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# Transcranial Magnetic Stimulation and the Understanding of Behavior

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## Keywords

Transcranial magnetic stimulation, TMS, state dependency, spike timing–dependent plasticity, STDP, neuroimaging, single unit recording

## Abstract

The development of the use of transcranial magnetic stimulation (TMS) in the study of psychological functions has entered a new phase of sophistication. This is largely due to an increasing physiological knowledge of its effects and to its being used in combination with other experimental techniques. This review presents the current state of our understanding of the mechanisms of TMS in the context of designing and interpreting psychological experiments. We discuss the major conceptual advances in behavioral studies using TMS. There are meaningful physiological and technical achievements to review, as well as a wealth of new perceptual and cognitive experiments. In doing so we summarize the different uses and challenges of TMS in mental chronometry, perception, awareness, learning, and memory.

## Contents



## INTRODUCTION

The ability to noninvasively stimulate the human brain has many important implications for psychology and cognitive neuroscience. During the first wave of human transcranial magnetic stimulation (TMS) studies of behavior, there was a disconnection between attempts to produce neuropsychological lesion-like effects and our understanding of the fundamental physiology of the method. The drive to understand the physiology was led by studies of motor cortex because of the reliability and accessibility of the motor evoked potential (MEP) (Ziemann 2008). As psychologists trying to mimic effects seen in neuropsychological patients or to test theories about the timing or sequences of processes, we had to try to translate our understanding of the excitatory and inhibitory effects of TMS over the primary motor cortex (M1) into the language of our own studies. It wasn't easy. If we reproduced a clinical effect such as, say, language deficits (Devlin & Watkins 2007), spatial neglect (Bjoertomt et al. 2002, Fu et al. 2017), impaired attention (Ellison et al. 2007), prosopagnosia (Pitcher et al. 2007), or dyscalculia (Cohen Kadosh et al. 2007, Göbel et al. 2006), had we shown that the stimulated area was the key causal area for a behavior, had we inadvertently stimulated a neighboring region due to current spread, or had we secondarily stimulated another, distal, anatomically connected region (Bestmann 2008, Bestmann et al. 2008b, Miniussi et al. 2013, Polanía et al. 2018, Romei et al. 2016b, Siebner et al. 2009b)? There were good grounds for making inferences about anatomical and physiological effects based on experimental controls for stimulation site, chronometry, and task specificity, and many of the findings were interesting and had face validity in a neuropsychological sense, but explaining the effects in any neural sense was more than merely difficult.

The problem was that most areas outside of M1 are silent, in the sense that they do not give a measurable output comparable with MEP. One might call this first wave of TMS studies in cognition (say, between 1987 and 2007/2008) the "point-and-shoot era," in which we identified an area of presumed neuropsychological interest and stimulated it with the intention of disrupting a function associated with region. Many interesting and replicable effects were found that remain so despite the limitations of the time, and they have been reviewed many times (e.g., de Graaf et al. 2014, Parkin et al. 2015, Walsh & Pascual-Leone 2003), but the absence of credible mechanistic explanations limited the impact of these findings and slowed our progress.

To imbue behavioral TMS findings with physiological credence, three mechanisms were postulated. The first was that the effects of TMS on cognitive functions were caused by neural noise (Miniussi et al. 2013, Walsh & Cowey 2000) whereby TMS induced disorganized activity

in the stimulated region, preventing it from carrying out its normal function. A competing concept (Harris et al. 2008) was that TMS suppressed neural activity—i.e., by decreasing the signal rather than adding noise. To account for behavioral enhancements as well as impairments caused by TMS, Schwarzkopf et al. (2011) proposed that TMS induced stochastic resonance effects such that at lower intensities it could facilitate stimulus detection. It was clear, however, that without direct recording experiments these proposals remained untested hypotheses.

