



## Review article

# Transcranial magnetic stimulation in basic and clinical neuroscience: A comprehensive review of fundamental principles and novel insights

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## ABSTRACT

Non-invasive brain stimulation methods, such as Transcranial Magnetic Stimulation (TMS), are widely used worldwide to make causality-based inferences about brain-behavior interactions. TMS-based clinical applications have been shown promising to treat neurological or psychiatric diseases. TMS works by inducing non-invasively electric currents in localized cortical regions thus modulating their excitability levels and ongoing activity patterns depending on stimulation settings: frequency, number of pulses, train duration and intertrain intervals. Proper use of TMS in the fundamental and clinical neuroscience research requires a deep understanding of its operational principles, risks, potential and limitations. In this article we present the principles through which TMS is thought to operate. Readers will be provided with the bases to be able to understand and critically discuss TMS studies and design hypothesis driven TMS applications for basic and clinical neuroscience. Moreover, some recently identified physiological phenomena which that can dramatically influence the efficacy and magnitude of TMS impact and technological and methodological developments to guide TMS interventions that are becoming mainstream in the field will be also reviewed.

## 1. General introduction

The emergence and development of non-invasive brain stimulation (NIBS) techniques has driven a conceptual and technological revolution in the fundamental and clinical neurosciences. Based on common principles, these techniques target specific cortical areas and inject within patterns of energy, to modify ongoing neural patterns of activity subtending specific cognitive processes and their associated behaviors. By doing so, NIBS aim to provide proof of a causal relation between anatomical regions and such behaviors and/or drive functional improvements in healthy participants or brain damaged patients. Thus far, the most popular source used by non-invasive stimulation devices has been electromagnetic. Nonetheless, novel technologies based in the use of ultrasound or wave length-specific light patterns might in the mid to

long term, become mainstream and extend to human use.

The use of either electrical stimulation vs. magnetic fields primarily characterizes the two NIBS technologies which to date are the most widely used: Transcranial current stimulation (tCS) and Transcranial magnetic stimulation (TMS). Rescued from forgetfulness more than decade ago after having been popular during the sixties, tDCS clinical applications have skyrocketed. Nonetheless, tDCS has limited applicability as an investigational causal tool, carving plenty of room for TMS to flourish and shine.

In this review we will describe in detail the operational principles of single pulse, paired pulse, short trains, repetitive and rhythmic TMS. We will also delineate physiological bases, possibilities and risks of TMS as a methodological approach for the fundamental and clinical neurosciences. Emphasis will be focused on our understanding of potential

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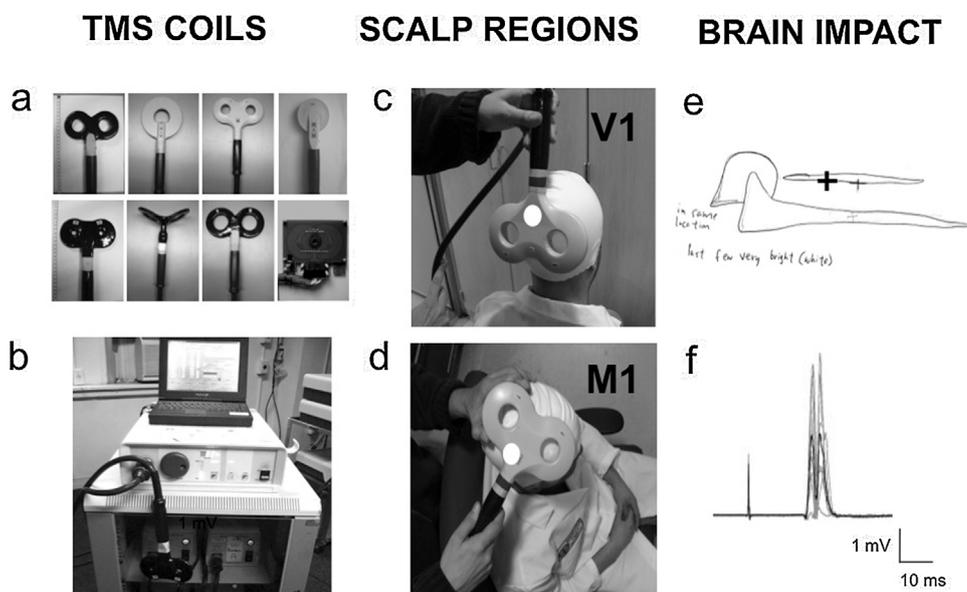
applications and limitations of TMS in cognitive experiments. Possible collateral effects of TMS, to which researchers have to pay particular attention, will be discussed. Our aim is not to describe in detail each technical aspects of the technique, which may be found in other publications, but to provide the reader an overview and a critical analysis of the fundamental principles of TMS as well as a short description of its strengths and weaknesses. Across the manuscript, and due to space restrictions, we aim to citing the pioneer (rather than the latest) studies supporting our statements, hence some of most recent studies providing additional demonstration and illustration might not be necessarily quoted in this review.

## 2. What is TMS? Why and how is TMS used to study the human brain?

TMS was first proposed as a potential brain stimulation tool by Barker and his colleagues in 1985 (Barker et al., 1985). It is based on magnetic induction principles discovered by Faraday in the first half of the 19th century (Wagner et al., 2007b): a brief and rapidly changing high intensity electrical current is passed through a loop of conducting wire inside a protected case and applied onto any area of the scalp. Such current generates a powerful magnetic field that penetrates the cranium and is capable of inducing an electric current in excitable tissues. Applied onto cortical areas, the induced current depolarizes nearby located neuron assemblies located beneath the coil and generates neurophysiological and/or behavioral effects depending on their contributing functions. In the human brain, TMS-evoked activity requires an initial current in the order of 4–8 kiloamperes (kAmp) combined with a rapid peak-to-peak rate of change of around 100–200  $\mu\text{s}$  to induce a current in the order of several hundreds of volts per meter (V/m), i.e. 7–15  $\text{mA cm}^{-2}$  (Pascual-Leone et al., 2001; Wagner et al., 2007b). Importantly, the direction of the induced current is perpendicular to the coil surface and its intensity is proportional to that of the original current though attenuated as a function of distance by bone, air, tissues, cerebrospinal fluid in subdural and subarachnoidal spaces and structural alterations of cortex (Wagner et al., 2006; Wagner et al., 2007a; Wagner et al., 2009). When applied onto the primary motor cortex (Fig. 1A), TMS pulses can activate corticospinal tract and associated circuits thus inducing twitches in muscles whose representation is being targeted by the stimulation (Amassian and Cracco, 1987;

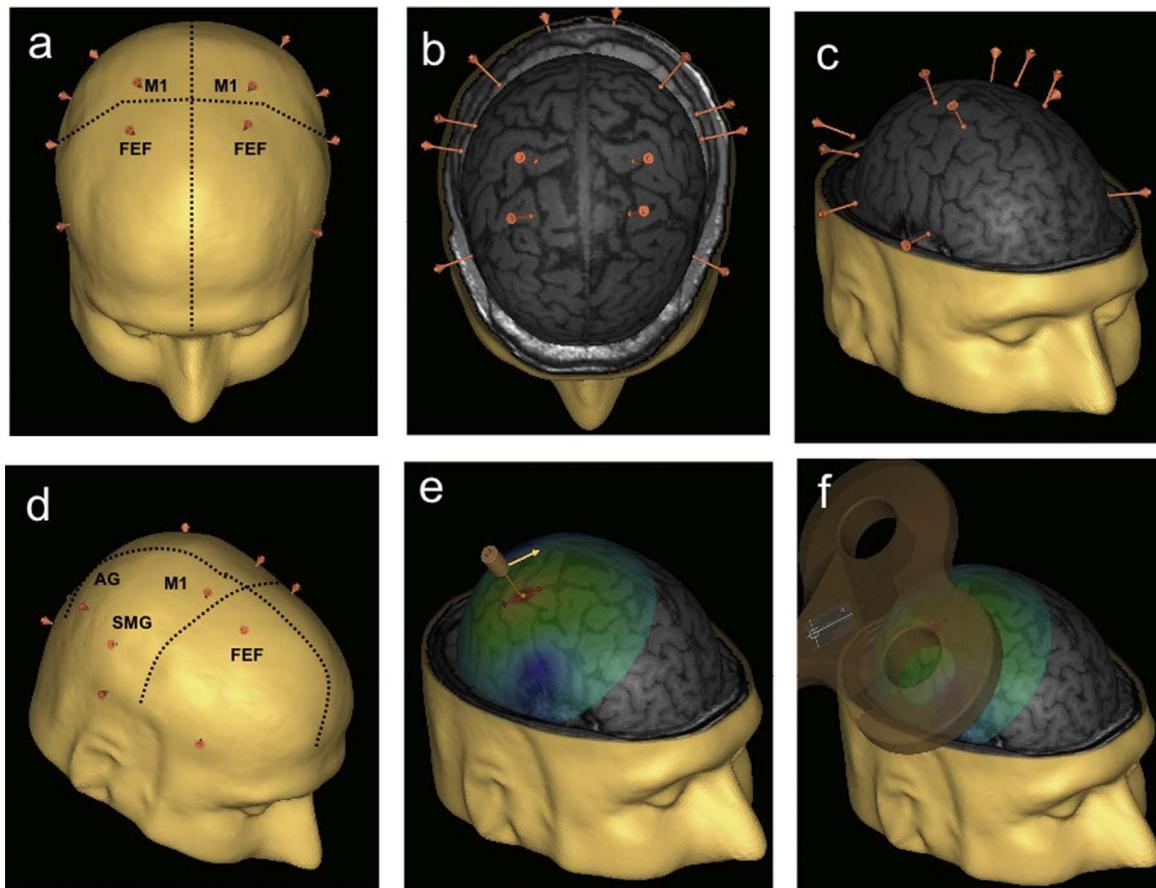
Amassian et al., 1990; Amassian et al., 1987; Barker et al., 1985). When applied onto the primary visual cortex (Fig. 1B), TMS can induce percepts such as of sparking lights, so-called phosphenes, in specific visual field locations depending upon retinotopic representation of stimulated occipital (Amassian et al., 1989; Elkin-Frankston et al., 2010; Fernandez et al., 2002; Kammer, 1999; Kammer et al., 2005a; Kammer et al., 2005b) or posterior parietal areas (Fried et al., 2011). In hierarchically higher cortical regions and associated networks subtending higher cognitive functions such as language, memory, attention, visuomotor coordination, etc., TMS induces neither muscle contractions nor subjective visual sensations, but can disrupt firing encoding rhythms and interfere with normal processing and communication of interconnected regions within the stimulated network. In other words, TMS can interfere with physiological and/or behavioral activities mediated by targeted cortical areas (Coslett and Monsul, 1994; Ganis et al., 2000; Mottaghy et al., 2000; Pascual-Leone et al., 1991; Pascual-Leone et al., 1994a; Robertson et al., 2001). Importantly thought, several studies have shown that TMS has not only local but distant effects conveyed through connectivity linking different regions of the same cerebral circuit (Fig. 7). Network effects may use connection pathways between brain areas and structures to evoke changes at a distance (Chouinard et al., 2003; Coubard and Kapoula, 2006; Paus et al., 2001; Strafella et al., 2001; Valero-Cabré et al., 2001; Valero-Cabré and Pascual-Leone, 2005; Valero-Cabré et al., 2007; Valero-Cabré et al., 2005) and are strongly influenced by the richness of the anatomical connectivity between regions and the number of synaptic steps (Valero-Cabré et al., 2007). The behavioral effects of TMS may thus be the result of the effect onto the targeted cortical area, the manifestation of impact onto connected regions or the combined effect of both, as a function of white matter connectivity (Quentin et al., 2013; Quentin et al., 2015; Quentin et al., 2016). Most importantly, knowledge on brain interactions and functional connectivity in the human brain responsible for network effects can be used to optimize research and therapeutics (Eldaief et al., 2011; Fox et al., 2014, 2012).

On the basis of the above mentioned capabilities and limitations, TMS technologies have been developed as *exploratory tools* in the field of human cognitive neurosciences research to: (1) establish causal relations through the direct manipulation of cortical site, between brain sites and their associated networks and specific cognitive processes and behaviors; (2) dissect out the spatial and temporal correlates of brain



**Fig. 1.** The TMS coil is positioned over the scalp region overlying specific cortical locations on which we would like to induce a current. (A) TMS of the primary motor region (M1) of the right hemisphere triggers involuntary twitches of muscles in segments of the upper limb contralateral to the stimulated hemisphere, and following their somatotopic organization in the motor cortex. This response can be characterized quantitatively by recording the latency and amplitude of the Motor Evoked Potentials (MEP), by means of electromyography (EMG) on specific hand or forearm muscles. (B) TMS of the primary visual cortex (V1–V4 bilaterally) right in the occipital pole induces the percept of phosphene reported as appearing in the central visual field. Participants may also subjectively describe some of its *qualia* (shape, motion, color) and localize its exact location in the visual field, which might slightly differ according to the TMS coil positioning in caudal regions, and its retinotopic organization. (C) Different stimulation coils used for TMS interventions which differ in field shape, size and depth: (first line left to right); 40-mm diameter figure-of-eight, butterfly or double coil, 70-mm circular coil, 70-mm butterfly coil, 50-mm circular coil; (second line) 45-

mm butterfly coil, bell-shaped coil, 50-mm butterfly coil, 50-mm butterfly coil with an integrated 0.7-mm thick heat-resistant card to be used in combination with intracranial recordings in animal models. (D) TMS monitor for single-pulse or repetitive TMS. Note the capacitors that store electrical charge to generate the magnetic field, the CPU and its associated computer, which control pulse synchronization, and the stimulation coil – here a 45-mm “butterfly” design- attached to the CPU by a flexible electrical cord.



**Fig. 2.** MRI-based frameless stereotaxic neuronavigation technologies increase the topographic precision of the delivered stimulation, hence improve the specificity of the behavioral effects modulated by the delivered magnetic pulses. Cortical target regions can be identified and marked beforehand on individual structural MRI images; (A–D) on the basis of macroscopic anatomic landmarks (based on gyral and sulcal patterns), regions exhibiting activation on fMRI tests carried out before the study and co-registered on the structural MRI, or mean normalized spatial coordinates of cortical target regions in Talairach or MNI (Montreal Neurological Institute) reference systems. Using MRI based frameless stereotaxic information, TMS coils can be positioned over the scalp site overlying a selected target cortical region in a given patient. These systems, based on infrared cameras, require a calibration at the beginning of each session to associate reference sites in the “native” head space of a given patient with those labeled on his/her MRI. Some systems model the distribution of electrical currents (E–F) under and around the TMS coil center. Moreover, the cortical target can be estimated and visualized in real time on a 3D rendering of each individual’s MRI volume. Neuronavigation systems can also record the position of the center of the coil ( $x$ ,  $y$ ,  $z$ , and orientation and tangent) at the time of each TMS pulse (F), the Euclidian distance shift (in mm) between the coil center and the region selected as target, and display such metrics in real time through a computer screen to the experimenter in charge of TMS, so that he/she can correct and optimize targeting precision on a trial by trial basis. Neuronavigation systems can also feed coil location data to a computer-controlled stimulation robots holding the TMS coil allowing the compensation of head movements and keeping targeting accurate AG: angular gyrus; FEF: frontal eye fields; SMG: supramarginal gyrus.

regions’ contributions to specific behaviors; (3) Coupled to brain mapping technologies (such as EEG, MEG or fMRI) to probe causally the anatomical and functional interactions between brain regions at rest or during their engagement in a task; (4) To document the level and extent of plastic properties across brain sites and networks in healthy participants or patients and their potential to drive adaptive cognitive and behavioral/clinical change.

As a *diagnostic* tool in neurological and psychiatric domains, TMS applications have been proven useful to: (2) Probe, particularly in motor systems, an estimate the level of intra-hemispheric and inter-hemispheric and cortico-spinal connectivity following brain lesions; (3) Identify biomarkers of disease severity or prognosis based on alterations of excitability at the local or at the network level mainly in motor and visual systems.

Last but not least, TMS regimes are increasingly being used in *therapeutic* applications in neurology, psychiatry and rehabilitation medicine, to: (1) Engage in focal or widespread brain damage plasticity mechanisms able to drive either remapping of lost functions in lesion spared regions, (2) Drive or facilitate compensatory processes, and (3) Entrain or restore either adequate excitability levels, local coding processes and functional connectivity patterns, which prove adaptive for the recovery of function.

### 3. Basic component description of TMS equipment

TMS equipment is made of (1) a stimulation coil containing the loops of copper wire to generate the magnetic field (Fig. 1C); (2) a central unit to set up the amount of current and synchronize its release at a given time (Fig. 1D); and (3) a group of capacitors to accumulate high loads of electric charge drawn from power supply lines (Fig. 1D). When a pulse is triggered, an electrical switch is activated and a given amount of charge (determined as a percentage of maximum stimulator output) stored in the capacitors is sent to the coil, circulates through the wire loops to produce the magnetic field. Thanks to a computer interface, it is possible to set the different stimulation parameters, namely *time course of events* when TMS occurs with regard to a trigger signal; *frequency* measured in Hertz, i.e. TMS stimuli per second; *intensity* usually indicated as percentage of maximum stimulator output; and in some equipment current level or density of induced charge in  $\text{mV}/\text{m}^2$  (Wagner et al., 2007b). The electrical current circulating at high speed in the stimulation coil’s wire loops produces with each pulse some abrupt contraction of conducting wire thus generating high-pitched, dry and brief sound – so-called click – as well as slight deformation of the coil plastic case surface. Depending on intensity level, the loops diffuse heat over time, which progressively increases coil temperature.

