack fine spatial resolution and entail the injection of a radioactive agent, online TMS-fMRI or tDCS-fMRI methods remain expensive and highly challenging due to the need to use non-ferromagnetic stimulation equipment and the presence of electromagnetic artifacts on recordings [66]. For this reason, combined NIBS and online or offline scalp EEG recordings, used to record either TMS-evoked cortico-cortical potentials or synchronization measures in response to individual TMS pulses [47,67], rhythmic TMS bursts [5,6,49], rTMS and tCS patterns have gained momentum during the last decade. More specifically, EEG-based recordings performed with electrodes and wide-range DC-amplifiers that are TMS-compatible have provided a low-cost and simple procedure to objectify the cortical impact of stimulation, titrate adequate NIBS intensity and assess the impact of episodic, elastic and plastic entrainment or modulatory phenomena of local brain rhythms and extended network synchronization by means of power, intertrial coherence and phase-locking coherence measures [5,6,49].

Taken together, the above mentioned neuroimaging and electrophysiological methods have served to confirm that NIBS induces local modulatory effects accompanied by distributed network effects verified as reversible elastic increases of activity, functional connectivity and inter-regional synchronization during NIBS-induced oscillatory entrainment [5,68] conveyed by white matter connectivity. Moreover, significant correlations found between diffusion tensor imaging (DTI) studies characterizing specific tracts and inter-individual variability in behavioral responses to stimulation has confirmed in humans a key role for white matter micro-structure on NIBS network effects [69–71], anticipated by animal tracing studies [24]. All in all, the combination of NIBS local and network effects emphasizes the relevance of local levels of activity, network functional connectivity (extracted from resting state or task-evoked fMRI) and structural connectivity (generated via diffusion weighted imaging) as predictive biomarkers of potential modulatory outcomes particularly for uses of neuromodulation technologies in the rehabilitation of focally brain-damaged patients via the induction of long-term plasticity across specific networks [72,73]. Furthermore, in order to directly operate on inter-regional connectivity to strengthen synchronization between two brain regions through Hebbian plasticity mechanisms, innovative protocols proposed multicoil TMS setups stimulating simultaneously [74] or in close succession [10,75], with two or more TMS coils, distinct brain regions such as the primary motor cortex and the visual cortex. Likewise, tCS scalp electrode arrays covering different regions of the scalp and delivering frequency-specific oscillated tACS currents to two separate scalp locations with a null phase difference (hence synchronized), compared to an opposite phase (180°, hence non-synchronized), have been able to effectively synchronize prefrontal and parietal regions [57].

5. Experimental clinical uses: online, offline effects, therapeutic regimes and state-dependency

As indicated above, NIBS effects can either be verified '*online*' during the delivery of stimulation for perturbational causal mapping purposes, or estimated during the so-called '*offline*' phase as reversible plastic 'after-effects' occurring during a transient period of time immediately following the end of a single NIBS session. Single TMS pulses or short bursts of rhythmic TMS made of just a few pulses (in general 4 or 5 delivered at 10 to 50 Hz) induce periodical trial-by-trial perturbational '*online*' effects without carry over impact over time. However, when repetitive TMS or sub-modalities of tCS are applied over longer periods of time (in general from 15 to 30 minutes), '*online*' effects are followed by modulatory '*offline*' effects outlasting the duration of NIBS which are weaker than the '*online*' effects [42,76]. The duration of '*offline*' effects vary considerably according to the stimulation parameters as well as the outcome measures used to evaluate NIBS-driven effects (behavioral performance, hemodynamic or electrophysiological recordings) [77]. It is estimated that '*offline*' effects can be observed on average for 30 min post-stimulation [67,78] but they can extend up to 60 min post-stimulation [75,79].

Both '*online*' and '*offline*' NIBS study designs have been used in the healthy subjects to investigate causal brain-behavior relationships. Although the duration of these effects span from a few milliseconds to several hours, both '*online*' and '*offline*' effects are entirely reversible and they can therefore be described as '*elastic*' changes, presenting as transient modulations of activity or excitability before the excitability or activity of the targeted region and associated networks nodes comes back to its initial state. A requisite to translate research uses of NIBS to clinical settings, and optimize their potential to restore impaired brain function via the modulation of deleterious brain activity causally associated to pathological symptoms, is to extend their effects from reversible 'elasticity' or short-term plasticity to enduring 'plasticity', which manifests as lasting changes of brain excitability, brain activity and/or local and interregional synchronization. To that end, individual modulation sessions periodically repeated at intervals of 24 h or less [40,80,81] have been shown to produce a progressive accumulation of modulatory effects and increased NIBS-driven changes of brain activity, subtended by signs of lasting neuroplasticity [80,82,83].

Daily stimulations sessions repeated over 5 or 10 days and for up to 5 weeks are routinely used in NIBS therapeutic protocols with very diverse outcomes. In neuropsychiatry, a field in which patients have been stimulated with the longest regimes, rTMS has proved an effective treatment for pharmaco-resistant depression [84–86], positive and negative signs of schizophrenia [87], obsessive-compulsive disorders [88,89] and the treatment of addictions to tobacco, alcohol and cannabis. Therapeutic strategies to improve cognitive decline in neurodegenerative [90–92] and aging populations [58] have also shown promising results with NIBS, particularly with anodal excitatory tDCS. Other current clinical applications include treatment of chronic pain [93] and the rehabilitation of motor, sensory and cognitive deficits, such as visuospatial neglect or hemianopsia, following stroke [94,95].

Finally, it is important to mention that elastic or plastic changes induced by NIBS do not operate on a passive brain 'at rest' and that the intensity and the sign of the net modulatory effects on a given brain system is highly influenced by ongoing

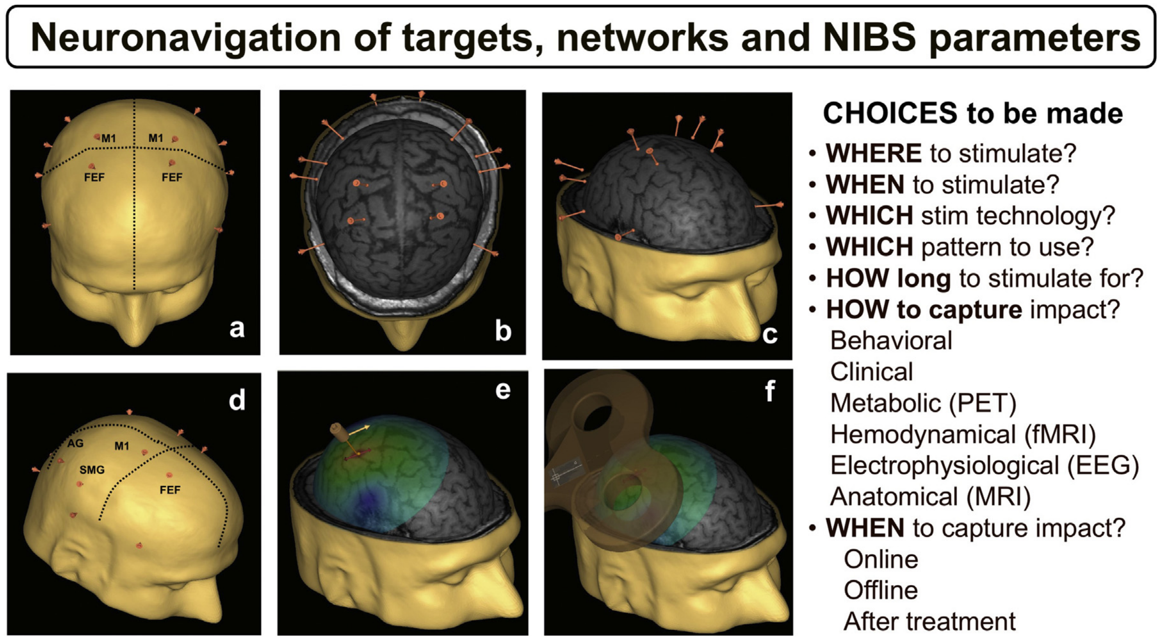

Fig. 5 – Frameless MRI-based stereotaxic neuronavigation system for accurate cortical targeting. Several questions need to be carefully answered when designing effective NIBS protocols for exploratory or interventional clinical purposes (see right panel). The question of the cortical targets for stimulation (*Where* to stimulate) is particularly relevant and accurate positioning of the TMS coil or tCS electrodes is needed to ensure maximal focality of the stimulation. (See left panels a-f). Cortical target regions can be selected and identified either based on anatomical landmarks (position of known gyrus/ sulcus or locations in the 10/20 EEG system), activated regions on an fMRI scan acquired for individual subjects prior to the stimulation or normalized coordinates in the Talairach or MNI systems extracted from the literature. Neuronavigation systems are based on infrared cameras and are calibrated at the beginning of the stimulation session to associate reference sites on the subject's head to his/her anatomical MRI scan. (e and f) Once a cortical target has been identified and labeled on the participant or patient's MRI, the stimulation TMS coil or tCS electrodes can be placed on the scalp to ensure minimal distance between coil or electrode center and cortical target, in order to maximize stimulation intensity reaching the cortex. TMS coil position can also be tracked in real time through the neuronavigation system to ensure accurate coil position throughout the stimulation session.