There are many high-quality introductions and reviews of the history and physics of TMS as well as of coil placement, differences between online and offline stimulation, and early TMS studies of cognition (Hoogendam et al. 2010, Parkin et al. 2015, Peterchev et al. 2012, Walsh & Pascual-Leone 2003, Wasserman et al. 2008). We focus here on the last 10–12 years, during which time there have been important technical, conceptual, and empirical advances. We address only TMS because the volume, intellectual substance, technical accomplishment, and psychological significance of the work over this period are immense and deserve a unified treatment. Advances have also been made in other areas of noninvasive human brain stimulation (transcranial direct current stimulation, transcranial alternating current stimulation, transcranial random noise stimulation, and low-intensity focused ultrasound stimulation), each of which deserves a separate treatment (see Antal & Herrmann 2016, Buch et al. 2017, Chrysikou et al. 2017, Fertonani & Miniussi 2017, Horvath et al. 2015, Parkin et al. 2015, Polanía et al. 2018, Reed & Cohen Kadosh 2018, Schroeder et al. 2017).

## THE FIVE BIG FACTORS IN THE NEW ERA OF TMS AND PSYCHOLOGY

The maturation of the field is based on five pillars of progress. The first of these is the link between physiological mechanisms and behavioral changes caused by TMS. We highlight recent work combining TMS and single-unit recording from nonhuman primates. The second pillar is the use of TMS with brain imaging to understand human cognitive networks. The third pillar is the adoption and development of paired associative stimulation (PAS) from studies of spike timing–dependent plasticity (STDP) in the motor system (Hebb 1949; Müller-Dahlhaus et al. 2010; Stefan et al. 2000, 2002; Wolters et al. 2003, 2005), which have led to inventive developments in dual-coil cortico-cortical PAS (ccPAS) in cognitive studies. The fourth pillar is state dependency, which places constraints on the formulation, execution, and interpretation of TMS experiments in cognition and has become a central concept in the design and interpretation of TMS studies in physiology (Pasley et al. 2009), ccPAS (Santarnecchi et al. 2018), TMS–functional magnetic resonance imaging (fMRI) (Johnen et al. 2015), TMS-electroencephalogram (EEG) (Herring et al. 2015), and perception (Mazzoni et al. 2017). The final pillar is behavior: At the end of the day, as psychologists we use TMS to improve our understanding of psychological functions and to test our theories of cognitive processes. Here, too, there has been significant progress since the point-and-shoot era. Some surprising findings have emerged in memory (van Lamsweerde & Johnson, 2017, Rose et al. 2016, Wang et al. 2014, Zokaei et al. 2014), visual and motor selection and eye tracking (Bestmann & Duque 2016; Vesia et al. 2010, 2019), and awareness (e.g., Allen et al. 2014, de Graaf et al. 2014, Rounis et al. 2010). Of course none of these pillars stands in isolation, and as methods and designs improve, as we discuss below, experiments and new findings increasingly stand on several pillars simultaneously. The work we cover here represents real progress, and we hope our overview and characterization of the field will provide a framework to help readers understand its significance and make their own contributions.

## PHYSIOLOGY AND BEHAVIOR

The questions received most often when presenting TMS findings are, How do you know what it is doing? How far does it spread? What other parts of a network does it disrupt? What is happening at the neuronal level? How long do the effects last? If we consider a single pulse of TMS we can now begin to give good responses to these concerns.