Stimulation coils are manufactured from different materials in

several sizes, shapes, and designs (Aglieo et al., 2002; Epstein and Davey, 2002; Hsu and Durand, 2001; Onuki et al., 1998; Ren et al., 1995; Roth et al., 2007; Thielscher and Kammer, 2002; Xu et al., 2005) (Fig. 1C). These features determine the magnetic field penetration and distribution capabilities (Roth et al., 2007; Salinas et al., 2007), the spatial spread of the magnetic field in the brain (determining to the spatial resolution of its effects or its ability to discriminate between two adjacent cortical locations), the ability to induce weaker or higher intensity intracortical currents, brain area localization (Hsu et al., 2003; Thielscher and Kammer, 2002), and thus potential motor, sensory or behavioral effects (Thickbroom et al., 1998). For example, flat circular coils are made with single high-density circular wire windings covered by a plastic sheath, so that the maximal induced current distributes like a doughnut under its perimeter. Such coils have high penetration power, but as trade-off they lack spatial selectivity ( $> 4\text{--}5\text{ cm}^2$ ), unless only the edge of the coil is used as stimulation surface (around  $1.2\text{--}1.5\text{ cm}^2$ ) (Amassian et al., 1991). Figure-of-eight coils – also referred to as double or butterfly shaped coils – are made of two side-by-side round coils having each a diameter of 25–70 mm, so that the electrical field under their junction summates thus ensuring a more focal ( $1.5\text{--}2\text{ cm}^2$ ) but also weaker magnetic field (Thielscher and Kammer, 2004). Special bell-shaped large figure-of-eight coils, i.e. with laterally curved loops, have also been designed to reach deep cortical regions, such as the portion of the motor strip containing motor representation of ankle and foot muscles (Pascual-Leone et al., 2001). Finally, H-shaped coils have been developed allowing as bell-shaped coils to stimulate deep brain areas (Levkovitz et al., 2007; Roth et al., 2007) (Fig. 1C).

In general, the smaller the coil (i.e. wire loop size) the more spatially selective but the less penetrating the induced magnetic field. Small coils overheat faster when used to deliver repetitive pulses for long periods of time so that they more often need to be cooled down or replaced. Special air-, water- or oil-cooled coils have been produced to overcome such overheating problems, particularly for therapeutic applications of TMS requiring continuing and long periods of time (Pascual-Leone et al., 2001).

A crucial issue for the correct use of TMS is the accuracy of coil placement on a given region of the scalp providing the tangential (hence shortest path, with the smallest angle) for the magnetic field penetration profile, to reach crossing the skull, a given cortical target. Generally, to correctly position the coil on the scalp area overlying a given cortical site, it is recommended to use online stereotaxic neuro-navigation systems (Fig. 2). These systems have been developed to be capable in real time to render and track the *online* visualization of the position of the TMS coil on a 3D reconstruction of each individual participant MRI head-brain volume (Fig. 2). They allow the targeting of specific cortical regions of the cortex according to either macroscopically visible/standardized anatomical or functional landmarks are used to target specific regions of the cortex. Functional landmarks can be determined as the regions producing a measurable physiological response to single-pulse TMS, for instance muscle activation (primary motor cortex, M1), the perception of static (generally on primary visual cortex, V1-V3) or moving (region V5/MT) flashing lights known as phosphenes or as the area showing significant hemodynamic BOLD activation in task-evoked fMRI studies. Anatomical regions can also be characterized using approximations based on fixed landmarks (specific distance relative to V1 or M1), or on the relation with a region easily identified functionally (M1 or V1-V3). An alternative option is to place the coil according to the 10–20 system used to place EEG electrodes (Herwig et al., 2003).

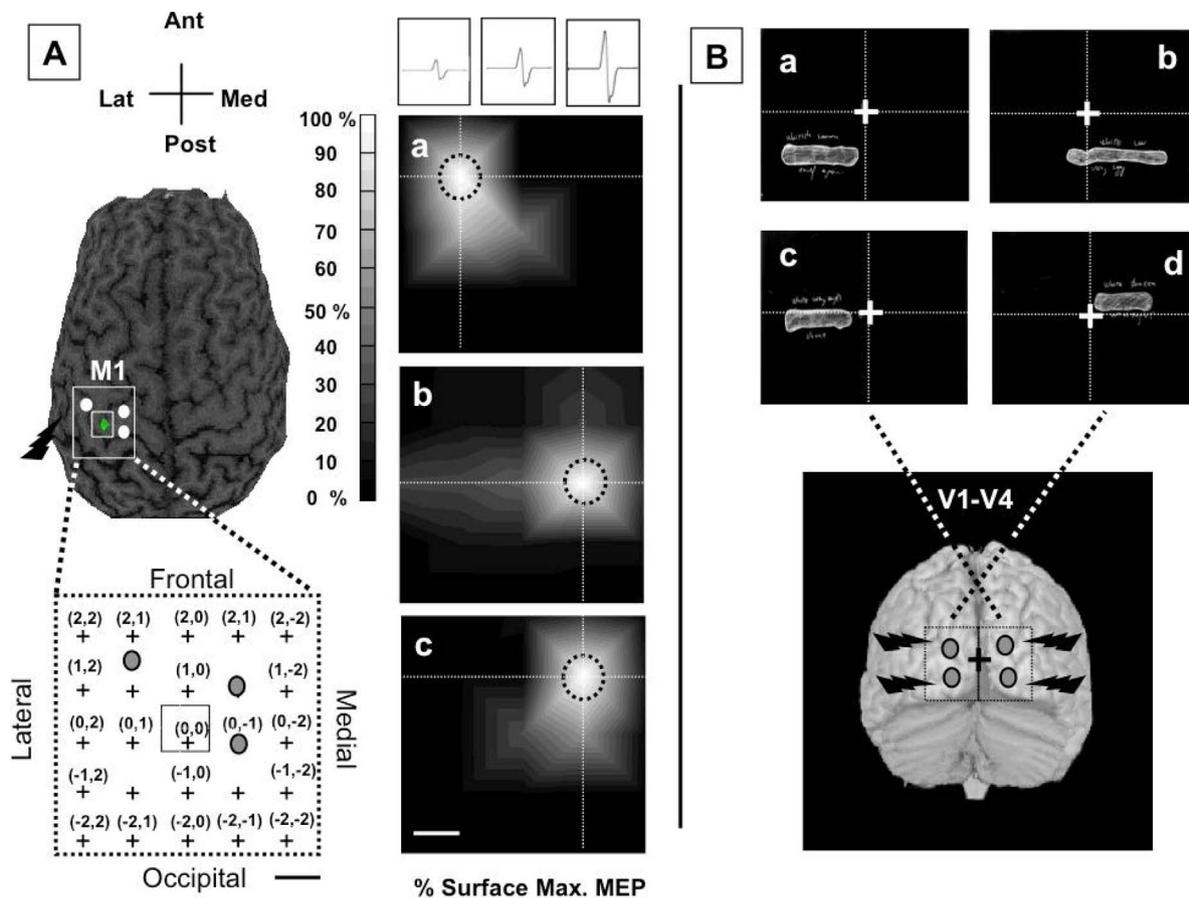
#### 4. Safety guidelines for TMS use in basic and clinical studies in neuroscience

TMS has been used worldwide in an exponentially growing number of laboratories of cognitive and clinical neuroscience for the last 31

years. Experience accrued during recruitment of large cohorts of participants in experimental research has allowed the identification of a series of TMS-induced adverse effects (Machii et al., 2006; Poreisz et al., 2007; Wassermann, 1998). To avoid these unwanted effects in future research, safety guidelines and precautions were reviewed at a consensus conference at *National Institutes of Health* (NIH) in June 1996 and endorsed by the *International Society for Transcranial Stimulation* (ISTS), the *International Federation for Clinical Neurophysiology* (IFCN), and *Food and Drug Administration* (FDA) (Wassermann, 1998). These recommendations were reexamined through the lens of new applications and new stimulation parameters by Rossi and colleagues (Rossi et al., 2009) and are in brief the following:

- 1) The only absolute contraindication to the use of TMS is the presence of metallic and or ferromagnetic material in contact to the discharging coil (such as pacemaker or cochlear implants). In these cases, the risk is to induce heat up, mobilize such material and damage or cause their dysfunction.
- 2) Conditions of increased risk of inducing epileptic seizure are:
  - a. Related to the stimulation protocol:
    - i. Any “new paradigm” (i.e. one which is not a classical method of rTMS at high/low frequency using a flat figure-of-eight coil and biphasic pulse waveform), including pre-conditioning (i.e. priming) protocols, TMS applied on more than one scalp region, and prolonged protocols of paired associative stimulation (PAS) belong to this category.
    - ii. Any protocol of conventional high-frequency rTMS with stimulation parameters (intensity, frequency, train length or between-train duration) exceeding safety limits known and updated according to Rossi et al. (2009).
  - b. Related to patient’s condition or disease:
    - i. Personal history of epilepsy (untreated patients with one or several past episodes of seizure), or patients under pharmacological treatment.
    - ii. Cerebral damage of any etiology (stroke, traumatic brain injury, tumor, infection, metabolic disease) including without history of seizure and anticonvulsant medication.
    - iii. Administration of drugs, which potentially reduce epileptic threshold, without concomitant administration of anticonvulsant medication potentially protecting from epileptic seizures.
    - iv. Deprivation of sleep, alcoholism.
- 3) Other conditions of risk or of uncertain risk are:
  - a. Related to healthy participant/patient’s condition:
    - i. Implanted cerebral electrodes (for ECoG, intracranial or deep-brain stimulation).
    - ii. Pregnancy.
    - iii. Severe or recent heart disease.
- 4) Minimal risk: none of previous conditions and TMS protocol with single or double pulse or of conventional rTMS with low or high frequency using stimulation parameters (intensity, frequency, train length or between-train duration) in safety limits according to Rossi et al. (2009)

Current safety TMS recommendations are not conceived to dismiss or reduce future responsibilities and increased accessibility to this technology for human populations does not reduce the ethical responsibility governing its uses. As TMS gains in popularity, scientists and clinicians may use it in patients suffering from acute or chronic brain damage or neuropsychiatric symptoms. In all cases TMS benefits have to carefully be weighted with respect to unknown consequences in compromised and unstable neural systems. Whilst prevention means respecting safety recommendations (Rossi et al., 2009), EMG monitoring (Pascual-Leone et al., 1998) or the use of questionnaires such as Transcranial magnetic stimulation Adult Safety Screen (TASS) questionnaire (Keel et al., 2001) are useful assets to prevent TMS related



**Fig. 3.** (A) Mapping of the frontal human cortex obtained with electromyography (EMG) recordings from 3 muscles of the upper right limb: *abductor pollicis brevis* (APB) (a), *flexor carpi radialis* (FCR) (b) and *biceps brachii* (BB) (c), in response to TMS over the primary motor cortex (M1) of the left hemisphere in a healthy participant. The grid is mapped on a 3D reconstruction of an MRI brain volume employed by a frameless stereotaxic neuronavigation system to ensure accurate targeting. The 3 grey points shown in the grid correspond to the M1 hot spot, from which motor evoked potentials (MEP) for hand (APB), forearm (FCR) and arm (BB) muscles were respectively evoked. For the mapping procedure, a grid of sites are labeled around the motor hot spot, distanced 1–2 cm (depending on the spatial resolution aimed for the mapping), on a lycra swim cap worn by the participant. Single pulse TMS is then delivered 10–15 times on each point at 110–120% of the motor threshold. The amplitude of the evoked MEP is averaged across samples, for each grid point and represented as percent of maximal map intensity, providing a normalized map of spatial distribution. This method is used to estimate changes in cortical primary motor representations associated to specific muscles or muscle synergies. (B) Phosphene percepts induced by single TMS pulses delivered in different regions of the occipital pole, perceived and drawn by a representative participant. Phosphene drawings correspond to percepts reported by the participant when a 70 mm “butterfly” TMS coil center was located either 1 cm right (a & c) or left (b & d) from the inion, along the occipital pole midline. These subjective measurements can be used to characterize a map of the retinotopic organization of the primary visual cortex (V1–V3) in specific participants and identify changes with interventions such as attentional orienting in space, visual perception and training, or the transient impact of TMS patterns delivered to occipital and non-occipital regions.

undesirable side-effects.

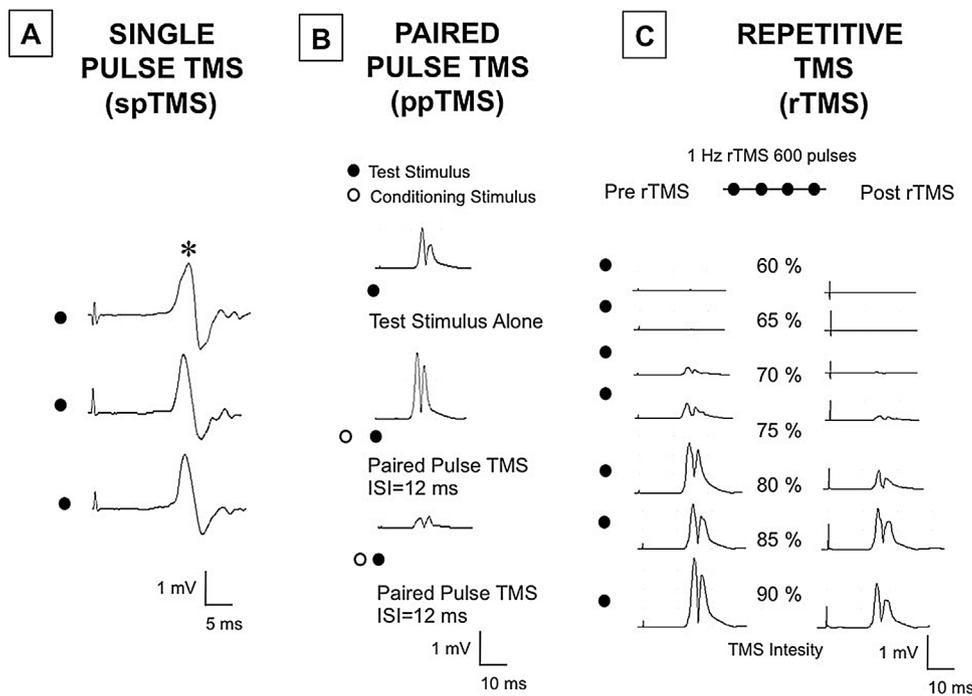
In pediatric populations, a systematic review of the literature of TMS safety in children by Allen et al. (2017) argued that the risk from TMS in children would be similar to that reported in adults recommending the consideration of the adult safety guidelines also in these populations. However, being long term monitoring of possible late effects in pediatric populations particularly critical and the available knowledge still scarce demands caution in extending the therapeutic use of TMS to children,

**5. Patterns of TMS: from single-pulse to rhythmic TMS**

The TMS coil can be placed on scalp specific areas following anatomical and functional coordinates. The latter may originate from TMS-evoked activations, motor or visual studies (Ganis et al., 2000; Pascual-Leone et al., 2001) or anatomo-functional correlates according to structural and functional landmarks (Boroojerdi et al., 1999) (Fig. 3). These landmarks are themselves based on previous MRI (Herwig et al., 2001) or fMRI (Sparing et al., 2008) studies using online neuronavigation methods or a scalp-referenced measure (such as the 10–20 EEG system) developed to place and distribute EEG scalp electrodes, which can be grossly associated to anatomical sulcal or gyral landmarks

(Herwig et al., 2003). On motor areas, the coil is generally oriented in a caudal-to-rostral and lateral-to-medial direction, with an angle of 45° with regards to the inter-hemispheric longitudinal fissure. Nonetheless, the ideal rotation angle varies with the neural substrate being targeted, the cortical area and related organization of its neural centers and fascicles. It is crucial to ensure that the coil center is located tangentially to the scalp area overlying the targeted cortical site.

TMS intensity has to be adjusted at a sufficient level to obtain effective current induction in neural tissue at such location and configuration. In motor and visual cortical areas this can be easily accomplished by adjusting TMS intensity at a level inducing visible muscle activation or a subjective report of phosphene perception (Fig. 3). Normalized measures of intensity such as motor threshold (TMS intensity eliciting a motor evoked potential – MEP – by 50 µV in half, i.e. 50% of the trials, generally 5 out of 10 trials, known as the 50% motor threshold) (Rossini et al., 1994) and phosphene threshold (TMS intensity eliciting a phosphene percept in half, i.e. 50%, of the attempts) are widely used to compare intensity levels across participants or studies. They are considered the simplest biomarkers of individual excitability levels for motor and primary visual areas, respectively. For cortical regions outside motor and visual areas, where no objective and well-localized physiological response can be registered, TMS intensity



low frequency rTMS regime (1 Hz) during 10 min (600 pulses). Note the decrease in the amplitude of the MEPs at different stimulation intensities recorded following the delivery of the 1 Hz rTMS pattern (post-rTMS) as compared to prior to it (Pre-rTMS). mV: millivolts; ms: milliseconds.

has to show an ability to induce significant behavioral changes in performance on a given cognitive task, in which the stimulated cortical area is likely to play a functional role. Different TMS modalities may be generated according to: (1) pulse number and duration, (2) time interval between pulses or pulse trains, and hence (3) interpulse or interburst discharge frequency. These parameters define three main modes of stimulation as follows (Fig. 5).

### 5.1. Single-pulse TMS

Single pulse TMS (sTMS) consists in discharge of single pulses separated by time intervals of at least 4 s (5–8 s to be in a safe zone), so that its individual effects do not sum up over time. As previously mentioned, sTMS induces brief intracortical currents that depolarize neurons and, depending on the impacted region location, they induce effects that can be objectively/subjectively reported, and directly/indirectly quantified such as (1) motor evoked activity in primary motor areas (Fig. 3A and 4A), (2) evoked visual activity or visual percepts, such as phosphenes (Fig. 3B), or (3) short-acting disturbances in cognitive tasks such as changes in performance (Pascual-Leone et al., 2001). The duration of a standard biphasic pulse is around 250–750  $\mu$ s depending on the technology used. After sTMS-induced depolarization, neurons recover rapidly from interference once the refractory period is over (Moliadze et al., 2003) and become ready to fire again.