excitability levels or activity patterns present in the target area during or following interventions. This so called 'state dependency' nature of neuromodulatory impact has been thoroughly studied in striate and extrastriate visual areas and motor regions [96], but remains harder to harness to maximize advantage of plastic reorganization in other brain systems. Moreover, neuroimaging and electrophysiological (mainly EEG) methods can be used to monitor levels and direction of ongoing activity and plan stimulation accordingly whereas computer-based tasks or exercises can be used to set brain activity levels at specifically 'favorable' states [97]. The currently known 'state-dependency rules' seem to suggest that ongoing low levels of local or network activity achieved for example via perceptual adaptation procedures would dwindle inhibitory effects but boost excitatory effects of NIBS, whereas vice-versa, during high levels of ongoing activity via task-induced activity or priming, NIBS approaches would ease inhibitory effects. This concept emphasizes the importance of having control over what stimulated healthy individuals or patients are engaged in during NIBS and, to the best of our abilities, manipulate cortical activity to maximize its outputs in terms of modulatory effects (see [98] for a review).

6. Operational principles: where, when, how to stimulate to optimally manipulate plasticity

As the list of cognitive systems and neurological and psychiatric conditions whose symptoms are treated with NIBS technologies expands, we insist on the importance to base any experimental or clinical intervention on accurate (or the best available thereof) anatomical, physiological and cognitive models characterizing the system we are trying to modulate and its specific state due to the impact of the disease. Particularly relevant for this, is to be in a position to make well-informed guesses about the target area to be stimulated (*Where*) and to localize it accurately in order to place the TMS coil or tCS electrodes accordingly. The use of a frameless stereotaxic neuronavigation system, based on the individual MRI of each subject, is crucial during TMS procedures but recommended for tCS interventions. These devices allow to localize in real time coil or electrode location on the participants' scalp and to maximize effects by ensuring an accurate transcranial targeting of specific location that minimizes penetration distance (Fig. 5, left panel). Targeting accuracy will be high with TMS (10–15 mm radius) and limited with tCS (5–7 cm radius) and in both cases local effects will spread, particularly during the *online* impact, throughout connected networks, whereas after effects will include, particularly in healthy individuals, reactive remapping and compensatory effects.

The question of when to stimulate or which temporal window to cover (*When*) will be particularly relevant in studies benefitting from the excellent temporal resolution of TMS and is paramount for online perturbation studies involving complex cognitive processes evolving over time and chronometric *online* TMS studies aimed at establishing the timing of causal contributions. On the basis of prior choices, one must identify the most suitable NIBS technology for the purposes at hand. TMS is the technology of choice for perturbational brain-behavior causal studies in the healthy subject, for entrainment or synchronization studies, for connectivity studies coupled to fMRI or EEG, for studies probing regional plasticity, or for therapeutic multiday regime trials pursuing plasticity for which a well circumscribed cortical target can be identified. In contrast, one will privilege the use of tCS approaches either in heathy individuals or in neurological patients when the target region to stimulate is wide and can only be defined unprecisely. It is important to decide on the duration of TMS or tCS patterns which in *online* trial-by-trial designs will depend on the total number of trials, whereas for *offline* rTMS and tCS designs will depend on the desired duration of *offline* after-effects which last approximately 50% of the total stimulation time, as a good rule of thumb to plan on session duration. In parallel, other stimulation parameters such as magnetic field or current intensity, coil shape and size or electrode montage, and frequency (in the case of rTMS or tACS patterns), need to be selected in full respect of current international guidelines for NIBS uses [16–18]. If means are available, one should couple NIBS stimulation to brain mapping neuroimaging (PET, fMRI, NIRS) or electrophysiology (scalp EEG, MEG) techniques to ensure targeting and dosage were adequate and to study how patterns will perturb or plastically reorganize whole-brain metabolism or hemodynamic function. Importantly, direct physiological correlates such as TMS-induced motor evoked potentials (MEPs) or phosphene reporting rates and associated computer-based cognitive task titrated in difficulty to be sensitive to perturbations or clinical scores would also be needed. Last but not least, the design should determine if the effects of stimulation will be measured during the presence of the NIBS patterns (*online*, chronometric and rhythmic TMS designs), prior and following the end of a single session of stimulation (*offline* design), or prior and following the end of a multiday stimulation regime (Fig. 5).

7. A research example: manipulating oscillations to better comprehend conscious perception

The localization, spread and features of activity and coding strategies subtending cognition and behavior, in healthy or pathological brains, have been most commonly investigated by recording task-evoked changes of neural function during behavioral performance. More specifically, the study of local and interregional oscillatory and synchronization coding events on cognition, performed via scalp and intracranial EEG, MEG or potentially resting-state fMRI, have provided extremely interesting correlation outcomes which require the addition of causal value.

For example, to characterize the neural basis of visuospatial attention orientation, prior research in primates and healthy humans reported the emergence of oscillatory activity, i.e., episodic rhythmic activity in the beta (15–35 Hz) or gamma (45–60 Hz) frequency band, locally and synchronized between frontoparietal regions of the attention network [99], during periods of attentional orientation followed by conscious visual perception [100–103]. Unfortunately, conclusions drawn from such correlational studies relied entirely on the co-occurrence in time of cortical activity patterns and behavioral changes and there is no assurance a 'true' causal relationship exists. In such a scenario, the brief manipulation of neural elastic and plasticity processes via NIBS technologies provides a unique strategy to rule out confounding epiphenomena from causal contributions and further characterize non-invasively the oscillation frequency bands, time windows, and cortical sites causally involved in attention orienting and the emergence of conscious visual perception. Importantly, these same approaches could preliminarily inform on the ability of NIBS to briefly malleably modify such functions and on such basis envision neuroenhancement strategies in healthy subjects or remediation approaches for attentional orienting and visual perception deficits (e.g., spatial hemineglect, hemianopsia or scotoma) for brain-damaged patients.

In a series of studies performed in such a context, we applied trial-by-trial brief rhythmic TMS bursts (4 pulses) delivered at 30 Hz (high-beta frequency band) over the right frontal eye field (FEF), a frontal node of the dorsal attention network, during a short time window directly preceding the onset of a lateralized low-contrast visual target (Fig. 6). For trials in which this high-beta frequency-specific perturbation was delivered (compared to other bursts delivered at a different frequency or at a mixed frequency), visual detection performances were significantly improved in healthy subjects [3,6]. Furthermore, interestingly, neuronal assemblies in the right FEF were able to multiplex two different visual perception operations (conscious visual sensitivity and perceptual decision-making) when entrained either at 30 Hz (high beta) and 50 Hz (low gamma) [3]. Ulterior concurrent TMS-EEG recordings during the same trial-by-trial online TMS behavioral paradigm demonstrated rhythmic TMS-driven entrainment of high-beta 30 Hz oscillations over frontal regions directly below the TMS coil and significant positive inter-subject correlations between the amplitude of TMS-evoked frontal oscillations and gains in conscious visual detection performance [6]. Most importantly, local entrainment effects on the right FEF were also noted over parietal regions distant from the stimulation site, an effect likely mediated by the enhancement of inter-regional phase-synchrony along a well-defined frontoparietal attention network [5] (Fig. 7).