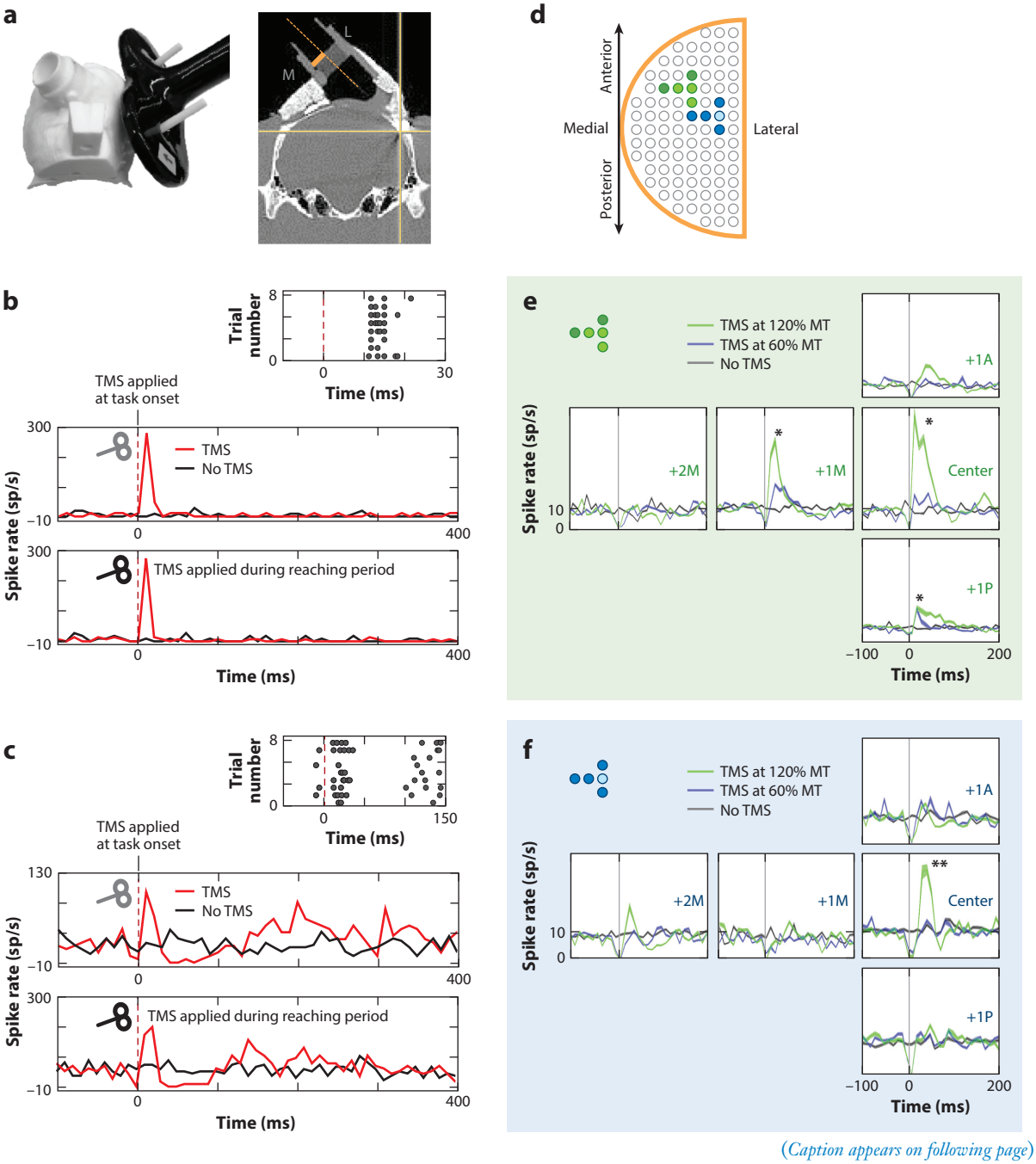
The question of spread was always an inferential one, based on the observation that MEPs or behavioral effects would diminish or disappear if the coil was moved by a few millimeters or rotated to a different angle (see Walsh & Pascual-Leone 2003, Wasserman et al. 2008). Modeling the physiological spread of TMS was difficult because cerebrospinal fluid and white/gray matter have different conductivities, modeling secondary effects is challenging, and of course the models do not address behavioral states (Aberra et al. 2018, 2020).