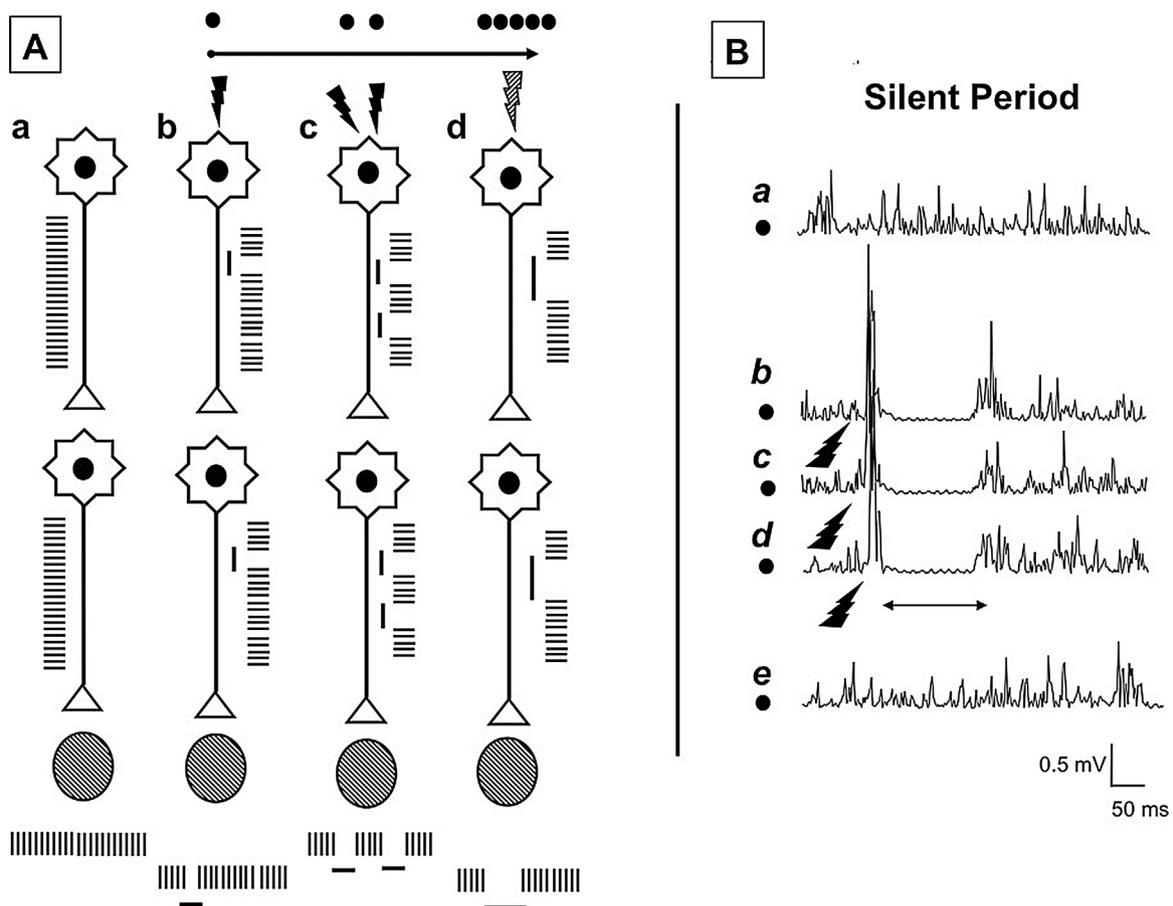
Different kinds of information may be extracted from the effects that follow the delivery of individual TMS pulses, hence serving different purposes. Single pulses can be used for diagnostic purpose to determine the viability and degree of corticospinal conduction disorders (assessing the MEP latency and amplitude) (Chen et al., 2008; Lamy et al., 2009) or in fundamental and clinical research to characterize motor or visual, cortical excitability changes (via the estimation of changes in MEP or phosphene thresholds, through shifts of the response recruitment (dose/response) curves at several TMS intensities). Single pulse TMS has been extensively used to map causally the spatial distribution and somatotopic/retinotopic representations of muscles (Levy et al., 1991) (Fig. 3A) and visual receptor fields (Elkin-Frankston et al., 2011; Fernandez et al., 2002; Fried et al., 2011; Kammer, 1999) (Fig. 3B). The

Fig. 4. The primary motor cortex has been used as the test bench to characterize the impact of different TMS patterns (based on intensity, number of pulses, frequency and intertrain interval and total duration) on local excitability by measuring changes such as the amplitude and the latency of Motor Evoked Potentials (MEPs) evoked by single or double pulses of TMS. The image shows several types of EMG signals recorded on the right Abductor Pollicis Brevis (APB) hand muscle, as evoked by single TMS pulses delivered on the muscle hotspot in the left primary motor cortex. (A) Three consecutive non-rectified (original signals) MEPs induced by single TMS pulses at an intensity of 120% of the motor threshold (MT) interleaved by a 5–10 s periods off-stimulation; Notice the consistency of MEP latency and amplitude across the three samples. (B) Rectified MEPs obtained in the context of a paired pulse TMS study by using a short (inhibitory) or long (facilitatory) interstimulus interval (ISI) between a subthreshold first pulse (conditioning stimulus, CS) delivered at 90% motor threshold, and an ensuing test stimulus (TS) pulse delivered at 120% of the motor threshold hence activating a muscle; Notice that at a short ISIs (1 ms) the amplitude of MEP induced by the TS shows an amplitude lower than that the one yielded by an unconditioned TS delivered alone, whereas the opposite effect is observed when a long ISI (12 ms) is employed between the CS and the TS. (C) Rectified MEPs obtained prior and following the delivery of a

same single pulse strategies may be used to assess changes produced for example by physical activity (Ziemann et al., 2001), light deprivation (Borojerdi et al., 2000), psychoactive drugs (Oliveri and Calvo, 2003; Ziemann, 2004; Ziemann et al., 1998), paralysis or blindness following brain damage (Covey and Walsh, 2000; Kew et al., 1994), or the impact of long trains of TMS known as repetitive TMS (rTMS) (for details see Section 5.3) (Gangitano et al., 2002; Maeda et al., 2000; Pascual-Leone et al., 1994b). As demonstrated in a seminal study performed by Amassian and colleagues, single TMS pulses delivered at different time intervals during the performance of a visual perceptual task can also be used to elucidate the time course of a complex neural process (Amassian et al., 1989).

### 5.2. Double pulse TMS

Double pulse TMS (dTMS) also known as paired pulse TMS (Fig. 4B), consists in the discharge of a test stimulus (TS) preceded by a conditioning stimulus (CS) delayed by an interstimulus interval (ISI). It has been mainly used to assess local primary motor system (M1) intracortical modulatory mechanisms or interregional interactions between two regions, with the M1 or sometimes the primary visual cortex, as the read-out systems. In general, TS intensity is set above individual motor (or phosphene) threshold (approximately from +10% to +30% above 50% motor threshold intensity) to induce sufficient and also consistent output, whereas CS is generally set up below (except some recently developed modalities which use a supraliminal CS). When short ISIs are used (< 7 ms, optimally 1–4 ms), intracortical neurons having been infraliminally influenced by the CS and requiring time to recover depolarization capabilities will not be immediately fully responsive. As a result, a TS produces the activation effect on a limited proportion of neurons resulting into a measurable lower output (in the motor cortex estimated as an MEP of lower amplitude as compared to the one generated by an isolated TS). In contrast for long ISI (> 7 ms up to a maximum of 10–12 ms), CS activates facilitatory intracortical mechanisms, whose outputs can augment the impact of a TS and increase the size of depolarization output with regards to those induced by a TS alone (Moliadze et al., 2005; Nakamura et al., 1997). Extensive



**Fig. 5.** Schematic drawing showing the hypothetical mechanisms subtending interferences induced by *online* TMS (A), and illustration of these phenomenon by means of compound physiological correlates integrating ensembles of neuronal discharges summed up temporally and spatially, as recorded by electromyography (EMG) on the surface of a muscle (B). Under normal conditions (a), neurons convey information encoded in terms of action potential discharge frequency and duration. The indirect action (using intracortical networks with the ability to modulate the excitability of pyramidal units) of single TMS pulses (b) depolarizes the neuron, generating a brief gap of electrical silence, lasting for a few milliseconds, that disappears as neurons emerge from the refractory period during which discharges are suppressed. This brief interference alters the coding of information and its transmission to other units across a synaptic chain, and the message at its end is noised. Burst of several TMS pulses (c, d) multiply the periods of electrical silence, which will be increasingly pronounced and longer-lasting as a function of TMS frequency and number of pulses. Single TMS pulses or short rTMS bursts at a moderate frequency (c) allow a quick recovery of neuronal units, until the next TMS pattern reaches. In contrast, high-frequency TMS (d) and longer TMS bursts make interferences more intense and longer-lasting, impairing dramatically the decoding of information at the output of the system or neuronal chain hence degrading any dependent cognitive process. Silent Period recordings in the cortico-spinal pathway are a prime example of the interference driven by TMS burst on cortical activity (B). The physiological EMG in the Abductor Pollicis Brevis (APB) muscle during voluntary motor activity is illustrated in panel a. Panels b to d show the impact on EMG of 3 single TMS pulses. Note that each pulse generates a stimulation artifact and an MEP, followed by a period of EMG silence due to the interference of descending corticospinal activity *via* the activation of intracortical networks, with the ability to modulate the excitability of descending M1 pyramidal neurons. Indeed, ~150–200 ms thereafter, these units regain normal excitability and firing rate levels while normal baseline EMG activity is recorded again (e), showing that single-pulse TMS does not induce any long-term effect. Silent period recordings demonstrate that single pulse TMS can transiently interfere with activity on a given brain region, hence allowing the study of its specific contribution to the processing of ongoing information.

research using a large variety of short (< 7 ms), intermediate (7–15 ms) and long (50–200 ms) ISI intervals and generally subthreshold CS and suprathreshold TS has revealed in M1 up to 5 intracortical modulatory phenomena: Intracortical facilitation, ICF (10–15 ms ISI), Short interval intracortical inhibition, SICI (1–4 ms ISI), Short interval intracortical facilitation, SICF (1–4 ms, with a suprathreshold CS and a subthreshold TS), long interval intracortical facilitation, LICF (100 ms, ISI), and finally, long interval intracortical inhibition LICI (50–200 ms ISI with a suprathreshold CS).

Paired-pulse measures (Fig. 4B) are always normalized with regards to isolated TS effects to explore inhibitory (short intervals mainly mediated by gamma-aminobutyric acid – GABA – activity) versus excitatory (long intervals mostly mediated by glutamatergic activity) intracortical mechanisms mediated through specific populations of interneurons, with the ability to influence the final output of pyramidal neurons (Di Lazzaro et al., 2006; Lang et al., 2006; Sohn et al., 2001; Ziemann et al., 2002). Indeed, in order to explain these effects (CS enhances TS output in long ISI and inhibit such in short ISI), it has been postulated that across a continuum of ISIs, a CS activate in specific

proportions, different circuits of interneurons (excitatory vs. inhibitory, as a function of their threshold, conduction time and length), hence modulating differentially cortical activity induced by the TS (Ilic et al., 2002).

Importantly, dTMS mechanisms have been well characterized for motor areas (Romero et al., 2002), and in the field of neurology, they have been evaluated as diagnostic biomarkers of abnormal states of low/high excitability after focal or diffuse brain damage (Chen et al., 2008). In other brain regions, such as the visual cortices (Pascual-Leone et al., 2001; Sparing et al., 2008) and non-motor and non-primary visual systems, dTMS has also been suggested to relay on anatomically invariant intracortical modulatory mechanisms and could produce short-term activation/inhibition and briefly disturb cognitive tasks, such as for example the conscious detection/localization visual (Fierro et al., 2006; Koch et al., 2005) or tactile (Oliveri et al., 2000) targets. Nonetheless their use in behavioral interference remains rather rare.

Finally, double pulses may be discharged with variable time intervals on pairs of distinct cerebral sites to determine presence or absence of connectivity and estimate the conduction time between the two

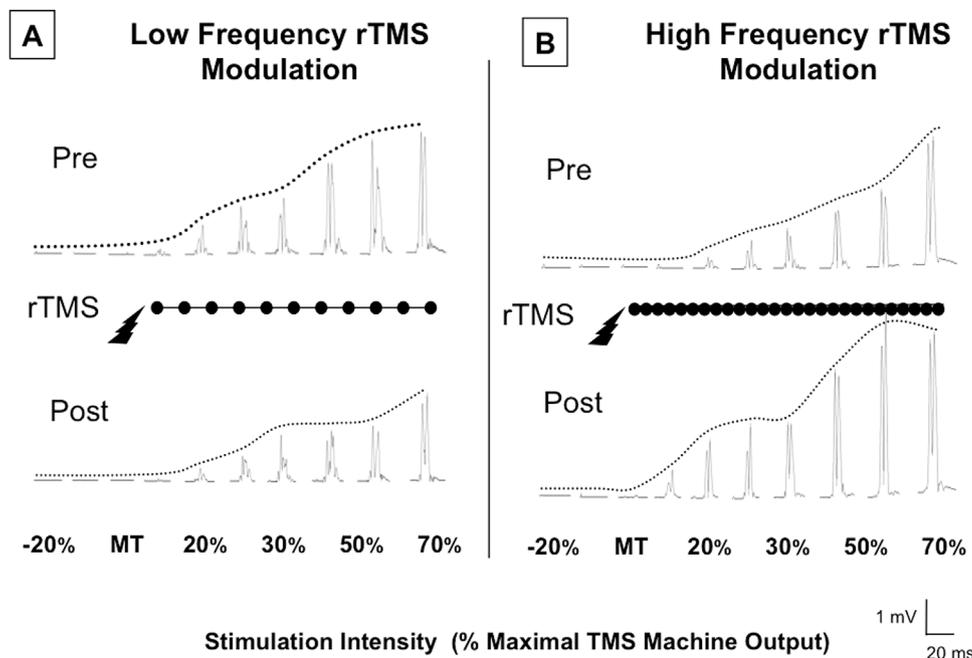


Fig. 6. Lasting modulation of the excitability of the primary motor cortex (M1) using repetitive TMS (rTMS) at either high or low frequency. Such *offline* modulations (also called after-effects) are evidenced by changes in Motor Evoked Potentials (MEP) in response to single-pulse TMS at increasing intensities, expressed in percent of motor threshold (MT) recorded in the First Dorsal Interosseous (FDI) muscle of the right hand. In the figure we show examples tested before and after a rTMS regime, consisting in a long pattern of (A) low (1 Hz) or (B) high (20 Hz) frequency rTMS delivered to the left hemisphere's M1 cortex during 28 min (Gangitano et al., 2002). Note in (A) decreases of MEP amplitude of post-stimulation MEPs, compared to pre-stimulation levels following low frequency rTMS across increasing pulse intensities. In contrast, high frequency rTMS increased MEPs amplitudes (B). These data demonstrate the ability of rTMS to modulate local excitability beyond the duration of the stimulation pattern (*offline* effects or after-effects). Importantly, this impact proved transient and disappeared during the recovery period (not shown in the figure). Changes of neurophysiological activity and behavior during the period immediately following rTMS (post) is often used to establish causal relationships between the stimulated regions and cognitive functions and processes under their command.

regions. These specific modalities of pair pulse tests allow the study of inter-hemispheric inhibitory (IHI) processes using 2 TMS pulses, a CS delivered to the M1 with an ISI of 8–10 ms, in order to modulate via *corpus callosum* the corticospinal output generated by a TS on the contralateral M1. Similarly, pair pulse studies have been applied to close (ipsilateral/contralateral Pre motor cortex to M1, ISI 4–20 ms) or distant areas (Intra parietal sulcus (IPS) to M1, 4–15 ms ISI) of the same or opposite hemispheres to study the timing and modulation direction of the interactions between two distant regions. The distance, direction and functional efficiency of such interactions can be characterized according to the changes that CS on cerebral area “A” (for example, motor or visual) exerts on electrophysiological (amplitude of evoked motor response), sensory (phosphene reportability rates, phosphene threshold or visual target acuity), or behavioral output of cerebral area “B” (Baumer et al., 2006; Pascual-Leone et al., 2001; Silvanto et al., 2005; Silvanto et al., 2009).

### 5.3. Repetitive TMS

Repetitive TMS (rTMS) refers to any combination of more than two pulses delivered with a time interval of 2 s or less (frequency of 0.5–1 Hz) (Figs. 4 C and 6) with an ability to produce different effects than the isolated pulses. This includes delivery of short bursts or trains of 3–4 pulses at high frequency (10–20 Hz, i.e. with a time interval between pulses around 50 ms) and of long periods of stimulation (until 20–30 min) at a fixed frequency, with or without interruption by stimulation-free intervals in between discharges. Simply, taking into account combinations of the most common TMS parameters used to design standard repetitive stimulation patterns (e.g., frequency, duration, number of pulses, number and duration of intervals between pulse trains) a massive number of potential TMS configurations arise. Moreover, given overt differences in the cytoarchitectural, neurochemical and neurophysiological organization across cortical areas or differences in ongoing resting or task activated activity at the time of stimulation, it is risky to assume that the effects of a given combination of parameters would be region-invariant. Given this high dimensional complexity, and in attendance of a more profound understanding of its region-dependent acting mechanisms, the choice of TMS/rTMS parameters is being guided by the accrued peer reviewed published experience informing on efficacy and the safety guidelines considering highly consensual

international criteria (Rossi et al., 2009; Wassermann, 1998) based on regularly published updates (Machii et al., 2006; Poreisz et al., 2007). Repetitive TMS patterns, particularly when delivered in long trains and in consecutive daily sessions have the potential to modulate function long-lastingly, through plastic mechanisms. Repetitive TMS delivered over targeted areas and impacting their associated networks produces three types of effects on cognition and behavior (Fig. 10).