Our rhythmic TMS reversible perturbation studies built on prior correlational findings from the nonhuman primate literature [100] and extended them to the human brain by also adding causal evidence. Moreover, our causal findings

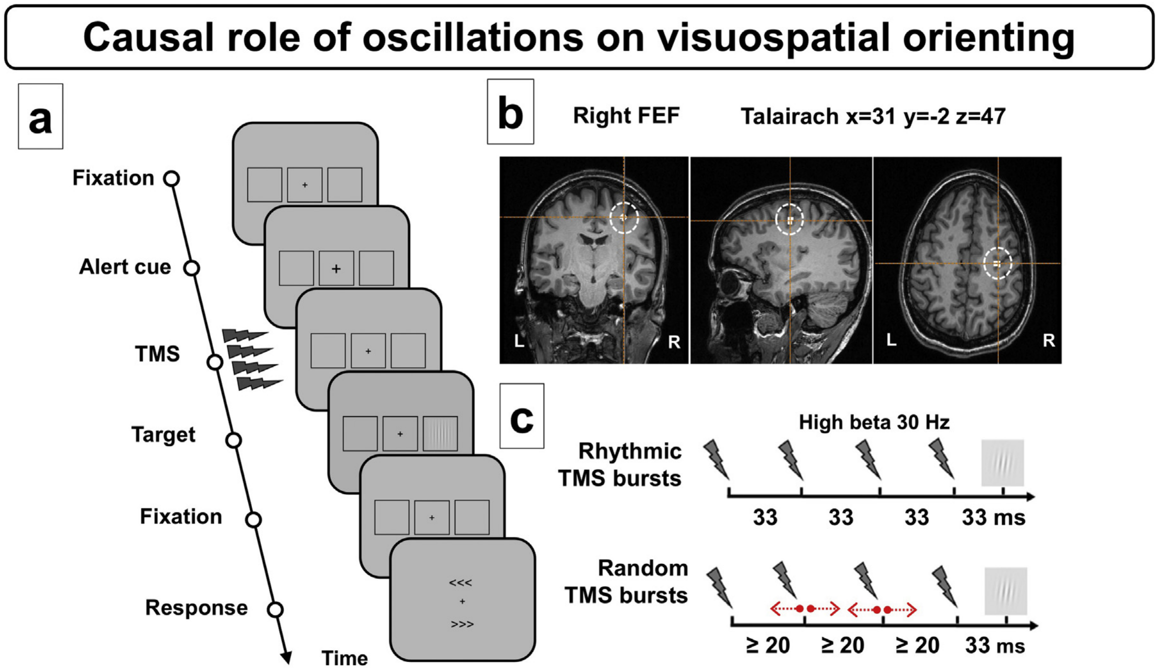

Fig. 6 – Example of modulation of oscillatory activity prior to target onset. (a) Conscious visual detection task. After a period of fixation, a central cross becomes slightly larger to alert participants of the upcoming appearance of the visual target; then active and sham *rhythmic* or *random* TMS patterns are delivered prior to the onset of a target that could appear briefly at the center of a right or left rectangular placeholder. Participants indicate whether they perceived a target or not and, if they saw it, where it appeared (right/left). In 20% of the trials, no target is presented in any of the placeholders. (b) Cortical stimulation target. Coronal, sagittal and axial MRI sections showing the localization of the right FEF (Talairach coordinates x = 31, y = −2, z = 47) in a T1-3D MRI of a representative participant. (c) Rhythmic and random TMS patterns for active and sham stimulation. 30 Hz *rhythmic* TMS is employed to entrain oscillatory activity at the input frequency, and the *random* stimulation is used as a control to isolate the effect of stimulation frequency.

allow to build an anatomical and neurophysiological rationale towards the development of new NIBS-based interventional strategies for healthy participants and patients. First, such findings contribute knowledge on the cortical regions (FEF) and activity patterns (high-beta activity) causally enabling visuospatial orientating and driving improvements of conscious visual perception, which can now be tested pre-clinically in hemispatial neglect and hemianopsia patients. Second, they demonstrated the ability of rhythmic TMS to entrain frequency-specific interregional synchrony, setting the stage for future avenues such as the manipulation of network synchronization patterns subtending other cognitive processes (such as sustained attention, executive control, memory consolidation, sleep, decision-making or language) and their disorders.

8. A clinical example: modulating plasticity for therapeutic purposes in semantic dementia

Semantic dementia, or the semantic variant of primary progressive aphasia (sv-PPA) is a neurodegenerative disease onsetting before 65 years of age [104] and characterized by impairments of the semantic system affecting conceptual knowledge, and resulting in anomia and difficulties in word comprehension [105]. Anatomically, sv-PPA is linked to damage to the left and often also right anterior temporal lobes (ATL) and is part of a larger family of early-onset and focal neurodegenerative diseases impairing language and communication including the non-fluent and logopenic variant of PPA, affecting Broca's area and the temporoparietal junction, respectively.

Hints towards potential benefits of NIBS in such family of neurodegenerative diseases came from post-stroke TMS aphasia neuromodulation supporting the ability of NIBS to interact with language networks and induce reversible or lasting improvement of language abilities subtended by plastic reorganization mechanisms. Stimulation strategies in the domain relied on a previously explored principle [106] by which left-lateralized language networks are built by left and right hemisphere homotopic regions connected by transcallosal mutually inhibiting rivalrous connections (inter-hemispheric inhibition) [107]. Accordingly, clinical improvement after left neurovascular or neurodegenerative damage affecting language can be achieved by directly boosting (e.g., high-frequency TMS, iTBS, or anodal tDCS) spared resources in the ipsilesional hemisphere, or by reducing a state of over-activity of right spared contralesional systems (e.g., low-frequency TMS, cTBS or cathodal tDCS) preventing the remapping of function in left-damaged areas [108,109].