#### 5.3.1. Online TMS effects

Online effects are caused by direct and measurable interference with patterns of ongoing neuronal discharge at the time of stimulation. They likely result from an induction of repeated depolarization events (with their respective refractory periods) in neuronal assemblies paced by the temporal structure of the pulse delivery. Neuronal discharge patterns, hence their coding and physiological rhythms employed for inter-neuronal communication are interfered or eventually degraded and so are their associated cognitive functions, leading to changes in behavioral performance (Fig. 5A). Online TMS interference effects have also been conceptualized as resulting from a local injection of electrical “noise” blurring communication between neurons. In general, functions are more or less impacted as a function of stimulation frequency (Moliadze et al., 2003; Valero-Cabr e et al., 2005); the higher the stimulation frequency the greater the *online* disruption of neural activity.

A TMS motor phenomenon, which illustrates well *online* TMS effects is the so called-silent period (see Fig. 5B). It consists in the suppression of electromyographic (EMG) signals during an ongoing voluntary hand muscle activation, induced by a TMS pulse applied over the primary motor cortex, until the cortico-spinal descending activity, hence EMG activity, recovers back. This phenomenon which provides a measure of cortico-spinal excitability (Pascual-Leone et al., 2001; Wilson et al., 1993; Ziemann et al., 1993), and has been used for diagnostic applications (Chen et al., 2008), epitomizes the ability of TMS patterns to transiently suppress ongoing cortically-and spinally-driven processes during its delivery, until impacted systems recover, and lay at the core of the so called *online* TMS effects that are a convincing proof of causation between the role of the stimulated brain regions and the modulated behavioral functions.

#### 5.3.2. TMS offline effects or after-effects

TMS *offline* effects (or after-effects) can be defined as the lasting

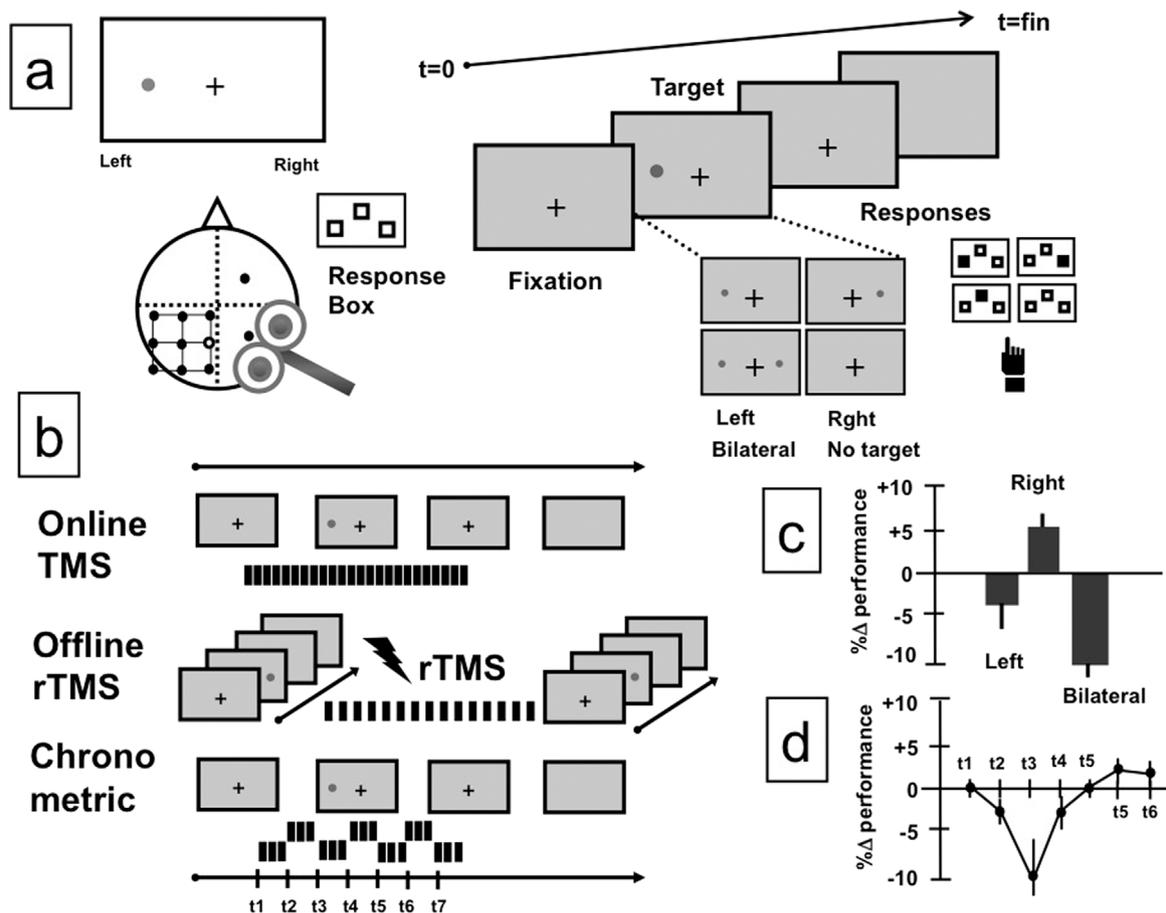
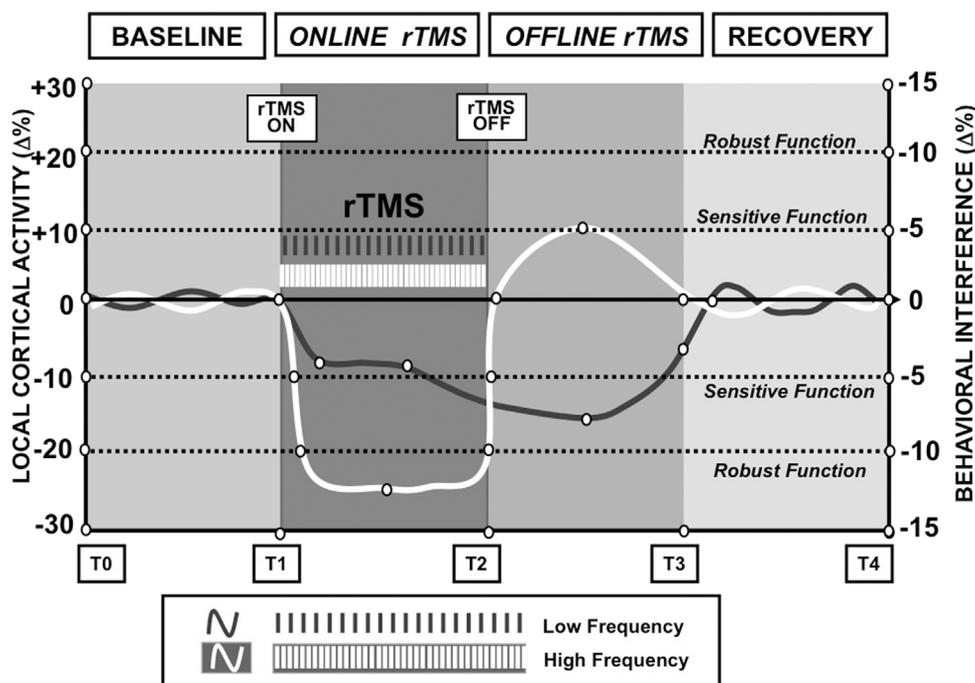


Fig. 7. Metabolic network effects ( $[C]^{14}$  2-deoxyglucose uptake, 2DG) of high-frequency TMS pulses delivered to the left posterior parietal cortex (VP visuo-parietal cortex) in a feline model of non-invasive stimulation combined with high resolution glucose metabolic labeling. Note the reduction of local activity in the stimulated VP cortex (a) in association with similar effects on interconnected cortical sites in primary visual areas (A18, A19), (b) the Splenial Visual Area (SVA) or subcortical regions such as the Pulvinar, the Lateral Posterior Complex of the Posterior Thalamus (P and LP) (not visualized in this figure), and (c) the superficial layers of the superior colliculus (SC) ipsilateral to the stimulation. (d) Note a significant decline in evoked metabolic activity of several cortical and subcortical regions holding rich connections with the VP cortex (also SVA layer 4th neurons and superficial layers of the SC) and an absence of effect on regions which did not belong to the same network (Medial Geniculate Nucleus, MGN, and Lateral Geniculate Nucleus, LGN). Measure bar (a) 2 mm. SS: Suprasylvian Sulcus; SVA: Splenial Visual Area; TMS: Transcranial Magnetic Stimulation; WM: white matter (Valero-Cabr  et al., 2007; Valero-Cabr  et al., 2005).

impact on cerebral processes (assessed in terms of brain activity, cognition or behavior), of a previously delivered pattern of repetitive stimulation. Indeed, consistent evidence points out that following TMS applied in long patterns of individual pulses with a given frequency (of at least 1 Hz, see below for further details), cortical activity remains altered (Allen et al., 2007; Aydin-Abidin et al., 2006; Romero et al., 2002; Valero-Cabr  et al., 2006) for an average period of 30 min post-stimulation (Huber et al., 2007; Thut and Pascual-Leone, 2010; Van Der Werf and Paus, 2006). Nonetheless for some TMS patterns, after-effects can extend up to 60 min post stimulation (Schindler et al., 2008). However, considerable variability on the duration of rTMS after-effects have been emphasized depending on the study details, rTMS parameters and the specific behavioral (task performance, reaction times), hemodynamic and metabolic (fMRI, PET) or electrophysiological (MEPs, EEG, MEG etc.) read out measures employed (Thut and Pascual-Leone, 2010). Therefore, the performance of either, motor, sensory or cognitive tasks (e.g., memory, learning, language, attention, etc.), tested during that period may be altered. However the intensity of this off-line disruption and of its network effects is always weaker than that observed *online* (Aydin-Abidin et al., 2006; Valero-Cabr  et al., 2007; Valero-Cabr  et al., 2006).

Depending on discharge frequency, rTMS may be qualified as slow (low frequency: 1 Hz or lower) or fast (high frequency: > 1 Hz, usually at least equal or above 5 Hz) rTMS (Aydin-Abidin et al., 2006; Siebner and Rothwell, 2003) (Fig. 6). During the period starting after the end of

stimulation trains, patterns of low frequency and continuous stimulation (of at least > 300–900 pulses) (Gerschlagler et al., 2001; Maeda et al., 2000; Thut et al., 2003; Valero-Cabr  et al., 2007) tend to produce sustained inhibition or suppression of excitability, within targeted cortical areas, either weakening their intrinsic level of activity, reducing the efficacy of their outputs, or silencing their contribution to cognitive processes in which they are involved (Chen et al., 1997; Gangitano et al., 2002; Maeda et al., 2000; Romero et al., 2002; Valero-Cabr  et al., 2007). In contrast, high frequency and discontinuous stimulation can produce lasting increase in cortical excitability or activity (Fierro et al., 2005; Gangitano et al., 2002; Maeda et al., 2002; Maeda et al., 2000; Rounis et al., 2005; Valero-Cabr  et al., 2007) (Fig. 8). This is true in the motor cortex, nonetheless specific studies are required to determine whether TMS excitatory/inhibitory properties apply to other cerebral areas and in which direction they may impact the behaviors contributed by the stimulated regions. Some studies have emphasized the importance of stimulation-free intervals between TMS bursts in high frequency stimulation pattern. Indeed, the use protocols of so called patterned TMS (for details see Section 5.4), based on the use of TMS pulse triplets delivered at 50 Hz frequency (20 ms inter-pulse interval), repeated at a 5 Hz frequency (200 ms in between triplets), investigators have shown long lasting modulatory effects of corticospinal excitability, whose direction (excitatory or inhibitory) depends on the presence and the duration of the intervals between trains (Franca et al., 2006; Huang et al., 2005; Huang and Rothwell, 2004). Other innovations linked to



function of the robustness of the behavior or cognitive process that we aim to interfere. According to their intrinsic sensitivity, necessary critical mass of neural resources and its remapping properties characterizing a given behavior can be more or less susceptible (hence more or less robust) to be altered by rTMS-driven interfering changes of local activity. Highly robust processes and behaviors will require modifications of activity of higher magnitude than those known to be sensitive and fragile. Moreover, a change of local activity does not necessarily imply that such effects will be visualized as a change in behavior.

combinations of isolated TMS short bursts priming longer lasting rTMS protocols (Fitzgerald et al., 2007; Iyer et al., 2003), the combination of TMS with other cortical neurostimulation methods, for example, transcranial Direct Current Stimulation (tDCS) (Siebner et al., 2004) or the stimulation of afferent peripheral pathways as in Paired Associative Stimulation (PAS) (Russmann et al., 2009) offer promising opportunities.

The use of different rTMS configurations (during or immediately following stimulation) allow researchers to change local activity levels and interfere with the bioelectrical coding developed by intracortical interneurons – by decreasing their signal/noise ratio – of targeted cerebral areas, so that they can study the causal relationship between some interference and a given task. Such an approach has been so-called “virtual lesion” (Pascual-Leone et al., 1999; Pascual-Leone et al., 2000; Walsh and Rushworth, 1999). Despite controversial character of its neurophysiological interpretation (Silvanto and Muggleton, 2008a), this reversible procedure has the merit of comparing the level of cognitive performance measured at baseline prior to TMS to the one present after TMS interventions, once disruptions have ceased and normal cerebral activity has recovered completely. This methodology makes *de facto* any participant his/her own control, minimizing the difficulty related to between-participant variability inherent in independent control group designs.

### 5.3.3. Prolonged effects, long-term effects and therapeutic potential

All hitherto described neuromodulation effects have a rather limited duration, which decays over time and have been estimated to last in the motor cortex around half of the time of the rTMS duration (Fig. 8). However, periodic repetition of stimulation sessions, usually administered with less than 24 h, inducing modulations of cortical activity in a single direction (excitatory or inhibitory), can generate long-term effects (Baumer et al., 2003; Maeda et al., 2002; Maeda et al., 2000) (Fig. 9). This strategy opens the opportunity to induce lasting neuromodulatory effects that may translate into meaningful therapeutic interventions.

Figs. 8 and 9 illustrate long-term effects in multiple sessions of

Fig. 8. Schematic drawing modeling dynamic changes of local brain activity driven by rTMS patterns at either low or high frequency across time. Evidence is based on animal studies combining 1 Hz vs. 20 Hz rTMS stimulation with injections of a glucose-bound metabolic tracing ( $[C]^{14}$  2-deoxyglucose, 2DG) which reveals that the impact of rTMS stimulation is pattern period- and pattern frequency- dependent. Indeed, changes in baseline activity can occur while rTMS patterns are being delivered (*online* rTMS impact) or following its offset (*offline* rTMS effects or after-effects) (Valero-Cabr  et al., 2005; Wagner et al., 2007b). Indeed, repetitive TMS has shown to reduce metabolic activity in the stimulated region while stimulation is being delivered with high frequency (trains of 20 Hz patterns interleaved with stimulation-free inter-train intervals) and also, although to a minor extent, with low frequency stimulation (continuous 1 Hz). In contrast, during the *offline* phase, formerly delivered high frequency rTMS patterns increases metabolic activity in the stimulated region, whereas low frequency rTMS decreases it. Additional data (not included in the figure) strongly suggests that network mediated impact of local rTMS effects on distant areas is strong and significant during the *online* phase and becomes mild or non-existent during the *offline* phase. Online or offline shifts of neural activity shown in this figure can result in behaviorally meaningful changes as a

rTMS. In this example, each of the stimulations generates on-line effects as well as off-line effects on behavioral performance in a given task. Repetition of sessions over a short period of time yields an accumulation in time of changes, depending on what is being measured, in either electrophysiological, metabolic or behavioral phenomena, resulting in magnitude increases of local effects on the target area and its related cerebral network (May et al., 2007; Valero-Cabr  et al., 2008). Based on this principle, the accrual of short-term and low intensity effects during individual sessions of rTMS can engage cortical plasticity mechanism and generate long-lasting changes that offer therapeutic potential.

It has been widely demonstrated that inter-session intervals longer than 24 hours (several days or weeks) are too long to lead to cumulative effects of isolated rTMS interventions (Maeda et al., 2002; Baumer et al., 2003) and most studies investigating plasticity induced by repeated rTMS sessions (Maeda et al., 2000; May et al., 2007; Valero-Cabr  et al., 2008) or therapeutic protocols in mental disorders (Bulteau et al., 2017; Dunlop et al., 2016) deliver daily rTMS sessions. However, shorter intervals between sessions (even as short as 10 or 15 minutes for example) hence delivered the same day, can strongly enhance both, the magnitude of rTMS effects and their duration, leading to longer-term effects lasting for up to several hours post-stimulation (Goldsworthy et al., 2012; Nyffeler et al., 2006).

### 5.4. Theta burst stimulation

Theta burst stimulation (TBS) is a patterned form of rTMS. Huang et al. (Huang et al., 2005) were the first to describe this very rapid method of conditioning the human motor cortex that yield controllable modulatory effects on motor cortical and corticospinal excitability physiology and impact on several types of behavior. In contrast with traditional rTMS patterns (such as 5 Hz, 1 Hz or 20 Hz) that induce significant but weak, variable and short-lasting modulatory effects on motor and non motor cortical excitability and behaviors, TBS appears to induce longer-lasting and powerful effects after a short period of 20–190 secs of stimulation. As such, it has been suggested to be a noninvasive method in humans comparable to long-term potentiation

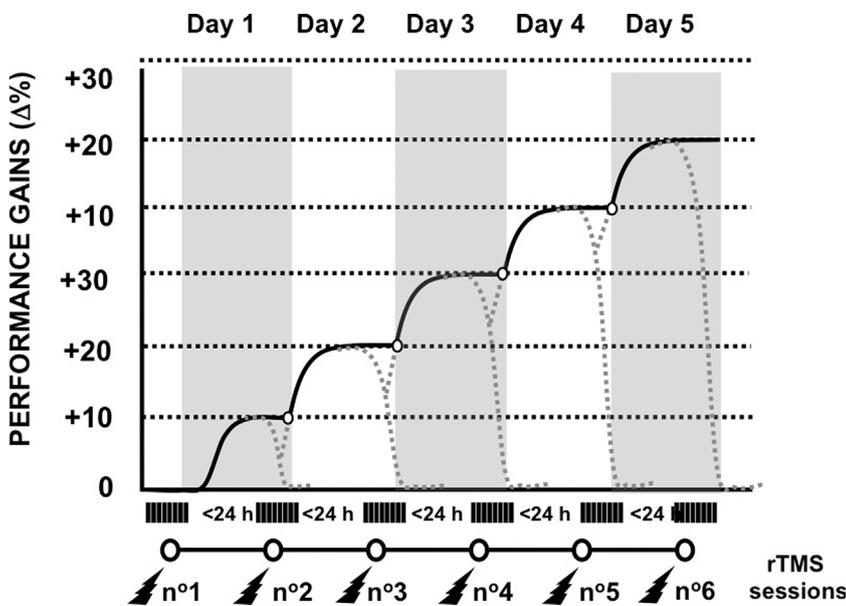


Fig. 9. Diagram showing how individual rTMS sessions delivered daily may result in longer lasting effects, which could prove useful therapeutically. Each of the individual stimulation sessions delivered periodically on the same cortical region generate *online* and *offline* effects on local cortical activity which can impact behavioral performance in the targeted area. Repetition over a short period of time (< 24 h between 2 consecutive rTMS sessions) results in the accrual of local functional modifications (electrophysiological, metabolic, hence eventually behavioral) over time, increasing the magnitude of local direct effects for rTMS. Based on such principles, short-term low-intensity effects on individual rTMS can produce long-term modulation of local activity which could prove therapeutically benefiting. The short duration, reversibility and non-cumulative effects driven by isolated single pulse/short TMS bursts allow the use of TMS as a causative tool in brain mapping studies. The long duration and the cumulative effects in multiple sessions of repetitive TMS can be of interest for therapeutic purposes (Valero-Cabr e et al., 2008).

in animals' hippocampus (Huang et al., 2005). More recently, TBS administered in three bursts of pulses delivered at 50 Hz and repeated every 200 ms (i.e. 5 Hz), has been suggested to be equal or superior for the treatment of depression than sham stimulation or classical high frequency rTMS patterns (Bulteau et al., 2017; Chung et al., 2015). However, recent studies have also noted substantial inter- and intra-individual variability of TBS effects, and further studies are needed before broad adoption or dismissal of conventional rTMS can be established.

### 5.5. Rhythmic TMS

It is well known that cognitive functions in humans involving large widespread cerebral networks are often subtended by oscillatory phenomena, which can be captured in humans by means of electroencephalography (EEG) and magnetoencephalography (MEG). However, the use of non-invasive stimulation methods, and notably TMS to explore causal relationships between oscillatory patterns and cognitive process has been developed only very recently. In 2009, it was first shown that single pulses of TMS enhanced the power of the so-called 'natural' (or predominant) frequency characterizing a given area (Rosanova et al., 2009), likely by resetting the phase of individual cortical oscillators and aligning their temporal dynamics. A pioneer study by Thut et al. (2011b) using concurrent TMS-EEG, demonstrated the ability of a periodic electromagnetic force, generated this time by series of regularly spaced TMS pulses (delivered at ~10 Hz to the posterior parietal cortex) to enhance the power of local brain oscillations, at the frequency dictated by the stimulating source. This phenomenon was proven in absence of any behavioral task and was hypothesized to be caused by a progressive alignment across the TMS bursts of phase of cortical oscillators (i.e. local circuits), which did not appear when irregular TMS patterns of the same duration and number of pulses were delivered. This has been referred to as oscillatory entrainment (Fig. 14C).

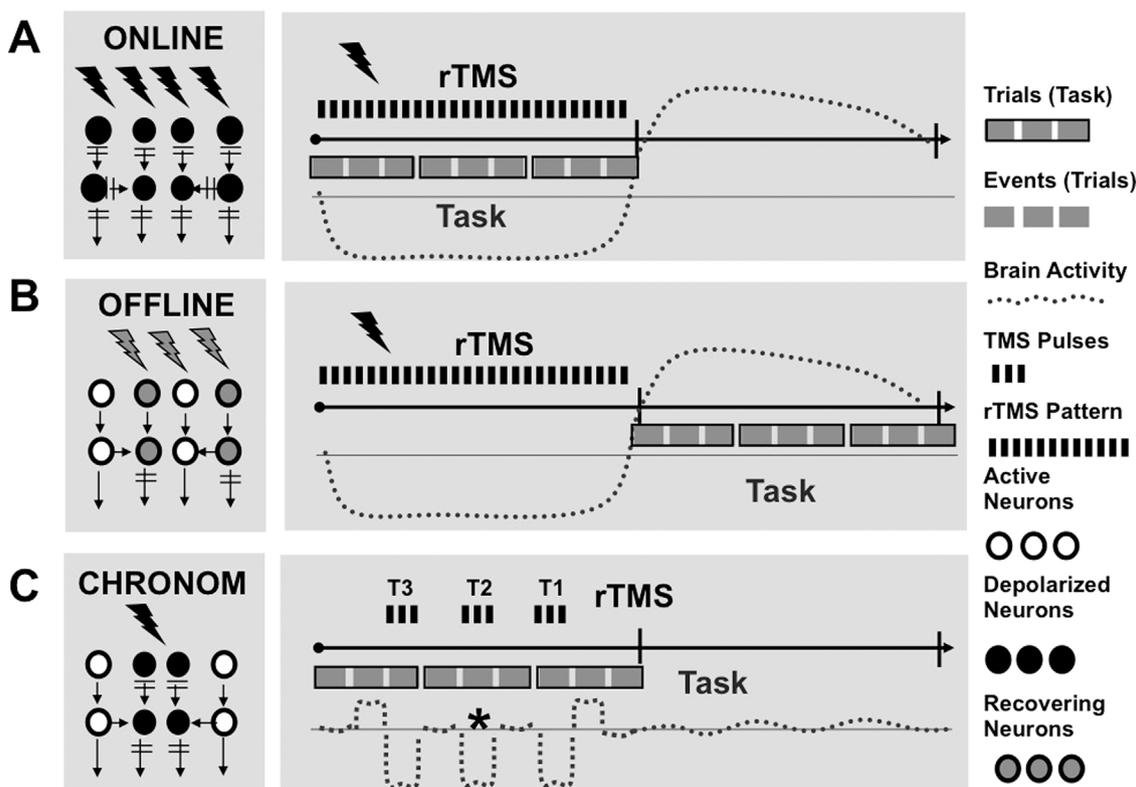
The same year, Romei et al. (2011) combined rhythmic TMS stimulation to the evaluation of a cognitive task and showed that TMS patterns at theta vs. beta rhythmic TMS frequencies were associated to conscious perception dominated by either global or local features, respectively. For occipital and posterior parietal alpha activity, levels of entrainment can be particularly boosted if single pulses or alpha bursts are delivered in phase with ongoing natural oscillations. More recent work in the field of attention inspired by correlational evidence in monkeys relating *high-beta* oscillatory activity in the right frontal eye

fields (FEF) with the endogenous allocation spatial attention, has causally demonstrated that 30 Hz rhythmic TMS patterns but not equivalent irregular TMS bursts increases conscious visual sensitivity (Chanes et al., 2013) or shifts the visual contrast sensitivity function (Quentin et al., 2015). Importantly, these effects have been correlated to indexes of structural white matter connectivity linking right frontal and posterior parietal locations, suggesting that local entrainment of frequency specific oscillations is distributed across networks and enhances inter-regional synchrony (Quentin et al., 2015; Quentin et al., 2016).

Among many others, these studies inaugurate new uses of either regular or irregular short bursts of active TMS aiming at establishing causal relations between cortical locations and their associated networks, oscillation frequencies and specific cognitive contributions (Thut and Miniussi, 2009; Thut et al., 2011a).

### 5.6. Multicoil TMS

In addition to the different kinds of stimulation pattern listed above, TMS can be delivered simultaneously with multiple coils to several brain regions to study interregional connectivity. Indeed, as already mentioned, for dTMS or paired-pulse protocols, conditioning and test pulses can be applied on two distinct brain regions to probe the existence of a link or an interaction between the two stimulated sites. Multicoil paired-pulse protocols have been proven instrumental to dissect connections, and determine the timing of interregional; interactions involved in the *top-down* control of motor decisions (Neubert et al., 2010), the *top-down* influence of frontal regions on the excitability of extrastriate visual areas (Silvanto et al., 2006) or to probe the impact of local *feedback* projections between extrastriate and primary visual occipital regions (Pascual-Leone and Walsh, 2001). Multicoil paired-pulse protocols also have enabled the manipulation of inter-regional connectivity, presumably through Hebbian-like plasticity mechanisms (Buch et al., 2011; Johnen et al., 2015). Even, more sophisticated approaches have used multiple TMS coils to simultaneously deliver frequency specific rTMS patterns to two cortical locations with the aim to modulate oscillatory synchronization between these regions (Plewnia et al., 2008). Finally daring even further, three TMS coil protocols have enabled the simultaneous manipulation of cortical excitability in one brain region while probing connectivity between two remaining sites (Davare et al., 2010; Silvanto et al., 2009).



**Fig. 10.** Study designs using TMS can be classified in three main groups, *online*, *offline* and *chronometric* studies. Online TMS designs use either single pulses or short stimulation burst at high frequency to interfere with the contributions of the targeted area in the processing of a given behavior. TMS stimulation depolarizes and keeps in refractory state a significant number of neurons, which during short lapses of time are unable to contribute their processing. The impact of online TMS has been also conceptualized as resulting from an addition of electrical interfering “noise”. Changes in performance are tested by having participants carry out a task while rTMS pulses are being delivered and comparing the trial-by-trial impact of active TMS to sham TMS (or active stimulation in a control site). Such designs provide strong interference effects. Nonetheless, participants can be sensitive to strong distractions posed by the TMS clicking noise and scalp tapping sensations, which need to be controlled for. Offline TMS designs take advantage of the transiently altered firing hence coding properties suffered by neurons within the targeted region to test changes in behavioral performance following the end of the stimulation patterns. The effects of active vs. sham or active stimulation are compared across. This design generates weaker local and distant network effects but minimizes the distracting effects on task performance produced by the clicking noise and tapping sensation associated to TMS stimulation. Chronometric studies are a subgroup of online studies in which single pulses or brief TMS bursts (of up to 3–4 pulses at a frequency between 10–50 Hz depending on the required temporal resolution) are delivered during specific time windows in which one hypothesizes a given area might contribute to a behavior. By comparing the impact on performance of delivering pulses in different temporal windows one can dissect out causally the temporal dynamics of such contributions.

## 6. TMS study models designs and paradigms in physiological and pathological studies

TMS studies generally follow a common overarching design: a set of measures (cognitive task, motor or visual excitability or any other correlate of neural activity) is compared with or without the impact of TMS-induced interference effects applied to a given cortical area. Considering the reversible nature of rTMS effects on the TMS targeted region and its associated network, the same set of measures performed at baseline, under TMS before or after stimulation, and after recovery may be statistically compared in classical pre-post and recovery (A-B-A configuration) designs. The same population of participants becomes its own reference population, so that potential bias related to between-participant variability when comparing to independent control groups is limited or null. However, intra-individual, test-retest variability is essential to consider and needs further study. Three main types of TMS studies are used to determine causal relationships between targeted cortical areas and cognitive tasks or measurable physiological signals (Robertson et al., 2003) (Fig. 10).

A demonstrative example of a TMS study using the three modalities, on-line, off-line and chronometric (Fig. 10), is presented in Fig. 11. Let us consider that the goal is to study the cerebral areas causally involved in a detection and localization task in which the target is presented in the left or right visual field unilaterally or bilaterally. TMS coil is applied over the right Intraparietal Sulcus (IPS) on the posterior parietal human cortex (Fig. 11A). There exist three possible study designs

(Fig. 11B). In the on-line study (Fig. 11B-Up), high-frequency pulses are delivered on the area at each trial, in a continuous way in the period preceding and following target presentation. In the off-line study (Fig. 11B-Middle), participants' performance is assessed on a significant number of trials in the same task immediately before and after TMS. In the chronometric study (Fig. 11B-Down, C, D), single pulses or short trains of rTMS are delivered to a given brain area at distinct time intervals.

### 6.1. On-line studies: with assessment during TMS

A set of behavioral or physiological measures is performed while the participant is simultaneously being stimulated by TMS (Fig. 6B-Up). Stimulation delivered to a specific region interacts with the ongoing neural coding activity engaged by the contribution of the stimulated region to a given task. Usually, short bursts of high-frequency rTMS (discharged at 5–20 Hz) are delivered during the crucial phases of cortical area contribution to the task. For example, transient and reversible signs of motor aphasia may be evoked by stimulating the inferior frontal gyrus (Broca's area) of the left (but not the right) hemisphere using rTMS at high frequency (20–25 Hz) while the participant is invited to perform a naming task (Pascual-Leone et al., 1991). Similarly, rTMS may interfere with visual or tactile perception or localization (Hamilton et al., 2000; Merabet et al., 2004; Pascual-Leone et al., 1994b). Ideally, fully embedded designs should be used. In those, performance levels estimated across trials for active vs. sham TMS

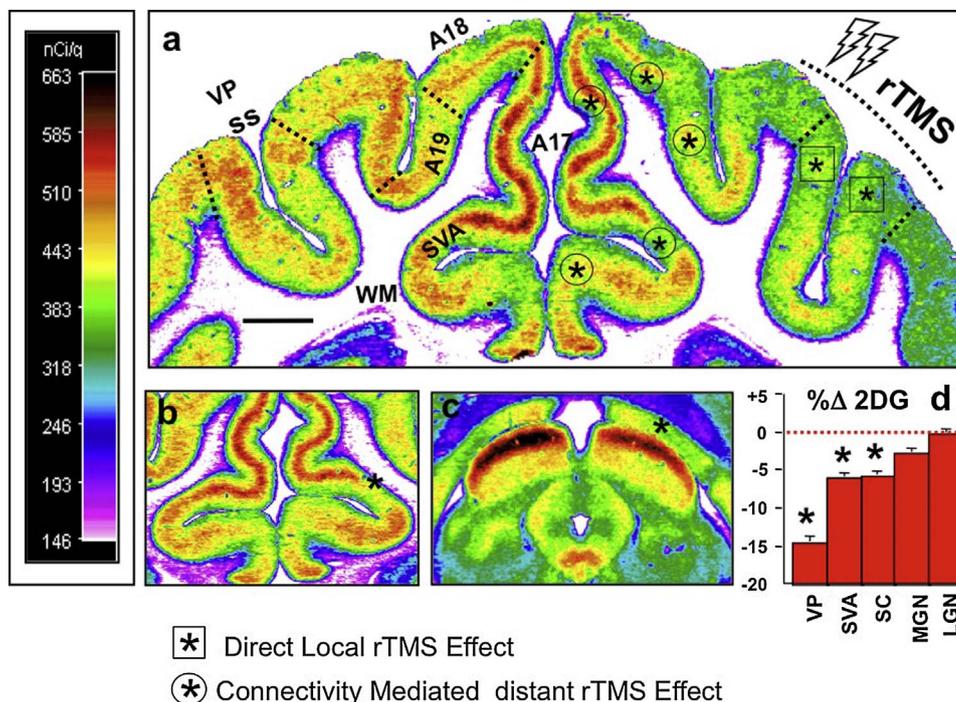


Fig. 11. Illustrative example of the 3 TMS study designs, *online*, *offline* and *chronometric* that can be applied to a given question, by using a specific published examples. Several studies have aimed to investigate if the right Intraparietal Sulcus (IPS) or Frontal Eye Fields (FEF) regions, part of the attentional orienting network, play a causal role in the detection and localization of low visibility targets displayed unilaterally/bilaterally in the left/right visual hemifields. (A) To this end participants perform a computer task in which they are requested, after a variable period of central fixation controlled via an eye tracking system, to indicate the appearance of a round target, by pressing in a response pad a key (right, left or center), signaling of a right, left or bilateral target, respectively. Catch (blank) trials, hence not showing any target, were interleaved in between target trials to estimate participants false alarm rate, hence consistency (Dambeck et al., 2006; Hilgetag et al., 2001; Pascual-Leone et al., 1994b) and perceptual criterion (Chanes et al., 2012; Chanes et al., 2013; Quentin et al., 2015). In all three study types, the TMS coil is positioned over the scalp region overlying the right IPS or FEF region. (B) Three models of TMS studies, *online*, *offline* and *chronometric*, have been used to tackle this research question (B, Top): In *online* TMS designs, high-frequency (20–50 Hz) TMS bursts covering a fixed time window were delivered prior to target onset over the right IPS (Pascual-Leone et al., 1994a) or the FEF region

(Chanes et al., 2013; Quentin et al., 2015). (B, Middle) In *offline* TMS designs, participant's detection/localization performance was evaluated immediately prior and following the delivery of 1 Hz low-frequency TMS pattern known to suppress IPS activity for about ~10–15 min (Hilgetag et al., 2001) to then compare detection/localization under active vs. sham rTMS performed in separate sessions, to avoid carry over effects. (C) Both types of interventions, *online* and *offline* designs have yielded significant modulations of correctly detected/localized targets in the left visual hemifield. (B, bottom). Additionally, chronometric TMS approaches (e.g., (Chanes et al., 2012) can also be used to determine at which timing the right IPS or FEF provides causal contribution to detection/localization performance. To this end, single TMS pulses (or short bursts) can be delivered between 50 and 150 ms prior/following target onset at different time intervals (see t1, t2, t3, t4, t5, t6, t7). This study model yields time-performance curves (D) on which statistics comparing the impact of active vs. sham TMS reveal relevant (t3) vs. non-causally relevant (t1, t2, t4, t5, t6 and t7) time windows.

bursts, interleaved following a random or pseudo-random distribution of trials are compared. Alternatively, one can also compare active online TMS vs. sham TMS (or other active control options, see Section 7) in separate blocks. It is worth remembering that collateral TMS effects related to click noise or tapping sensation on the scalp which temporally coincide with the assessment of cognitive performance must be controlled for. Such study designs are commonly used as the initial approach trying to identify support for causal relationships between cerebral areas and behavioral functions, while admitting biases caused by TMS collateral effects (Dambeck et al., 2006; Hilgetag et al., 2001; Kosslyn et al., 1999; Mottaghy et al., 2000; Mottaghy et al., 2003; Muellbacher et al., 2002; Pascual-Leone et al., 1996; Pascual-Leone et al., 1994b; Thut et al., 2003).