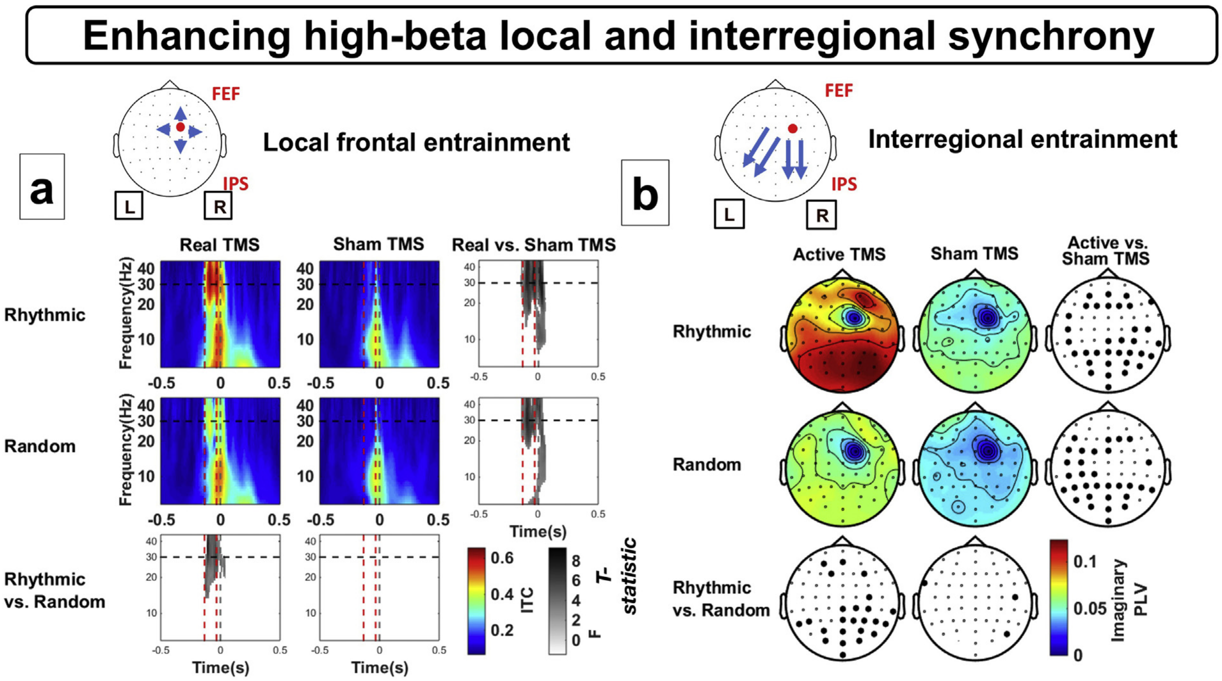

Fig. 7 – Local and network effects of rhythmic TMS over the right FEF. (a) Time-frequency maps of the inter-trial coherence (ITC) during the stimulation ([–1330]ms, centered on target onset) for the frontal electrode located directly below the TMS coil (electrode FC2). Time is centered (vertical dotted gray line, t = 0) to the onset of the visual target. Vertical dotted red lines signal the time window between the 1st (-133 ms) and the last (-33 ms) TMS pulses of the delivered stimulation patterns. The horizontal dotted black line indicates the frequency of TMS rhythmic stimulation pattern (30 Hz). Bottom and right maps present the outcomes of the statistical tests either for the active/sham rhythmic vs. active/sham random comparisons (right column) or active rhythmic/random vs. sham rhythmic/random comparisons (bottom row). Local oscillatory activity over the stimulated right FEF is significantly phase-locked during rhythmic, as compared to random, TMS patterns. (b) Topographic maps of imaginary Phase-Locking Value (Imaginary PLV) in the high-beta frequency band ([25-35] Hz) for each scalp electrode compared to the signal recorded by the electrode closest to the targeted right FEF region (electrode FC2), during the stimulation ([–1330]ms, centered on target onset). Bottom and right topographies present the outcomes of the statistical tests, with large black dots indicating EEG electrodes for which imaginary PLV differences reached statistical significance between TMS conditions (*P* < 0.05), either active/sham rhythmic TMS vs. active/sham random TMS (right column) or active rhythmic/random TMS vs. sham rhythmic/random TMS (bottom row). Phase-synchronization between right frontal and right parietal regions was significantly increased during active rhythmic TMS compared to active random TMS. FEF: Frontal Eye Field. IPS: Intra-Parietal Sulcus.

In a double-blind cross-over controlled pre-therapeutic trial [92] in sv-PPA patients, we compared to sham tDCS the impact of a single session of anodal or cathodal stimulation delivered to the left and right ATL, respectively. We pursued evidence that, via reversible plasticity mechanisms, we would be able to transiently improve semantic access in such patients in view of future therapeutic studies using a long periodical regime of stimulation engaging plasticity. Briefly, each patient performed a baseline (pre-tDCS) evaluation of performance levels in a semantic association task. This was followed by 20 minutes of stimulation (1.59 mA intensity with 25 cm^2 round electrodes, current density of 0.06 mA/cm^2) either with the anode (active electrode) placed, under MRI-based frameless neuronavigation guidance, over the left ATL and the cathode (return electrode) over a right supraorbital region; or the cathode (active electrode) placed on over the right ATL and the anode (return electrode) over a right supraorbital region. Immediately after the end of each stimulation session, patients underwent a post-tDCS evaluation block of the semantic association task, using a different version of the task to avoid intrasession learning biases. The three stimulation sessions (left anodal tDSC, right cathodal tDCS and sham tDCS) were performed one week apart to avoid carry-over effects and counterbalanced to avoid order biases.

Data from this pre-therapeutic trial showed significant beneficial effects on a verbal semantic association paradigm after both active (anodal and cathodal) tDCS strategies, but not for sham tDCS. Most importantly, internal semantic dissociations emphasized the intra-semantic-specificity of the effects, with higher improvements for items belonging to a 'living' category, which appeared as the most impaired in these patients prior to treatment, as compared to a 'non-living' category [92]. Crucially, biophysical modeling of transcranial direct current fields in a standard head model predicted

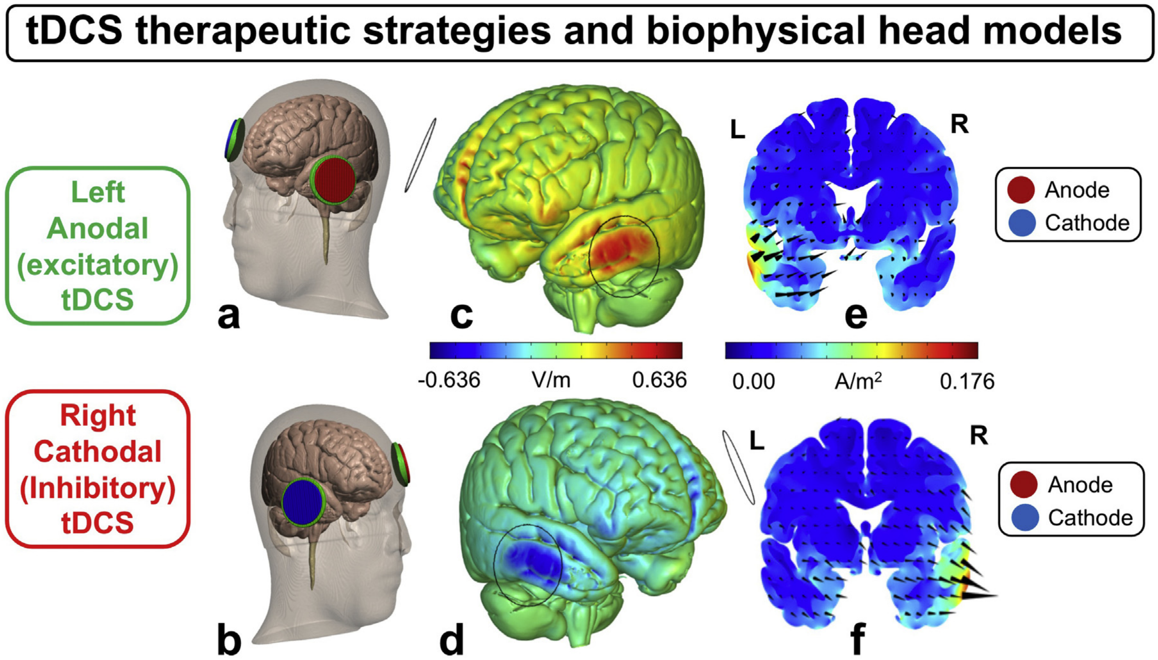

Fig. 8 – Finite Element Method (FEM) biophysical models of electrical current distribution in the cortex for given sets of TMS (target site, coil type and size, and pulse intensity) or tCS (electrode location, size, montage, and intensity) parameters. Models take in consideration permittivity and volume of the tissue layers (skin, bone, epidural air space, subdural cerebrospinal fluid, gray and white matter) current needs to cross to reach the target. The figure shows (a and b) FEM models of two tDCS montages (a: Anodal left anterior temporal lobe stimulation: x = −52, y = 2, z = −28, right supraorbital cathode on AF8 (in the 10/20 EEG system); b: Cathodal right anterior temporal pole stimulation, MNI coordinates: x = 53, y = 4, z = −32 and left supraorbital anode on AF7 (in the 10/20 EEG system) with 25 cm^2 round electrodes at 1.59 mA intensity, employed in sv-PPA patients [92]. For each electrode, we show (c and d) the spatial distribution of the radial electrical field (V/m) on the cortical surface, (e and f) current density (A/m^2) and electrical flow direction on a coronal section at target. Whereas anodal tDCS increases current density and drives radial 'inward' currents into the left anterior temporal lobe, cathodal stimulation in the right temporal lobe induces opposite local effects (c-f). L: Left R: Right (Adapted with permission from Teichman et al., 2016 [92] and Sanches et al., 2021 [110]).

excitatory and inhibitory impact of left anodal and right cathodal tDCS, respectively, and supported our stimulation strategy (Fig. 8).

On such pre-clinical basis, a double-blind randomized clinical trial to engage long-term plastic effects via two weeks of tDCS in a larger cohort of sv-PPA patients monitored on language tasks and via a PET-MRI battery to identify biomarkers predictive of baseline clinical severity or response to tDCS [111] is currently ongoing.

9. Conclusions and final outlook

We here provided a quick overview of NIBS technologies and strategies with regards to their ability to manipulate short-term reorganization (elasticity) or long-term plasticity in exploratory and therapeutic applications, respectively. The advent and dynamic development of this domain has fostered, for the last four decades, cognitive and clinical neuroscience with a unique set of causal technologies and procedures to characterize brain systems in terms of excitability, connectivity patterns, coding properties and their subtended cognitive and behavioral outputs. Such knowledge has allowed to gauge the plastic malleability of neural systems in healthy individuals and contribute new approaches to treat the symptoms of several neuropsychiatric diseases.