## 6.2. Off-line studies: with assessment before/after TMS

In this TMS modality, physiological or behavioral measures are performed before TMS and during a limited time period following (after effects) the delivery of a long TMS patterns (Fig. 6B-Middle). Ideally the same measures are also recorded during the recovery period to show that sometime after TMS activity modulations wear off and performance effects do return to baseline. Researchers have to keep in mind that TMS interference effects following stimulation may decrease fast often following unpredictable dynamics (varying depending on factors such as TMS parameters, the targeted area, or participant's characteristics). Hence it is necessary to assess participants immediately after the offset of TMS pulses, within a relatively narrow window of time. As TMS is not delivered simultaneously with the behavioral task, it is less critical to control for collateral effects (click and tapping) than in *online* TMS designs. This is true unless TMS collateral effects may generate long-lasting interferences in the task, which are assessed using sham or active stimulation controls. However independent experiments are often required to estimate the potential confound of participant fatigue

(likely degrading performance) or intra-task learning effects (likely increasing performance), particularly if assessment sessions are long and behavioral paradigms challenging.

## 6.3. Chronometric studies: a particular case of studies with assessment during TMS

In this design, we take advantage of the excellent temporal resolution of single pulses (~1 ms) or short TMS bursts to dissect the temporal course of a given task and determine the exact time at which the contribution of a given area becomes causally critical (Fig. 6B-Down, C, D). To achieve this goal, a set of single pulses or trains of pulses at high frequency of short duration are delivered at different time windows, preceding or following a given event (e.g., visual stimulus presentation or motor command execution order). Only active TMS pulses delivered at precise crucial time intervals (so-called temporal windows) for the hypothetical contribution of selected cerebral site to a given task will interfere with performance. Such contribution is unveiled by a higher error rate and/or longer reaction times, as compared to time intervals which did not significantly impact performance. Temporal windows at which TMS fails to show an impact on task performance serve as embedded control conditions of TMS collateral effects and of the task, given that the same brain area showing causal involvement in the task is receiving TMS pulses of identical intensity, simply not at non-relevant time intervals (Beckers and Homberg, 1991; Chambers et al., 2004; Juan and Walsh, 2003; Mottaghy et al., 2003; Porro et al., 2007; Sack et al., 2005; Walsh and Pascual-Leone, 2003). This is true unless TMS collateral effects (clicking noise, tapping sensation) could be suspected to interfere with the task only in the time windows for which TMS is effective. If this is likely the case, then the use of sham TMS pulses is highly recommended.

## 7. Control conditions: a crucial aspect of TMS experimental studies

TMS generates a brief but intense clicking noise, capable to activate the auditory system through air and bone transmission, even if earplugs or headphones are used (Siebner et al., 1999). TMS also generates a scalp tapping sensation where a magnetic pulse is delivered. These two phenomena are caused by the shock of copper wire loops between them and against the plastic casing of the coil, in response to passing high intensity and short duration electrical currents to generate the magnetic pulse. These auditory and tactile sensory effects have to be controlled, particularly when they are likely to distract participants' attention and impact performance during online TMS designs. They may also simply interfere the activity of the cerebral networks, which are being probed causally, or impact task execution through sensory interference/facilitation. Moreover TMS pulses can produce annoying electrical interferences with electrical devices used either to present behavioral tasks (screens) or measures of nerve, muscle (EMG) and cortical (EEG, fMRI) activity. This challenging issue has been dealt to by electrically isolating devices and recording units, using wide-range pre-amplifiers, removing TMS artifacts and interpolating signals or eventually decoupling by a few milliseconds, stimulation and recordings. Finally for long trains of rTMS, stimulation coils may heat up and increase scalp temperature (34–37 °C), bothering participants and often requiring a coil change in the middle of the experiment. Nonetheless, the development of air-, water- or oil-cooled rTMS coils able to keep temperature low, allow long stimulation rTMS durations and has limited the impact of this problem.

The following control conditions may be applied to control for TMS potential collateral effects mentioned above (Robertson et al., 2003).

### 7.1. Control condition based on the use sham or placebo TMS

The same experiment is conducted under placebo TMS, by using commercially available sham TMS coils (Ruohonen et al., 2000), or by means of a standard coil with one of its sides placed perpendicularly (at 90°) to the surface of the skull (Lisanby et al., 2001) so that the magnetic field emitted by the plane surface is discharged outside of the skull (Basso et al., 2006; Hilgetag et al., 2001; Kosslyn et al., 1999; Thut et al., 2005; Valero-Cabré et al., 2006). Nonetheless, some studies have warned on weak effects generated by active TMS pulses delivered in the sham TMS configuration indicated above particularly when coil angulation is not well taken care of. Fortunately, in spite of their high price, the quality of sham coils mimicking clicking and tapping sensations has significantly been ameliorated in the last decade improving the quality of placebo control conditions and better ensuring participants' blinding (Loo et al., 2000; Rossi et al., 2007; Sommer et al., 2006).

### 7.2. Control condition based on a behavioral dissociation

This method consists in demonstrating the task-, behavior- or cognitive process specificity of a TMS intervention on a given cortical area. In the control condition, the exact same stimulation parameters delivered on the same area show not being able to elicit changes over an alternative behavioral task of equivalent difficulty. The limitation of this method is the difficulty to identify so called control tasks and titrate their difficulty level (as indexed by performance levels without TMS or under sham TMS) so that they are potentially equally sensitive to interference by active TMS as the original task did.

### 7.3. Control condition based on stimulating an alternative cortical site

This control method is based on evaluating the impact of stimulating a second area, which is distant by at least 1.5–2 cm (i.e. the distance corresponding to the spatial resolution of TMS in the human brain under standard stimulation conditions) from the region causally

involved in the processing of a given task. TMS is applied to this control area in the same conditions and using the same parameters than those set for the originally targeted area. Such an intervention should not yield any significant effect, or if any least of similar magnitude, on the same behavioral or physiological measures as compared to the one that initially produced measurable impact (Chambers et al., 2004; Gobel et al., 2001). In general, it is recommended to identify as control site, a region, we have no reasons to believe that it should contribute to the task. Given that neural excitability may vary between cortical areas depending upon anatomical and neurochemical properties (Borojerd et al., 2002), the difficulty of this approach consists in ensuring that the control cortical area can be efficiently stimulated using the same TMS parameters used for the experimental cortical area. Ideally, a region, which is the closest possible (hence in the same hemisphere) to the one stimulated in the experimental condition, should be chosen. Alternatively the scalp vertex region (corresponding to 10–20 EEG system coordinate Cz) or the homotopic region on the opposite hemisphere is chosen when there is certainty that it does not contribute or it does it in a different spatial domain (visual hemi-field, hemi-space, limb) than the experimental site. However, for right or left lateralized TMS targets, rather than the scalp vertex, it is highly recommended to define active TMS control sites that are equally lateralized from the inter-hemispheric longitudinal fissure, so that equally lateralized clicking and tapping sensations are emulated.

### 7.4. Behavioral double dissociation studies

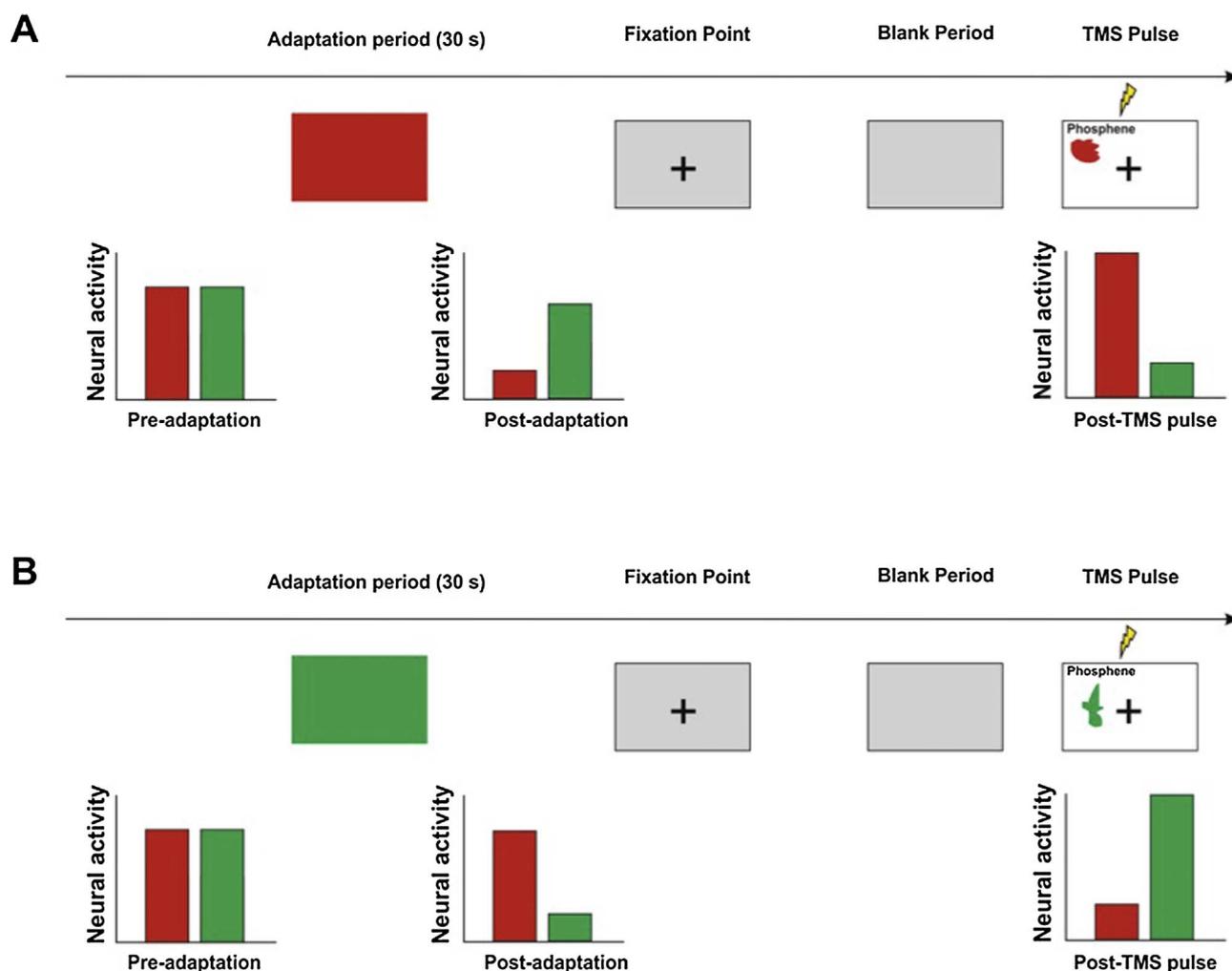
Inspired from double dissociation paradigm of neuropsychology (Shallice, 1988), this method minimizes the weaknesses of the two previously described approaches, by combining them together. The methodology consists in comparing the impact of TMS at identical parameters on two independent cortical areas A and B by means of two distinct but equally difficult behavioral tasks X and Y titrated to be equated in difficulty, which we hypothesize are processed by one but not the other region and vice-versa. When successful, these designs provide evidence that the same TMS intervention has an effect on task X but not on task Y when applied on area A, and on task Y but not X when applied to area B (Ellison et al., 2004; Matthews et al., 2001; Nakamura et al., 2006; Pourtois et al., 2004; Silvanto et al., 2005). This outcome allows rule out the possibility that a lack of effect generated by TMS in a control site region is not simply caused by inefficient stimulation parameters.

## 8. Interindividual variability of TMS outcomes

TMS approaches have demonstrated a capacity to interact with brain function and impact different aspects of human cognition. However, the long list of un-replicated results from small studies and unable to survive larger-scale trials, or the publication of contradicting outcomes with using identical or similar TMS interventions in equivalent populations has grown a lot of frustration in the field. All in all, non-invasive neurostimulation is perceived a technique for which a large level of inter-individual variability exists. A myriad of sources to explaining such variability have been identified. Let's briefly review those that we can account for, eventually control in order to limit their influence, or ultimately accept and use to our advantage.

### 8.1. Influence of age and gender

Demographic factors such as age have been able to explain TMS effect in single and paired pulse techniques (Peinemann et al., 2001) or inter-hemispheric inhibition (Talelli et al., 2008) in older subjects. Nonetheless, the debate on age dependency of rTMS effects in humans, likely mediated *via* changes in NMDA and their role in plasticity receptors remains open. In spite of some occasional observations with rTMS cortico-spinal modulations (Pitcher et al., 2003), gender-related



**Fig. 12.** Graphic summaries of an *online* TMS (A) and an *offline* rTMS (B) study which have shown the influence of white matter connectivity on the distribution of TMS effects across brain networks. In the first example (A), prior to the appearance of a near threshold visual target (A1), participants were stimulated on the right FEF with short rhythmic TMS bursts at 30 Hz compared to a non-frequency specific pattern with the same duration and number of pulses (A.2). Frequency specific but neither sham nor non-frequency specific stimulation improved visually sensitivity ( $d'$ ) for the group. Individual results revealed high levels of variability (A.3). Most importantly, individual levels of TMS driven improvement were predicted by the volume of the 1st branch of superior longitudinal fasciculus (SLF), a white matter tract linking the right FEF with the right IPS, estimated in MRI diffusion imaging studies. (\*\* p value < 0.05 corrected, \* p value < 0.05 uncorrected). Together with (Quentin et al., 2013), this was one of the first results to a growing series of reports (Quentin et al., 2015; Quentin et al., 2016) showing that white matter connectivity influenced the network-based impact of TMS on behavior. In the second example (B), participants performed a task consisting in left or right elbow extension movements to direct a pointer towards the position of a moving target displayed on a computer screen. Low frequency (1 Hz) TMS patterns were delivered over the right anterior Intraparietal Sulcus (IPS) for 15 min to transiently suppress local activity. Following the delivery rTMS pattern, participants experienced higher error rates with movements performed with the right hand (b) that normalized 30 min thereafter. Interestingly, some clusters of the contralateral superior longitudinal fasciculus (SLF II) showed FA values, which significantly predicted the impact of rTMS in terms of error increases with right hand movements (Rodríguez-Herreros et al., 2015). Note that for both cases (A & B) white matter tractography estimates correlated inversely with the behavioral effects driven by online or offline rTMS stimulation suggesting paradoxically that less probable tracts might be better correlated to increases of TMS-driven performance.

differences of TMS effects *via* differences between men and women on plasticity remain also controversial. However, excitability levels following rTMS differed significantly across the menstrual cycle, suggesting an influence of hormonal rhythms in female participants, which could be taken into account at the time of recruitment or documented as covariate.

### 8.2. Influence of scalp-to-cortex distance

Since the electric field generated by the TMS coil drops-off rapidly with distance from the coil, small inter-individual differences in scalp thickness and scalp-to-cortex distance influences the amount of current reaching the cortical tissue, explaining differences in MEP amplitude (Herbsman et al., 2009) or variability in clinical effectiveness for the treatment of depression in adults (Nahas et al., 2001). This source of variability becomes also important when the impact of TMS on two different cortical regions located at different distance from the scalp

surface are compared, assuming that an equivalent level of TMS intensity is delivered on each one. Simple metrics taking into account the decay of TMS intensity with depth and differences in scalp to cortex distance have been developed to estimate the compensatory increases of intensity throughout scalp regions (Stokes et al., 2005).

### 8.3. Influence of individual excitability and neurophysiological traits

The characterization motor and visual excitability markers, overcoming the confounding of scalp-to-cortex distances, such as pair pulse motor studies, demonstrate the high variability of intrinsic excitability across individuals. Such traits, which would be determined by regional neurochemical, cytoarchitectural organization of cortical cell layers, their relative orientation, and their individual/coordinated spontaneous/evoked firing patterns, are not easy to document with current neuroimaging techniques. Their influence can be grossly indexed, through the estimation of 50% excitability thresholds in primary motor

or visual regions, hence limited by stimulating participants at a fixed percentage of their individual thresholds. For non motor/non visual regions researchers have opted either for time consuming strategies based on preliminary testing of TMS cognitive tasks at different intensities, or have been relying on previously published intensity levels effectively employed in the same region using a similar task. Recently however, using a robotic TMS stimulation, standardized atlases indexing cortical excitability estimates of cortical excitability have been developed, by recording TMS evoked cortical potentials with EEG throughout brain regions (Harquel et al., 2016; Harquel et al., 2017).