Nonetheless, many challenges and room for improvement lay ahead. Future steps to ensure progress could rely on four main domains: first, the development of novel stimulation technologies using electricity, magnetic fields or other sources of energy (namely, to date, ultrasound or near-infrared light or laser) to enhance stimulation focality, efficacy and ability to steer the stimulation field when inducing elastic and plastic effects; second, the adoption by the NIBS community of invasive stimulation models used in clinical settings combined with ECoG or intracranial SEEG recordings–such as intracranial stimulation in implanted epilepsy, Parkinson's disease, obsessive-compulsive-disorder and awake neurosurgery brain tumor removal patients–to better understand the impact of electrical currents on brain dynamics, cognition and plasticity events; third, a giant 'move' towards embedding NIBS strategies, mostly tCS-based, in EEG-based closed-loop systems allowing individualized and real-time tailoring of currents according to specific features of ongoing activity;

fourth and last, the mainstream use of accurate predictive MRI-based computational models to simulate and optimize TMS and tCS stimulation parameters and montages to customize and optimize interventions.

In forty years of technological development, fundamental NIBS-based plasticity research and clinical applications have fully established neurostimulation approaches as an essential player in fundamental and clinical neuroscience. For some, it will also become a lucrative multimillion market exploiting the field of *electroceuticals* to supplement or eventually replace pharmacological treatments. The future is ours to see, nonetheless no technological development will be able to replace the need for further progress and parallel advances expanding our comprehension of how the human brain is organized to produce behaviors, generate neuropsychiatric diseases and the major role played by the built-in elasticity and plasticity mechanisms neurostimulation relies on.

Disclosure of interest

The authors declare that they have no competing interest.

Author agreement

All authors have approved the final manuscript.

Acknowledgements

The activities of the laboratory of Dr. Valero-Cabré at the ICM CNRS UMR 7225 have been supported by research grants IHU-A-ICM-Translationnel, Agence Nationale de la Recherche (ANR) FLAG-ERA JTC 2017 '*CAUSALTOMICS*', and ANR APG '*OSCILLOSCOPUS*', PHRC Regional 'NEGLECT', PHRC National 'STIM-SD' and the Fondation Recherche Alzheimer (FRA). The authors thank the FRA foundation for logistic and equipment support and the Naturalia & Biologia Foundation for financial assistance for traveling and attendance to meetings.

REFERENCES

[1] Polanía R, Nitsche MA, Ruff CC. Studying and modifying brain function with non-invasive brain stimulation. Nat Neurosci 2018;21:174–87. http://dx.doi.org/10.1038/s41593-017-0054-4.

[2] Valero-Cabré A, Amengual JL, Stengel C, Pascual-Leone A, Coubard OA. Transcranial magnetic stimulation in basic and clinical neuroscience: A comprehensive review of fundamental principles and novel insights. Neurosci Biobehav Rev 2017;83:381–404. http://dx.doi.org/10.1016/j.neubiorev.2017.10.006.

[3] Chanes L, Quentin R, Tallon-Baudry C, Valero-Cabré A. Causal Frequency-Specific Contributions of Frontal Spatiotemporal Patterns Induced by Non-Invasive Neurostimulation to Human Visual Performance. J Neurosci 2013;33:5000–5. http://dx.doi.org/10.1523/JNEUROSCI.4401-12.2013.

[4] Chanes L, Quentin R, Vernet M, Valero-Cabré A. Arrhythmic activity in the left frontal eye field facilitates conscious visual perception in humans. Cortex 2015;71:240–7. http://dx.doi.org/10.1016/j.cortex.2015.05.016.

[5] Stengel C, Vernet M, Amengual JL, Valero-Cabré A. Causal modulation of right hemisphere fronto-parietal phase synchrony with Transcranial Magnetic Stimulation during a conscious visual detection task. Sci Rep 2021;11:3807. http://dx.doi.org/10.1038/s41598-020-79812-y.

[6] Vernet M, Stengel C, Quentin R, Amengual JL, Valero-Cabré A. Entrainment of local synchrony reveals a causal role for high-beta right frontal oscillations in human visual consciousness. Sci Rep 2019;9:1–15. http://dx.doi.org/10.1038/s41598-019-49673-1.

[7] Beckers G, Hömberg V. Impairment of visual perception and visual short term memory scanning by transcranial magnetic stimulation of occipital cortex. Exp Brain Res 1991;87:421–32. http://dx.doi.org/10.1007/BF00231859.

[8] Porro CA, Martinig M, Facchin P, Maieron M, Jones AKP, Fadiga L. Parietal cortex involvement in the localization of tactile and noxious mechanical stimuli: A transcranial magnetic stimulation study. Behav Brain Res 2007;178:183–9. http://dx.doi.org/10.1016/j.bbr.2006.11.011.

[9] Davare M, Rothwell JC, Lemon RN. Causal Connectivity between the Human Anterior Intraparietal Area and Premotor Cortex during Grasp. Curr Biol 2010;20:176–81. http://dx.doi.org/10.1016/j.cub.2009.11.063.

[10] Johnen VM, Neubert F-X, Buch ER, Verhagen L, O'Reilly JX, Mars RB, et al. Causal manipulation of functional connectivity in a specific neural pathway during behaviour and at rest. ELife 2015;4:e04585. http://dx.doi.org/10.7554/eLife.04585.

[11] Ruff CC, Driver J, Bestmann S. Combining TMSand fMRI: From 'virtual lesions' to functional-network accounts of cognition. Cortex 2009;45:1043–9. http://dx.doi.org/10.1016/j.cortex.2008.10.012.

[12] Mandonnet E, Margulies D, Stengel C, Dali M, Rheault F, Toba MN, et al. I do not feel my hand where I see it": causal mapping of visuo-proprioceptive integration network in a surgical glioma patient. Acta Neurochir 2020;162:1949–55. http://dx.doi.org/10.1007/s00701-020-04399-2.

[13] Perlmutter JS, Mink JW. Deep Brain Stimulation. Annu Rev Neurosci 2006;29:229–57. http://dx.doi.org/10.1146/annurev.neuro.29.051605.112824.

[14] Amengual JL, Vernet M, Adam C, Valero-Cabré A. Local entrainment of oscillatory activity induced by direct brain stimulation in humans. Sci Rep 2017;7:41908. http://dx.doi.org/10.1038/srep41908.

[15] Kringelbach ML, Jenkinson N, Owen SLF, Aziz TZ. Translational principles of deep brain stimulation. Nat Rev Neurosci 2007;8:623–35. http://dx.doi.org/10.1038/nrn2196.

[16] Antal A, Alekseichuk I, Bikson M, Brockmöller J, Brunoni AR, Chen R, et al. Low intensity transcranial electric stimulation: Safety, ethical, legal regulatory and application guidelines. Clin Neurophysiol 2017;128:1774–809. http://dx.doi.org/10.1016/j.clinph.2017.06.001.

[17] Rossi S, Hallett M, Rossini PM, Pascual-Leone A. Safety, ethical considerations, and application guidelines for the use of transcranial magnetic stimulation in clinical practice and research. Clin Neurophysiol 2009;120:2008–39. http://dx.doi.org/10.1016/j.clinph.2009.08.016.

[18] Rossi S, Antal A, Bestmann S, Bikson M, Brewer C, Brockmöller J, et al. Safety and recommendations for TMS use in healthy subjects and patient populations, with updates on training, ethical and regulatory issues: Expert Guidelines. Clin Neurophysiol 2021;132:269–306. http://dx.doi.org/10.1016/j.clinph.2020.10.003.

[19] Bystritsky A, Korb AS, Douglas PK, Cohen MS, Melega WP, Mulgaonkar AP, et al. A review of low-intensity focused ultrasound pulsation. Brain Stimulat 2011;4:125–36. http://dx.doi.org/10.1016/j.brs.2011.03.007.

[20] Song P, Han T, Lin H, Li S, Huang Q, Dai X, et al. Transcranial near-infrared stimulation may increase cortical excitability recorded in humans. Brain Res Bull 2020;155:155–8. http://dx.doi.org/10.1016/j.brainresbull.2019.12.007.

[21] Barker AT, Jalinous R, Freeston IL. Non-invasive magnetic stimulation of human motor cortex. Lancet Lond Engl 1985;1:1106–7. http://dx.doi.org/10.1016/s0140-6736(85)92413-4.

[22] Hallett M. Transcranial magnetic stimulation: a primer. Neuron 2007;55:187–99. http://dx.doi.org/10.1016/j.neuron.2007.06.026.

[23] Kobayashi M, Pascual-Leone A. Transcranial magnetic stimulation in neurology. Lancet Neurol 2003;2:145–56. http://dx.doi.org/10.1016/S1474-4422(03)00321-1.

[24] Valero-Cabré A, Payne BR, Rushmore J, Lomber SG, Pascual-Leone A. Impact of repetitive transcranial magnetic stimulation of the parietal cortex on metabolic brain activity: a 14C-2DG tracing study in the cat. Exp Brain Res 2005;163:1–12. http://dx.doi.org/10.1007/s00221-004-2140-6.

[25] Kammer T. Phosphenes and transient scotomas induced by magnetic stimulation of the occipital lobe: their topographic relationship. Neuropsychologia 1998;37:191–8. http://dx.doi.org/10.1016/S0028-3932(98)00093-1.

[26] Nitsche MA, Paulus W. Excitability changes induced in the human motor cortex by weak transcranial direct current stimulation. J Physiol 2000;527:633–9. http://dx.doi.org/10.1111/j.1469-7793.2000.t01-1-00633.x.

[27] Vöröslakos M, Takeuchi Y, Brinyiczki K, Zombori T, Oliva A, Fernández-Ruiz A, et al. Direct effects of transcranial electric stimulation on brain circuits in rats and humans. Nat Commun 2018;9:483. http://dx.doi.org/10.1038/s41467-018-02928-3.

[28] Miranda PC, Lomarev M, Hallett M. Modeling the current distribution during transcranial direct current stimulation. Clin Neurophysiol 2006;117:1623–9. http://dx.doi.org/10.1016/j.clinph.2006.04.009.

[29] Nitsche MA, Seeber A, Frommann K, Klein CC, Rochford C, Nitsche MS, et al. Modulating parameters of excitability during and after transcranial direct current stimulation of the human motor cortex. J Physiol 2005;568:291–303. http://dx.doi.org/10.1113/jphysiol.2005.092429.

[30] Rahman A, Reato D, Arlotti M, Gasca F, Datta A, Parra LC, et al. Cellular effects of acute direct current stimulation: somatic and synaptic terminal effects. J Physiol 2013;591:2563–78. http://dx.doi.org/10.1113/jphysiol.2012.247171.

[31] Terney D, Chaieb L, Moliadze V, Antal A, Paulus W. Increasing human brain excitability by transcranial high-frequency random noise stimulation. J Neurosci 2008;28:14147–55. http://dx.doi.org/10.1523/JNEUROSCI.4248-08.2008.

[32] Datta A, Elwassif M, Battaglia F, Bikson M. Transcranial current stimulation focality using disc and ring electrode configurations: FEM analysis. J Neural Eng 2008;5:163–74. http://dx.doi.org/10.1088/1741-2560/5/2/007.

[33] Datta A, Truong D, Minhas P, Parra LC, Bikson M. Inter-individual variation during transcranial direct current stimulation and normalization of dose using MRI-derived computational models. Front Psychiatry 2012;3:91. http://dx.doi.org/10.3389/fpsyt.2012.00091.

[34] Pascual-Leone A, Bartres-Faz D, Keenan JP. Transcranial magnetic stimulation: studying the brain-behaviour relationship by induction of "virtual lesions.". Philos Trans R Soc Lond B Biol Sci 1999;354:1229–38. http://dx.doi.org/10.1098/rstb.1999.0476.

[35] Walsh V, Rushworth M. A primer of magnetic stimulation as a tool for neuropsychology. Neuropsychologia 1999;37:125–35. http://dx.doi.org/10.1016/S0028-3932(98)00087-6.

[36] Amassian VE, Cracco RQ, Maccabee PJ, Cracco JB, Rudell A, Eberle L. Suppression of visual perception by magnetic coil stimulation of human occipital cortex. Electroencephalogr Clin Neurophysiol Potentials Sect 1989;74:458–62. http://dx.doi.org/10.1016/0168-5597(89)90036-1.

[37] Pascual-Leone A, Walsh V, Rothwell J. Transcranial magnetic stimulation in cognitive neuroscience–virtual lesion, chronometry, and functional connectivity. Curr Opin Neurobiol 2000;10:232–7. http://dx.doi.org/10.1016/S0959-4388(00)00081-7.

[38] Moliadze V, Giannikopoulos D, Eysel UT, Funke K. Paired-pulse transcranial magnetic stimulation protocol applied to visual cortex of anaesthetized cat: effects on visually evoked single-unit activity. J Physiol 2005;566:955–65. http://dx.doi.org/10.1113/jphysiol.2005.086090.

[39] Nakamura H, Kitagawa H, Kawaguchi Y, Tsuji H. Intracortical facilitation and inhibition after transcranial magnetic stimulation in conscious humans. J Physiol 1997;498:817–23. http://dx.doi.org/10.1113/jphysiol.1997.sp021905.

[40] Maeda F, Keenan JP, Tormos JM, Topka H, Pascual-Leone A. Modulation of corticospinal excitability by repetitive transcranial magnetic stimulation. Clin Neurophysiol 2000;111:800–5.

[41] Pascual-Leone A, Valls-Solé J, Wassermann EM, Hallett M. Responses to rapid-rate transcranial magnetic stimulation of the human motor cortex. Brain 1994;117:847–58. http://dx.doi.org/10.1093/brain/117.4.847.

[42] Valero-Cabré A, Payne BR, Pascual-Leone A. Opposite impact on 14C-2-deoxyglucose brain metabolism following patterns of high and low frequency repetitive transcranial magnetic stimulation in the posterior parietal cortex. Exp Brain Res 2007;176:603–15. http://dx.doi.org/10.1007/s00221-006-0639-8.

[43] Chen R, Classen J, Gerloff C, Celnik P, Wassermann EM, Hallett M, et al. Depression of motor cortex excitability by low-frequency transcranial magnetic stimulation. Neurology 1997;48:1398–403. http://dx.doi.org/10.1212/WNL.48.5.1398.

[44] Romero JR, Anschel D, Sparing R, Gangitano M, Pascual-Leone A. Subthreshold low frequency repetitive transcranial magnetic stimulation selectively decreases facilitation in the motor cortex. Clin Neurophysiol 2002;113:101–7. http://dx.doi.org/10.1016/S1388-2457(01)00693-9.

[45] Huang Y-Z, Edwards MJ, Rounis E, Bhatia KP, Rothwell JC. Theta burst stimulation of the human motor cortex. Neuron 2005;45:201–6. http://dx.doi.org/10.1016/j.neuron.2004.12.033.

[46] Buzsáki G, Draguhn A. Neuronal oscillations in cortical networks. Science 2004;304:1926–9. http://dx.doi.org/10.1126/science.1099745.

[47] Rosanova M, Casali A, Bellina V, Resta F, Mariotti M, Massimini M. Natural frequencies of human corticothalamic circuits. J Neurosci 2009;29:7679–85. http://dx.doi.org/10.1523/JNEUROSCI.0445-09.2009.

[48] Thut G, Schyns PG, Gross J. Entrainment of perceptually relevant brain oscillations by non-invasive rhythmic stimulation of the human brain. Front Psychol 2011;2. http://dx.doi.org/10.3389/fpsyg.2011.00170.

[49] Thut G, Veniero D, Romei V, Miniussi C, Schyns P, Gross J, et al. Causes local entrainment of natural oscillatory

signatures. Curr Biol 2011;21:1176–85. http://dx.doi.org/10.1016/j.cub.2011.05.049.

[50] Albouy P, Weiss A, Baillet S, Zatorre RJ. Selective entrainment of theta oscillations in the dorsal stream causally enhances auditory working memory performance. Neuron 2017;94:193–206. http://dx.doi.org/10.1016/j.neuron.2017.03.015 [e5].

[51] Jaegle A, Ro T. Direct control of visual perception with phase-specific modulation of posterior parietal cortex. J Cogn Neurosci 2014;26:422–32. http://dx.doi.org/10.1162/jocn_a_00494.

[52] Romei V, Gross J, Thut G. On the role of prestimulus alpha rhythms over occipito-parietal areas in visual input regulation: correlation or causation? J Neurosci 2010;30:8692–7. http://dx.doi.org/10.1523/JNEUROSCI.0160-10.2010.

[53] Sauseng P, Klimesch W, Heise KF, Gruber WR, Holz E, Karim AA, et al. Brain oscillatory substrates of visual short-term memory capacity. Curr Biol 2009;19:1846–52. http://dx.doi.org/10.1016/j.cub.2009.08.062.