In rhythmic TMS applications (for details see Section 5.5), increases of power at a specific frequency band by phase resetting or entrainment are optimally achieved when the frequency of the stimulation source matches either the so called ‘natural’ (predominant) frequency of a given region, or the individual maximal oscillation peak (within a frequency band), characteristic for each participant. The advantages of tailoring individually peak entrainment frequencies have been demonstrated for the entrainment of the occipito-parietal alpha peak (Thut et al., 2011b) in spatial attention tasks and central beta peak (Romei et al., 2016) for optimal cortico-spinal resonance effects. This result suggests the specific regional features of ‘natural’ rhythms (frequency band and the peak frequency within) dictated by its cytoarchitecture and neural dynamics of local circuits holds the potential to influence local and distributed resonance induced by rhythmic TMS.

#### 8.4. Influence of white matter connectivity

TMS spreads its local effects across networks, hence the latter have been found influenced by the richness and sign of structural white matter pathways and weakened across synaptic steps (Valero-Cabré et al., 2007; Valero-Cabré et al., 2005; Wagner et al., 2007b). Moreover inter-individual microstructural properties of white matter pathways, estimated using MRI-based diffusion weighted imaging, of dorsal fronto-parietal connectivity relevant for the attentional modulation of visual detection has been found significantly correlated (inversely) with the impact of single pulse of rhythmic TMS patterns on conscious visual behaviors, being identified as one of the most important factors explaining inter-individual variability of TMS outcomes (Quentin et al., 2013; Quentin et al., 2015; Quentin et al., 2016) (Fig. 12A). Such inverse correlations have been recently extended to inferior parieto-frontal circuitry inhibited by offline rTMS delivered prior to execution of motor task (Rodríguez-Herreros et al., 2015) (Fig. 12B), suggesting that white matter connectivity could be used to predict behavioral response to stimulation across participants (Quentin et al., 2015). Using hypothesis-based approaches, correlations between TMS outcomes and estimates for specific white matter tracts could be used to disambiguate which connectivity is most likely responsible to drive network effects relevant for task performance, without requiring imaging (fMRI, EEG, MEG) evidence (Quentin et al., 2013).

#### 8.5. Influence of genetic phenotypes

It is well known that LTD and LTP mechanisms by which single consecutive sessions of rTMS might operate engage reorganization and plasticity programs. The neural substrate of these mechanisms rely on the expression of activity dependent genes (such as *egr-1*, *c-fos*, or *Arc*) and others. These genes code for proteins such as neurotrophic factors (NGF, BDNF, NTF3, NTF4-Trk2, BDNF) and their receptors (TrkA, TrkB, LNGFR, p75), adhesion molecules (Integrines, IgSF, CAMS, Caderines), voltage-dependent receptors units/subunits (GABA A, GABA B, AMPA, NMDA NR2 subunit) and neurotransmitters (GABA, Glutamate) involved in synaptic plasticity by unmasking existing “silent” connection or *via* the sprouting of dendritic spines and axonal branches.

Some non invasive stimulation studies have pointed out that individual differences in the expression of specific genes might play a role in predicting the modulatory effects of rTMS, in particular for the

neurotrophic factor BDNF (Brain Derived Neurotrophic Factor), which by having an action on dendrogenesis, synaptogenesis, neurotransmitter signaling and regulation (Glutamate, GABA, NMDA) plays a role influencing memory and learning. It has been long shown that BDNF polymorphisms may also influence M1 excitability changes induced by a finger-tapping task, tested with TMS mapping (Kleim et al., 2006). In the same vein, it has been reported that the offline modulatory effects of inhibitory and excitatory rTMS protocols were nearly absent in participants carrying the ‘Val66Met’ allele of the BDNF gene, concluding that the latter were less susceptible to the impact of TMS than those carrying the ‘Val66Val’ allele (Cheeran et al., 2008). In sum, although a pre-hoc population selection according to specific gene expression traits is complex to implement, the dwindling costs of determining BDNF polymorphisms in saliva or small blood samples could be useful *post-hoc* to identify and exclude from main analyses potential outliers or be integrated in composite predictors of response to stimulation.

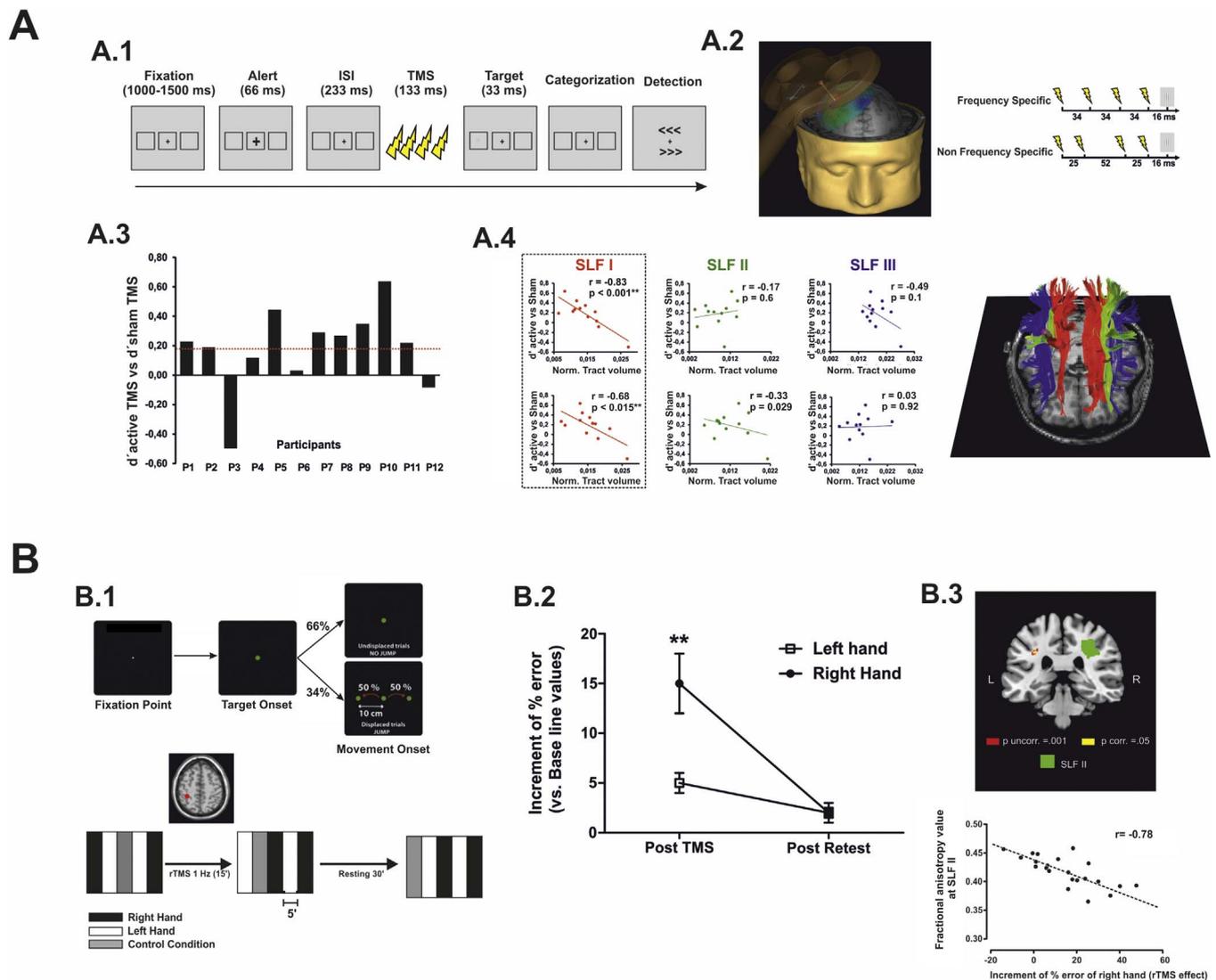
### 9. State dependency of TMS effects

A very influential finding for the field of TMS stimulation has been the fact that the magnitude and direction of TMS and rTMS driven modulatory effects can be influenced dramatically by the level and patterns of ongoing activity operating on the targeted region at the time of receiving TMS stimulation patterns (for reviews see Silvanto and Muggleton, 2008a; Silvanto and Pascual-Leone, 2008).

More specifically, these studies showed that within a given region hosting several subpopulations of neurons devoted to process different visual properties (e.g., specific motion directions, line orientations, or colors), a single TMS pulse or burst will primarily activate those resources of the targeted area showing the lowest levels of excitability (Silvanto et al., 2007a). Similarly, excitatory rTMS patterns would be more likely to induce lasting further excitation on neuronal clusters kept at low level of excitability whereas inhibitory rTMS patterns would induce further suppression of neuronal clusters kept at high level of excitability (Silvanto et al., 2007a). Taken to the extreme, studies have even shown an inversion of the expected direction of modulatory effects with excitatory TMS patterns resulting into inhibitory effects over brain systems at a very high state of activity, or the opposite, excitatory effects driven by conventional inhibitory rTMS patterns when applied to regions kept at a very low state of excitability (Fig. 13).

These phenomena demonstrate the so-called *state-dependency* nature of neurostimulatory effects (for reviews see Silvanto and Muggleton, 2008a; Silvanto and Pascual-Leone, 2008). On that basis, approaches such as sensory adaptation by continued exposure to a specific sensory pattern (contrast, orientation, motion, color) able to decrease neuronal activity of the associated population, can be used to maximize the activation driven by online stimulation or the modulatory effects induced by offline excitatory TMS. In contrast, this same strategy can be used to render specific neuronal subpopulations within a given region less prone or immune to suppressive rTMS patterns. In contrast, one could employ specific sensory (displaying visual targets on a specific retinotopic location), motor (the voluntary activation of a specific muscle) or cognitive (engaging the cortex in a specific operation) priming tasks to increase the level of activity of specific neuronal subpopulations prior or during stimulation to facilitate the suppressive effect of inhibitory patterns or render such populations less sensitive to the impact of excitatory rTMS patterns.

All in all, specific states of activity driven by the execution of behavioral paradigms prior or during rTMS stimulation will strongly determine the magnitude and the direction of the modulatory effects. Therefore, an intelligent and well-suited manipulation of activity state may allow either researchers or clinicians to shape the direction, the selectivity and magnitude of the neurostimulatory effects on small and complex regions, hosting mixed neuronal populations with diversity of functions, by doing so overcoming the limitations in spatial resolution



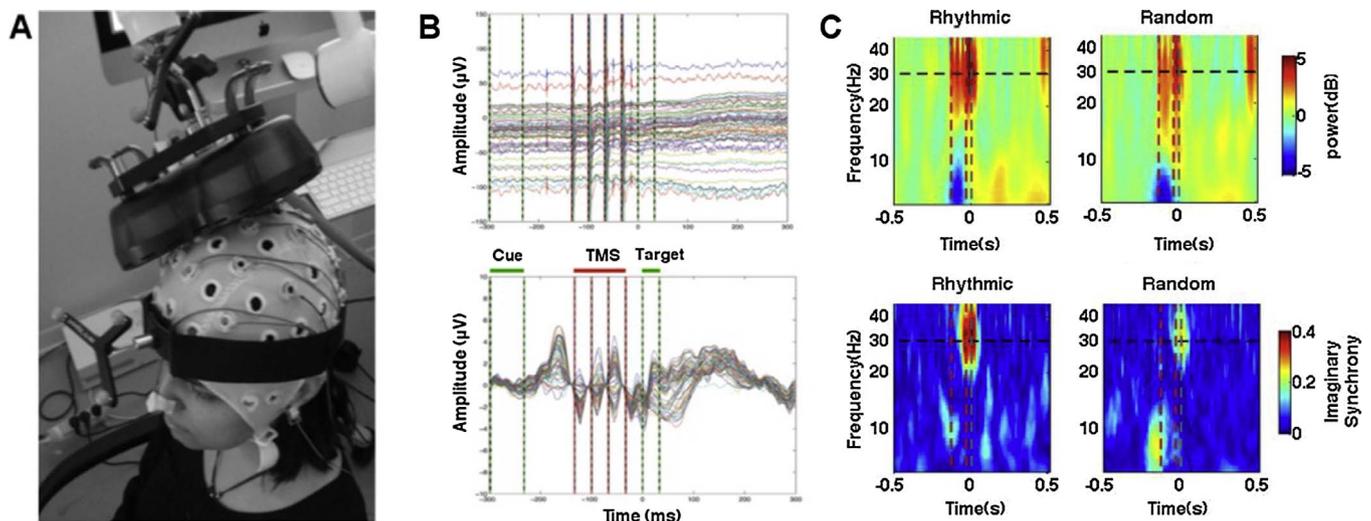
**Fig. 13.** The state-dependency nature of TMS impact has been demonstrated in perceptual systems by means of a color adaptation paradigm, manipulating activity levels of neuronal subpopulations embedded within the occipital (V1-V4) regions (for details see [Silvanto et al., 2007a,b](#)). In the upper (A) and lower (B) rows of the panel, we show two types of trials of computer based paradigm used to reveal the state dependency of TMS impact (top) and their hypothesized changes in neural activity induced by such on two populations of V4 neurons, coding either for red or for green colored stimuli (bottom). In this experiment, participants were required to adapt during 30 s to a red background filling the computer screen. This adaptation period induced the decrease of neural activity for the adapted red color in area V4 generating a difference in activity between the neuronal populations coding for either the adapted red and the non-adapted green color. The delivery of single TMS pulse in such “manipulated state” generated a phosphene sensation (see Section 9) that was reported by participants as being “red”. Conversely, when participants adapted to the “green” color for 30 s, the same TMS pulse delivered exactly in the same occipital region induced according to participants a “green” phosphene. This simple but witty experiment suggests that TMS pulses delivered to a large occipital area, has the ability to primarily activate the subpopulation of neurons at the lowest levels of activity. Moreover, it puts forward the idea that ongoing levels of activity on a TMS stimulated region, and its manipulation via adaptation paradigms has the ability to shape in magnitude and neuronal selectivity the impact of TMS stimulation. Similar strategies have been employed to manipulate visual motion sensitivity ([Silvanto and Cattaneo, 2010](#)), visuo-spatial attention orienting tasks ([Chanes et al., 2012](#)) or short-term visual memory (for details see [Silvanto and Muggleton, 2008a,b](#)).

of TMS approaches in the human brain ([Li et al., 2016](#); [Romei et al., 2016](#)). Importantly, the state-dependency nature of TMS modulatory effects emphasizes the importance of controlling the state of activity of the targeted cortical region and associated networks of a given participant or patient by means of specific innocuous control task during the delivery of rTMS patterns for research or clinical applications.

### 10. Network effects: coupling of TMS with brain mapping technologies

The last decade has seen an increase of TMS behavioral studies coupling different brain mapping technologies. These novel methodological combinations have aroused to address two main challenges. First, cognitive functions and behaviors, which are the main target of non-invasive neurostimulation, emerge from the activity across

extended networks of cerebral sites. In contrast, TMS current technologies can perturb only one region at a time, and probing a complete set of networked regions for a given behavior can be extremely time-consuming for participants and experimenters. Given that TMS local effects spread with a network-specificity, the concurrent use of TMS with a whole brain mapping technique could ease such task. Second, in motor and primary visual areas read out measures based on physiological outputs evoked by TMS (MEPs and phosphenes) can be used to probe effective stimulation and excitability changes. In contrast, in non-motor and nonvisual brain regions one must rely on changes of performance recorded with computer-based behavioral paradigms. Particularly in absence of a significant behavioral effect, local efficacy and spatial extent of TMS/rTMS remain uncertain warranting adequate interpretation of TMS outcomes. To that end, the use of objective physiological biomarkers for TMS showing the local impact on correlates of



**Fig. 14.** Increasingly often and particularly after the advent of rhythmic TMS to manipulate oscillatory activity and synchrony, TMS is combined with neurophysiological mapping approaches recordings, such as scalp high-density electroencephalography (EEG) to capture the local and distributed impact of stimulation (cortico-cortical evoked activity, phase resetting and entrainment of local oscillations) with an outstanding temporal resolution and an acceptable spatial detail. (A) TMS coil positioning over the right FEF, on top of EEG electrodes. The position of both the subject's head and the TMS coil is monitored with a frameless stereotaxic neuronavigation system (for details on this procedure see Fig. 2); Panel (B) shows the effect of TMS-EEG electrical artifact removal procedure. In this case, 4 pulse of 30 Hz rhythmic TMS bursts were delivered shortly before the onset of a 50% visibility target, preceded by a central alerting cue. The top image shows the EEG signal before artifact removal in which each of the 4 TMS pulses induced high amplitude short-lasting electrical artifact impacting nearly all EEG leads. Artifacts were removed by cutting the signal in a window of 8–12 ms and interpolating the eliminated signals with a spline function. The bottom image shows the EEG signal after cleaning of the TMS artifact and filtering ([1 50] Hz band-pass filter). Panel (C) shows individual time-frequency analyses performed on TMS-EEG data for which EEG signals were transformed into the frequency domain. Time was referenced to visual target onset (see dotted gray line). The dotted red lines signal the time window between the 1st (–133 ms) and the 4th and last (–33 ms) TMS pulses of the burst. The dotted black line indicates frequency at which TMS stimulation was delivered (30 Hz). Following rhythmic TMS the 30 Hz power over the right FEF (EEG signal at electrode FC2) was increased as compared to a random control, in which these same 4 TMS pulses delivered non-uniformly were delivered (top graphs). During the bursts, right fronto-parietal synchronization, i.e. synchrony between EEG signals uptaken by electrode FC2 and a group of right centro-parietal and parietal electrodes was also increased following rhythmic but not random stimulation (bottom image). Note that oscillatory entrainment by rhythmic TMS occurs essentially during the delivery of the burst and as reported elsewhere, it does not seem to last beyond for more than a cycle and a half following stimulation offset.

brain activity becomes critical.