[54] Kanai R, Chaieb L, Antal A, Walsh V, Paulus W. Frequency-dependent electrical stimulation of the visual cortex. Curr Biol 2008;18:1839–43. http://dx.doi.org/10.1016/j.cub.2008.10.027.

[55] Marshall L, Helgadóttir H, Mölle M, Born J. Boosting slow oscillations during sleep potentiates memory. Nature 2006;444:610–3. http://dx.doi.org/10.1038/nature05278.

[56] Herrmann CS, Rach S, Neuling T, Strüber D. Transcranial alternating current stimulation: a review of the underlying mechanisms and modulation of cognitive processes. Front Hum Neurosci 2013;7. http://dx.doi.org/10.3389/fnhum.2013.00279.

[57] Polanía R, Nitsche MA, Korman C, Batsikadze G, Paulus W. The importance of timing in segregated theta phase-coupling for cognitive performance. Curr Biol 2012;22:1314–8. http://dx.doi.org/10.1016/j.cub.2012.05.021.

[58] Reinhart RMG, Nguyen JA. Working memory revived in older adults by synchronizing rhythmic brain circuits. Nat Neurosci 2019;22:820–7. http://dx.doi.org/10.1038/s41593-019-0371-x.

[59] Noury N, Hipp JF, Siegel M. Physiological processes non-linearly affect electrophysiological recordings during transcranial electric stimulation. NeuroImage 2016;140:99–109. http://dx.doi.org/10.1016/j.neuroimage.2016.03.065.

[60] Uhlhaas PJ, Singer W. Neural synchrony in brain disorders: relevance for cognitive dysfunctions and pathophysiology. Neuron 2006;52:155–68. http://dx.doi.org/10.1016/j.neuron.2006.09.020.

[61] Driver J, Blankenburg F, Bestmann S, Vanduffel W, Ruff CC. Concurrent brain-stimulation and neuroimaging for studies of cognition. Trends Cogn Sci 2009;13:319–27. http://dx.doi.org/10.1016/j.tics.2009.04.007.

[62] Bestmann S, Baudewig J, Siebner HR, Rothwell JC, Frahm J. Functional MRI of the immediate impact of transcranial magnetic stimulation on cortical and subcortical motor circuits. Eur J Neurosci 2004;19:1950–62. http://dx.doi.org/10.1111/j.1460-9568.2004.03277.x.

[63] Chouinard PA, Van Der Werf YD, Leonard G, Paus T. Modulating Neural networks with transcranial magnetic stimulation applied over the dorsal premotor and primary motor cortices. J Neurophysiol 2003;90:1071–83. http://dx.doi.org/10.1152/jn.01105.2002.

[64] Paus T, Jech R, Thompson CJ, Comeau R, Peters T, Evans AC. Transcranial magnetic stimulation during positron emission tomography: a new method for studying connectivity of the human cerebral cortex. J Neurosci 1997;17:3178–84.

[65] Lee L, Siebner HR, Rowe JB, Rizzo V, Rothwell JC, Frackowiak RSJ, et al. Acute remapping within the motor system induced by low-frequency repetitive transcranial magnetic stimulation. J Neurosci 2003;23:5308–18. http://dx.doi.org/10.1523/JNEUROSCI.23-12-05308.2003.

[66] Bestmann S, Ruff CC, Driver J, Blankenburg F, Concurrent TMS. and functional magnetic resonance imaging: methods and current advances. Oxf Handb Transcranial Stimul 2008. http://dx.doi.org/10.1093/oxfordhb/9780198568926.013.0036.

[67] Van Der Werf YD, Paus T. The neural response to transcranial magnetic stimulation of the human motor cortex I. Intracortical and cortico-cortical contributions. Exp Brain Res 2006;175:231–45. http://dx.doi.org/10.1007/s00221-006-0551-2.

[68] Bächinger M, Zerbi V, Moisa M, Polania R, Liu Q, Mantini D, et al. Concurrent tACS-fMRI reveals causal influence of power synchronized neural activity on resting state fMRI connectivity. J Neurosci 2017;37:4766–77. http://dx.doi.org/10.1523/JNEUROSCI.1756-16.2017.

[69] Quentin R, Chanes L, Migliaccio R, Valabrègue R, Valero-Cabré A. Fronto-tectal white matter connectivity mediates facilitatory effects of non-invasive neurostimulation on visual detection. NeuroImage 2013;82:344–54. http://dx.doi.org/10.1016/j.neuroimage.2013.05.083.

[70] Quentin R, Chanes L, Vernet M, Valero-Cabre A. Fronto-parietal anatomical connections influence the modulation of conscious visual perception by high-beta frontal oscillatory activity. Cereb Cortex 2014;25:2095–101. http://dx.doi.org/10.1093/cercor/bhu014.

[71] Quentin R, Elkin Frankston S, Vernet M, Toba MN, Bartolomeo P, Chanes L, et al. Visual contrast sensitivity improvement by right frontal high-beta activity is mediated by contrast gain mechanisms and influenced by fronto-parietal white matter microstructure. Cereb Cortex 2015;26:2381–90. http://dx.doi.org/10.1093/cercor/bhv060.

[72] Toba MN, Godefroy O, Rushmore RJ, Zavaglia M, Maatoug R, Hilgetag CC, et al. Revisiting 'brain modes' in a new computational era: approaches for the characterization of brain-behavioural associations. Brain 2020;143:1088–98. http://dx.doi.org/10.1093/brain/awz343.

[73] Toba MN, Zavaglia M, Malherbe C, Moreau T, Rastelli F, Kaglik A, et al. Game theoretical mapping of white matter contributions to visuospatial attention in stroke patients with hemineglect. Hum Brain Mapp 2020;41:2926–50. http://dx.doi.org/10.1002/hbm.24987.

[74] Plewnia C, Rilk AJ, Soekadar SR, Arfeller C, Huber HS, Sauseng P, et al. Enhancement of long-range EEG coherence by synchronous bifocal transcranial magnetic stimulation. Eur J Neurosci 2008;27:1577–83. http://dx.doi.org/10.1111/j.1460-9568.2008.06124.x.

[75] Buch ER, Johnen VM, Nelissen N, O'Shea J, Rushworth MFS. Noninvasive Associative Plasticity Induction in a Corticocortical Pathway of the Human Brain. J Neurosci 2011;31:17669–7. http://dx.doi.org/10.1523/JNEUROSCI.1513-11.2011.

[76] Aydin-Abidin S, Moliadze V, Eysel UT, Funke K. Effects of repetitive TMS on visually evoked potentials and EEG in the anaesthetized cat: dependence on stimulus frequency and train duration: rTMS effects on cat VEPs. J Physiol 2006;574:443–55. http://dx.doi.org/10.1113/jphysiol.2006.108464.

[77] Thut G, Pascual-Leone A. A review of combined TMS-EEG Studies to characterize lasting effects of repetitive TMS and assess their usefulness in cognitive and clinical neuroscience. Brain Topogr 2009;22:219. http://dx.doi.org/10.1007/s10548-009-0115-4.

[78] Huber R, Esser SK, Ferrarelli F, Massimini M, Peterson MJ, Tononi G. TMS-induced cortical potentiation during wakefulness locally increases slow wave activity during