In this context, the coupling of TMS stimulation with brain mapping methods has aimed to gain objective evidence showing the impact of focal neurostimulation on brain activity and providing additional information about its mechanisms of action and spatial/temporal extent. Combining *online* TMS designs with brain mapping approaches as those reported above, has provided biomarkers of regional and network activation and allowed the investigation of dynamic modulations of local activity and inter-regional functional interactions induced by TMS patterns. In *offline* designs or multiday therapeutic TMS regimes, combined rTMS and neuroimaging approaches aim to study longer-lasting changes in local brain activity and interregional functional connectivity, causing compensatory and plasticity mechanisms (Driver et al., 2009).

The most tested technological combinations developed to those ends have married TMS/rTMS with PET, fMRI and EEG (all three allowing *offline* and also *online* concurrent recordings). More recently some uses of rTMS with MEG in *offline* designs have arisen. TMS-PET was the first methodological coupling of choice given the lack of interferences between these two methods and provided the first examples in healthy humans or neurological patients of TMS local and distributed impact (Chouinard et al., 2003; Paus et al., 1997; Strafella et al., 2001; Strafella et al., 2003). Although, due to the low spatial resolution of PET and the use of radioactivity, combined online/offline applications remain rare, rTMS-PET application combined with receptor specific pharmacological ligands (such as [ $^{11}$ C] raclopride for dopaminergic systems) have proven unique to explore the impact of cortical rTMS on basal ganglia dopaminergic neurochemical systems in both healthy participants and Parkinson's patients (Strafella et al., 2001; Strafella et al., 2003).

Capitalizing on MRI's excellent whole brain high spatial resolution, pioneering effort combining TMS-fMRI online recordings were used to characterize the network activated following stimulation of either the primary motor or premotor cortex (Bestmann et al., 2004) aiming at

local and inter-hemispheric motor modulatory effects or the Frontal Eye-Fields (FEF) to study top-down modulation of perception (for a review on on-line TMS-fMRI studies see (Ruff et al., 2006; Ruff et al., 2009). Among many other examples, off-line fMRI recordings have been also used to characterize compensatory activations after inhibitory rTMS on the right premotor cortex (Driver et al., 2009; O'Shea and Walsh, 2007; Ruff et al., 2009). Due to the complexity of manipulating a brief lasting TMS magnetic field within a static high MRI magnetic field, this approach is yet to become mainstream. Non-ferromagnetic TMS coils have been developed for its use inside an MR bore (Bohning et al., 1997). Nonetheless, their presence perturbs the homogeneity of magnetic field (Bestmann et al., 2008; Bohning et al., 1997), distorting EPI images ordinarily used for fMRI (Baudewig et al., 2000). Moreover, the artifact on task-relevant fMRI BOLD signals generated by each TMS pulse needs to be avoided by delaying the acquisition of EPI volumes through careful synchronization of stimulation patterns during MRI silent periods (Bestmann et al., 2008; Shastri et al., 1999).

TMS has also been combined more recently with *online* EEG recordings. This methodological coupling which has been explored for the last 15 years has taken special *momentum* with the advent of rhythmic TMS (see Section 5.5) applications (Thut et al., 2017; Thut and Miniussi, 2009). Indeed, TMS-EEG coupled recordings have served to demonstrate increases in power of *natural* regional oscillatory activity, either with single TMS pulse by local phase reset (Rosanova et al., 2009) or through *online* oscillatory entrainment through short rhythmic TMS bursts (Thut et al., 2011a) and explore their causal bearing on cognitive domains such as attention and perception, decision making, motor planning and memory consolidation (Thut et al., 2017). As for concurrent TMS-fMRI recordings, coupled TMS-EEG online methods require TMS compatible EEG equipment, which employ special Ag/AgCl electrodes less sensitive to eddy currents that do not overheat during rTMS. They also require high-range fast recovering DC EEG pre-amplifiers designed to avoid saturation and slow drifting signal offset

generated immediately (7–12 ms) after each TMS pulse (Ilmoniemi and Kicic, 2010). Regardless, individual TMS pulses will induce electrical artifacts on the recorded EEG signal hence several TMS artifact cancellation approaches have been proposed (Litvak et al., 2007; Rogasch et al., 2014; Thut et al., 2017; Thut et al., 2005) to clean as much as possible stimulation artifacts from post-pulse EEG evoked and oscillatory signals and allow event-related analyses in the frequency domain (Fig. 14).

Lastly, on the basis of experiments combining TMS and brain imaging showing how focally delivered pulses, brief patterns or long TMS trains often induce distributed effects across extended brain networks, TMS interventions on cortical motor regions have also been coupled and synchronized to EMG recordings and peripheral nerve stimulation. Such approaches have been used to search for electrophysiological evidence in support of extended cortical influences reaching far as the spinal cord segments. Indeed, one of the most demonstrative examples of long distance connectivity-mediated phenomena driven by cortical TMS has been the modulation of the spinal cord H-reflex during or following TMS patterns delivered over primary motor regions (Guzmán-López et al., 2015; Valero-Cabré et al., 2001; Valero-Cabré and Pascual-Leone, 2005).

## 11. Computational modeling of electric field induced by TMS

According to the Faraday's induction law, the rapidly varying magnetic field penetrates through the skull and induces an electric field in the cortical region closest to coil scalp location. Electrical currents reaching locally a patch of gray matter will interact with ongoing brain patterns and generate a local effect that will then travel generating distant postsynaptic effects across anatomical networks as a function of their connection richness (for full details see Section 3). The effects of the local activation effects produced by TMS patterns delivered on the scalp surface at sufficient intensity can be objectively measured using the most popular concurrent or combined TMS-brain mapping techniques presented in the Section 10 (e.g., TMS-fMRI or TMS-EEG). Nonetheless, prior to TMS delivery, experimenters are generally blind about the penetration, distribution and dose-effects of the induced current fields generated by a TMS pulse travelling across head and brain tissue layers towards an identified cortical target.

Accurate knowledge about the anatomical features (geometry, thickness, volume, structural *inhomogeneities* such as cortical *sulci* and *gyri* in the healthy, or cortical atrophy and focal lesions in patients) and also the biophysical properties (e.g., conductive and capacitive tissue properties determined by material resistance and permittivity) of the different *media* that the magnetic field has to go across to reach a cortical target can help model and predict the stimulation effects (peak current at target, anatomical location of current maxima, and field decay) for a given combination of coil position, stimulation intensity and TMS paradigm. The implementation of that information in either standardized (calculated on a single model head) or individualized (taking into account individual skull and brain features) models is becoming pivotal for an accurate design of the TMS interventional strategies (Paffi et al., 2015; Wagner et al., 2009; Wagner et al., 2007b).

The estimation of the electrical field distribution is based on differential calculus approaches in which two different “objects” need to be estimated. First, a head and brain *model* that simulates the space in which the spread of the current distribution will occur. The simplest head/brain models used a decade ago consisted of multilayered homogeneous spheres (Deng et al., 2013). Nonetheless, more sophisticated models currently rely on individual 3D renderings based on layer-segmented high-resolution Magnetic Resonance Imaging skull volumes, which accurately reproduce scalp and brain surface morphology, eventually coregistered with white matter connectivity estimated patterns (De Geeter et al., 2012; Nadeem et al., 2003). The second element that defines a model is the computational method used to estimate the distribution of the electrical field across the modeled head/brain

volume. Different methods based on different a priori notions with regards to how the electrical field propagates on the skull and brain tissues have been developed, among them, the finite difference time-domain method, the impedance method (De Geeter et al., 2012; Nadeem et al., 2003), the boundary element method (Nummenmaa et al., 2013), the surface integral equation method (Cvetkovic et al., 2015) and the most used approach which is the finite element method (FEM) (Sekino and Ueno, 2004).

To calculate a model, an individual or an average MRI volume is generally segmented into 6 conductive volumes: normally air, skin, skull, cerebral spinal fluid (CSF), gray matter, and white matter. Then a FEM is generated using an adaptive tetrahedral meshing algorithm leading to meshes (with approximately 10 million quadratic elements). Models of field distribution on the FEM are calculated using electrostatic volume conductor physics taking into account different tissue conductivities from a combination of in vivo (Quentin et al., 2015; Wagner et al., 2007b) and/or in vitro measurements. To that end, the boundary conditions to simulate TMS and Internal boundaries between tissues are assigned the continuity condition and solved via the Laplace equation. The resulting cortical electric field is interpreted as the correlate for TMS stimulation. The surface of the TMS coil is assigned inward normal current densities calculated according to the estimated current shape generated (for details see Sections 2 and 3). All other exterior surfaces are electrically insulated. The radial electric field is calculated as the vector projection of cortical magnetic field onto the cortical surface normal ( $n \cdot E$ ) (Wagner et al., 2007b).

Once taking into account a given coil location and stimulation parameters current distribution map has been computed, one could estimate the intensity of the current reaching the cortical targeted region (defined by its MNI coordinates), the decay of peak current across radial distance from it (which informs on spatial resolution) and the distance shift with regards to the regional cortical location receiving the current maxima (or peak current). On that basis, one can simulate different coil locations to according to individual head features such as skull convexity and shape or *sulcal* pattern and choose the TMS coil location ensuring the highest impact on the defined cortical target. Keeping a fixed scalp location providing the shortest distance to target, one can also titrate TMS intensity levels to make sure that sufficient current reaches the chosen cortical location. Finally, it can be studied if local current dosage at target correlates with the behavioral impact of the stimulation or with clinical outcomes. A neuron activation function model (Quentin et al., 2015; Wagner et al., 2007b) can be coupled to current distribution biophysical models and assuming a relative orientation of neurons within cortical layer with regards to the TMS coil surface placed tangential to the scalp (Wagner et al. Cortex 2009), calculate if a given level of current will be sufficient to make regional neurons fire (Quentin et al., 2015). Finally standardized or individualized FEM models also allow probing the impact of altered anatomical variables, such as regional gradients of cortical atrophy expected by natural progression on a given patient, or the impact on current maps of a brain lesion with abrupt lesion borders, resulting in increases of highly conductive CSF volume on the stimulated area. The next challenges in line, are to develop biophysical models implementing activation functions for individual neurons and synchronized circuits coupled to additional structural and functional connectivity maps able to predict how much and where local TMS effects will be distributed across specific networks and the level of behavioral or clinical impact.

In sum, biophysical models taking into account head and brain organization and morphology are increasingly being used as tools to optimize TMS interventions, inform about potential mechanisms and ideally generate testable predictions on how stimulation may affect brain activity and behavior. At the same time, the accuracy and validity of any models need to be explored experimentally in humans using a combination of neurostimulation and mapping methods as those reported in Section 10.

## 12. Transcranial magnetic stimulation vs. transcranial current stimulation

Complementary to TMS, transcranial current stimulation (tCS) is an alternative technology that uses direct electrical current to manipulate brain activity. By means of at least two surface electrodes (an anode and a cathode, required to build the simplest tCS montage) placed on the scalp, tCS techniques can apply either a *constant* (transcranial Direct Current Stimulation, tDCS), an *alternating* (transcranial Alternating Current Stimulation, tACS) or a *random* (transcranial Random Noise Stimulation, tRNS) low intensity current (between 1 and 2 mA) flowing between the two, and influence rather large brain areas. Transcranial DCS (tDCS), is by far the most popular and widely employed of the three approaches mentioned above. It impacts brain function by spatially redistributing electrical charges in the extracellular *milieu*, shifting resting membrane potential of underlying neuronal layers and bringing them either closer (depolarization, anodal stimulation) or away (hyperpolarization, cathodal stimulation) from their firing threshold. Transcranial ACS, delivering a sinusoidal-varying electrical current, has shown to induce frequency specific oscillatory activity across large brain areas, and as rhythmic TMS, could contribute to the synchronization of cortical networks (Thut et al., 2017). Finally, tRNS, the most recently developed modality, has the ability to modulate regional excitability and desynchronize oscillatory activity by injecting low levels of noise.

Compared to TMS, all three tCS approaches, but particularly tDCS benefits from the low cost and high portability of the device, extreme easiness of use, an outstanding safety profile and the possibility to generate an excellent sham condition, indistinguishable from active tDCS stimulation (Gandiga et al., 2006) (see Table 1). However, these techniques also impact the brain with a much lower spatial resolution than TMS. Indeed, standard electrodes used for tCS are rather large (25–35 cm<sup>2</sup>) and current field head/brain estimated models have shown widely distributed currents in the brain surface, which are not necessarily restricted to cortical areas underlying the scalp electrodes (Bikson et al., 2009; Wagner et al., 2007a; Wagner et al., 2007b). Focality of tCS can be enhanced by using smaller electrodes or high-definition tDCS ring or 4 × 1 (1 active electrode surrounded by 4 returns) approaches (Edwards et al., 2013; Minhas et al., 2010). Nonetheless, the magnitude and spatial distribution patterns of the current field reaching the brain during tDCS depend on a lot of additional factors which are not only related to the electrode montage (electrode size and placement), but also individual anatomical head/brain features (skull shape and thickness, scalp to cortical target distance and physiological cortical anisotropies such as gyri and sulci etc.) rendering the location of the current peak and the shape of the current field spread even more difficult to predict (Datta et al., 2012; Torres et al., 2013; Wagner et al., 2007a; Wagner et al., 2007b). Even if these same factors can also influence the impact of TMS (Stokes et al., 2007; Wagner et al., 2008), pulsed magnetic fields penetrate the scalp with less interferences (Hallett, 2007), leading to the known better focality and to an acceptable predictability of the influenced regions, compared to tDCS (Torres et al., 2013). TMS also benefits from a better temporal resolution than tDCS, with an ability in *online* designs, to immediately influence neurons and induce behavioral effects operating within few milliseconds following stimulation (Torres et al., 2013). In contrast, tDCS acts by modulating neuron's membrane resting potentials, and unable to directly depolarize neurons, it has to be applied for at least a few seconds (Nitsche and Paulus, 2000), and most generally, for a few minutes before an *online* impact can be observed on behavioral measures (Nitsche et al., 2008).

Overall, tDCS is a widely used tool that capitalizes on its low cost, portability, excellent safety profile and a high quality sham to manipulate rather large brain regions, hence particularly indicated for exploratory or clinical studies in rather widespread conditions, without a need for high focality. At difference, TMS remains more specifically

**Table 1**

Comparative table contrasting similarities differences between rTMS vs. tDCS across 22 criteria including: (1) portability, (2) device cost, (3) treatment cost, (4) easiness of use, (5) potential for self-administration and (6) equitable access, (7) mechanism of action, estimated (8) spatial and (9) temporal resolution, (10) estimated current density levels, (11) magnitude of local effects, (12) presence and magnitude of network distributed impacts, (13) duration of *offline* impact or aftereffects, (14) possibility to modulate local oscillations and synchrony, (15) long-term carryover impact after a single session, (16) bidirectionality of effects on activity or excitability, safety profile for (17) mild and (18) severe side-effects, (19) accompanying sensory sensations, (20) quality of sham interventions, (21) scientific potential, and (22) clinical potential.

	rTMS	tDCS
1. Device Portability	Low (~90 kg, 75.000 cm <sup>3</sup> )	High (~0.3 kg, 250 cm <sup>3</sup> )
2. Device Cost	Expensive (~50–65k\$)	Affordable (~1–3k\$)
3. Treatment Cost	Expensive	Moderate
4. Easiness of use	Low	High
5. Self-administration?	Unlikely	Possible
6. Equitable access?	Difficult	Possible
7. Mechanism of action	Generation of action potentials on interneurons	Modulation of resting membrane potential in targeted regions
8. Spatial resolution	Good (1.5–2 cm radius)	Poor (> 5–7 cm radius)
9. Temporal resolution	Excellent ('milliseconds)	Poor (seconds/minutes)
10. Current density	High (1.6–2.9 A/m <sup>2</sup> )	Weak (0.05–0.1 A/m <sup>2</sup> )
11. Effect Magnitudes		
- On-line effects	Very strong	Strong
- Off-line effects	Rather weak	Likely strong
12. Network effects	Common	Controversial
13. After effects	Short (15–20 min)	long (45–90 min)
Duration		
14. Effect on oscillations	Yes, with rhythmic TMS	Yes, With tACS
15. Carry-over impact > 24h	Unclear	Unclear
16. Bidirectional effects	Yes Frequency dependent	Yes Polarity dependent
17. Mild adverse effects	Common	Non-frequent
18. Severe adverse effects	Rare but possible	Non-existing
19. Sensory effects		
- Auditory	Present & intense	None
- Tactile scalp	Present & intense	Mild & transient
20. Quality of sham	Poor	Excellent
21. Scientific potential	Very high	Moderate
22. Clinical potential	Moderate	High

suitable for research applications aiming to elucidate the precise temporal or spatial contributions of brain cortical regions and their associated networks to cognitive processes and has been proven extremely useful in therapeutic interventions requiring focal and intense neurostimulation.

## 13. General conclusions

Thanks to its ability to sculpt excitability and activity levels of brain areas and their associated networks and interfere with high temporal and spatial resolution with cognitive processing, TMS has become an inescapable tool for the fundamental and clinical neurosciences. For the fundamental neurosciences, TMS combined with brain mapping technologies has contributed to establish a cartography of causal relationships between brain regions and networks cognitive activities and related cerebral disorders, which allow a better understanding of the interaction between cerebral areas. In a clinical context, the wide array of paradigms and repetitive TMS modalities provides a selective manipulation of neural networks, and the discovery of novel strategies for the therapeutics of brain damaged patients and the optimization of cognitive abilities in healthy individuals.

Given their increasing success and their well-characterized safety when one strictly follows international guidelines, TMS offers an extremely valuable and unique potential as a research and diagnostic tool in the fundamental and clinical neuroscience. Particularly important is

to explore its local and distributed effects across extended neural regions by coupling its application to brain mapping techniques (EEG, MEG, fMRI) and develop the use of biophysically and anatomically plausible computational models of current distribution in brain volumes. Moreover, the efficient and enduring manipulation of specific cortical locations of cerebral networks inaugurates a novel generation of procedures with a unique potential for mastering and guiding at will neural plasticity phenomena in therapeutic applications.

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