sleep. PLOS ONE 2007;2:e276. http://dx.doi.org/10.1371/journal.pone.0000276.
[79] Schindler K, Nyffeler T, Wiest R, Hauf M, Mathis J, Hess CW, et al. Theta burst transcranial magnetic stimulation is associated with increased EEG synchronization in the stimulated relative to unstimulated cerebral hemisphere. Neurosci Lett 2008;436:31–4. http://dx.doi.org/10.1016/j.neulet.2008.02.052.
[80] Bäumer T, Lange R, Liepert J, Weiller C, Siebner HR, Rothwell JC, et al. Repeated premotor rTMS leads to cumulative plastic changes of motor cortex excitability in humans. NeuroImage 2003;20:550–60.
[81] Maeda F, Gangitano M, Thall M, Pascual-Leone A. Inter- and intra-individual variability of paired-pulse curves with transcranial magnetic stimulation (TMS). Clin Neurophysiol 2002;113:376–82. http://dx.doi.org/10.1016/S1388-2457(02)00008-1.
[82] May A, Hajak G, Gänßbauer S, Steffens T, Langguth B, Kleinjung T, et al. Structural brain alterations following 5 days of intervention: dynamic aspects of neuroplasticity. Cereb Cortex 2007;17:205–10. http://dx.doi.org/10.1093/cercor/bhj138.
[83] Valero-Cabré A, Pascual-Leone A, Rushmore RJ. Cumulative sessions of repetitive transcranial magnetic stimulation (rTMS) build up facilitation to subsequent TMS-mediated behavioural disruptions. Eur J Neurosci 2008;27:765–74. http://dx.doi.org/10.1111/j.1460-9568.2008.06045.x.
[84] Bulteau S, Sébille V, Fayet G, Thomas-Ollivier V, Deschamps T, Bonnin-Rivalland A, et al. Efficacy of intermittent Theta Burst Stimulation (iTBS) and 10-Hz high-frequency repetitive transcranial magnetic stimulation (rTMS) in treatment-resistant unipolar depression: study protocol for a randomised controlled trial. Trials 2017;18:17. http://dx.doi.org/10.1186/s13063-016-1764-8.
[85] Concerto C, Lanza G, Cantone M, Ferri R, Pennisi G, Bella R, et al. Repetitive transcranial magnetic stimulation in patients with drug-resistant major depression: A six-month clinical follow-up study. Int J Psychiatry Clin Pract 2015;19:252–8. http://dx.doi.org/10.3109/13651501.2015.1084329.
[86] Nitsche MA, Boggio PS, Fregni F, Pascual-Leone A. Treatment of depression with transcranial direct current stimulation (tDCS): a review. Exp Neurol 2009;219:14–9. http://dx.doi.org/10.1016/j.expneurol.2009.03.038.
[87] Haraldsson H. Transcranial Magnetic Stimulation in the investigation and treatment of schizophrenia: a review. Schizophr Res 2004;71:1–16. http://dx.doi.org/10.1016/j.schres.2003.10.006.
[88] Berlim MT, Neufeld NH, Van den Eynde F. Repetitive transcranial magnetic stimulation (rTMS) for obsessive–compulsive disorder (OCD): an exploratory meta-analysis of randomized and sham-controlled trials. J Psychiatr Res 2013;47:999–1006. http://dx.doi.org/10.1016/j.jpsychires.2013.03.022.
[89] Dunlop K, Woodside B, Olmsted M, Colton P, Giacobbe P, Downar J. Reductions in cortico-striatal hyperconnectivity accompany successful treatment of obsessive-compulsive disorder with dorsomedial prefrontal rTMS. Neuropsychopharmacology 2016;41:1395–403. http://dx.doi.org/10.1038/npp.2015.292.
[90] Boggio PS, Ferrucci R, Mameli F, Martins D, Martins O, Vergari M, et al. Prolonged visual memory enhancement after direct current stimulation in Alzheimer's disease. Brain Stimulat 2012;5:223–30. http://dx.doi.org/10.1016/j.brs.2011.06.006.
[91] Doruk D, Gray Z, Bravo GL, Pascual-Leone A, Fregni F. Effects of tDCS on executive function in Parkinson's disease. Neurosci Lett 2014;582:27–31. http://dx.doi.org/10.1016/j.neulet.2014.08.043.
[92] Teichmann M, Lesoil C, Godard J, Vernet M, Bertrand A, Levy R, et al. Direct current stimulation over the anterior temporal areas boosts semantic processing in primary progressive aphasia: tDCS in Semantic Primary Progressive Aphasia. Ann Neurol 2016;80:693–707. http://dx.doi.org/10.1002/ana.24766.
[93] Antal A, Terney D, Kühnl S, Paulus W. Anodal transcranial direct current stimulation of the motor cortex ameliorates chronic pain and reduces short intracortical inhibition. J Pain Symptom Manage 2010;39:890–903. http://dx.doi.org/10.1016/j.jpainsymman.2009.09.023.
[94] Bucur M, Papagno C. Are transcranial brain stimulation effects long-lasting in post-stroke aphasia?. A comparative systematic review and meta-analysis on naming performance. Neurosci Biobehav Rev 2019;102:264–89. http://dx.doi.org/10.1016/j.neubiorev.2019.04.019.
[95] Xiang H, Sun J, Tang X, Zeng K, Wu X. The effect and optimal parameters of repetitive transcranial magnetic stimulation on motor recovery in stroke patients: a systematic review and meta-analysis of randomized controlled trials. Clin Rehabil 2019;33:847–64. http://dx.doi.org/10.1177/0269215519829897.
[96] Silvanto J, Muggleton N, Walsh V. State-dependency in brain stimulation studies of perception and cognition. Trends Cogn Sci 2008;12:447–54. http://dx.doi.org/10.1016/j.tics.2008.09.004.
[97] Bergmann TO. Brain State-dependent brain stimulation. Front Psychol 2018;9. http://dx.doi.org/10.3389/fpsyg.2018.02108.
[98] Romei V, Thut G, Silvanto J. Information-based approaches of noninvasive transcranial brain stimulation. Trends Neurosci 2016;39:782–95. http://dx.doi.org/10.1016/j.tins.2016.09.001.
[99] Corbetta M, Shulman GL. Control of goal-directed and stimulus-driven attention in the brain. Nat Rev Neurosci 2002;3:201. http://dx.doi.org/10.1038/nrn755.
[100] Buschman TJ, Miller EK. Top-down versus bottom-up control of attention in the prefrontal and posterior parietal cortices. Science 2007;315:1860–2. http://dx.doi.org/10.1126/science.1138071.
[101] Hipp JF, Engel AK, Siegel M. Oscillatory synchronization in large-scale cortical networks predicts perception. Neuron 2011;69:387–96. http://dx.doi.org/10.1016/j.neuron.2010.12.027.
[102] Tallon-Baudry C, Bertrand O. Oscillatory gamma activity in humans and its role in object representation. Trends Cogn Sci 1999;3:151–62.
[103] Wyart V, Tallon-Baudry C. Neural dissociation between visual awareness and spatial attention. J Neurosci 2008;28:2667–79. http://dx.doi.org/10.1523/JNEUROSCI.4748-07.2008.
[104] Mesulam M-M, Rogalski EJ, Wieneke C, Hurley RS, Geula C, Bigio EH, et al. Primary progressive aphasia and the evolving neurology of the language network. Nat Rev Neurol 2014;10:554–69. http://dx.doi.org/10.1038/nrneurol.2014.159.
[105] Gorno-Tempini ML, Hillis AE, Weintraub S, Kertesz A, Mendez M, Cappa SF, et al. Classification of primary progressive aphasia and its variants. Neurology 2011;76:1006–14. http://dx.doi.org/10.1212/WNL.0b013e31821103e6.
[106] Norise C, Hamilton RH. Non-invasive brain stimulation in the treatment of post-stroke and neurodegenerative aphasia: parallels, differences, and lessons learned. Front Hum Neurosci 2017;10. http://dx.doi.org/10.3389/fnhum.2016.00675.

[107] Ferbert A, Priori A, Rothwell JC, Day BL, Colebatch JG, Marsden CD. Interhemispheric inhibition of the human motor cortex. J Physiol 1992;453:525–46. http://dx.doi.org/10.1113/jphysiol.1992.sp019243.

[108] Hamilton RH, Chrysikou EG, Coslett B. Mechanisms of aphasia recovery after stroke and the role of noninvasive brain stimulation. Brain Lang 2011;118:40–50. http://dx.doi.org/10.1016/j.bandl.2011.02.005.

[109] Luber B, Lisanby SH. Enhancement of human cognitive performance using transcranial magnetic stimulation (TMS). NeuroImage 2014;85:961–70. http://dx.doi.org/10.1016/j.neuroimage.2013.06.007.

[110] Sanches C, Stengel C, Godard J, Mertz J, Teichmann M, Migliaccio R, et al. Past, present, and future of non-invasive brain stimulation approaches to treat cognitive impairment in neurodegenerative diseases: time for a comprehensive critical review. Front Aging Neurosci 2021;12. http://dx.doi.org/10.3389/fnagi.2020.578339.

[111] Sanches C, Levy R, Benisty S, Volpe-Gillot L, Habert M-O, Kas A, et al. Testing the therapeutic effects of transcranial direct current stimulation (tDCS) in semantic dementia: a double blind, sham controlled, randomized clinical trial. Trials 2019;20:632. http://dx.doi.org/10.1186/s13063-019-3613-z.