The approach needed to illuminate the mechanistic questions was direct physiological recording. Initially these recordings were carried out on anaesthetized preparations (Allen et al. 2007, de Labra et al. 2007, Moliadze et al. 2003, Pasley et al. 2009). From these studies we learned that TMS had specific excitatory or inhibitory effects in two phases (i.e., inhibition followed by a longer period of excitation); that the effects of paired-pulse TMS in M1 were mirrored in evoked potential activity in the visual cortex (Moliadze et al. 2005), and that TMS–evoked potential activity was state dependent (i.e., related to the level of neuronal activity prior to stimulation) (Pasley et al. 2009). All this pointed in the right direction with regard to behavioral TMS findings, but as was discovered in the era of single-unit recording in the visual cortex during the 1960s and 1970s, "the cortex dissolves in anesthesia" (Gross 1998, p. 197). Making the link between physiology and behavior required recordings from awake, behaving monkeys. Ortuno et al. (2014) showed two interesting effects when stimulating the primary visual cortex (V1) and recording from the lateral geniculate nucleus (LGN) in monkeys performing a visual detection task. The TMS-induced LGN changes in activity were direct evidence of organized activity at a secondary location, and the effects were state dependent. From a psychological point of view, it was of particular interest that these effects were induced using a paradigm developed in human studies (~1 Hz offline; see Gangitano et al. 2002). Mueller et al. (2014) then developed the methods that allowed recording from single units in the area of stimulation.

The most comprehensive and recent advance of relevance to psychologists is from single-unit recordings in nonhuman primates trained on a visually cued reach, grasp, lift, and hold task Romero et al. 2019a). On some trials the monkeys received single-pulse TMS over PFG at either 60% or 120% of motor threshold (MT). Recordings were taken from over 500 cells in area PFG of the inferior parietal cortex contralateral to the hand used in the task and analyzed as a function of TMS intensity, distance from the stimulating coil, and task relevance (**Figure 1**). At 120% of MT there were clear effects of TMS on single units. The TMS pulse induced an artifact, of course, so the experiment analyzed activity from 10 ms after the pulse. The main effect of TMS was to induce a volley of action potentials during the first 50 ms. In neurons that were not task related this occurred irrespective of the stage of the task (i.e., cue, lift, grasp, hold) at which TMS was delivered. In other units the early excitation was followed by a period of inhibition and by a third phase of excitation that could last as long as 250 ms in a small number of neurons (population average <100 ms). Analysis of the distance from the coil and comparisons of neighboring neurons showed that TMS effects were limited to as little as 2–3 mm. At 60% of MT, TMS had almost no physiological effects.

The final physiological gift from this experiment was the finding that single-pulse TMS also induced an increase in low-frequency oscillations in both the center and the periphery of the stimulated regions. These oscillations, mostly in the delta and lower theta ranges, are strong

candidates for the generation of evoked potentials and long-range, cortico-cortical effects of TMS. The oscillations are less salient than those elicited by TMS in EEG studies (Bergmann et al. 2016, Fecchio et al. 2017, Herring et al. 2015, Rogasch et al. 2015, Rosanova et al. 2009, Thut et al. 2017). However, as Romero et al. (2019a) point out, single-unit responses and EEG




(*Caption appears on following page*)

**Figure 1** (*Figure appears on preceding page*)

The effects of transcranial magnetic stimulation (TMS) on single cells in the macaque parietal cortical area PFG (Romero et al. 2019a). (*a*) 3D model of the monkey head and TMS coil, showing the angle of approach of the recording electrode. (*b*) The response of a single cell to TMS at 120% of motor threshold (MT) during the reach-and-grasp task. Irrespective of whether the TMS was applied at task onset (*gray symbol*) or during the reaching period (*black symbol*), the stimulation evoked a burst of activity (*red curve*) between approximately 10 and 40 ms. On no-TMS trials there was no change in activity (*black curve*). The raster plot gives an example of the consistency of the response. (*c*) Another class of responses was excitation–inhibition–excitation. The response from this neuron showed the same initial excitatory burst as the cell in panel *b*. When the TMS was applied at the task onset (*gray symbol* and *inset raster plot*), there were three phases of activity: excitation (0–40 ms), inhibition (40–100 ms), and excitation (100 ms+). In some cells a longer-lasting phase of activity could extend to 300 ms. The black curves show the activity of the neuron on no-TMS trials. (*d*) A grid of recording sites in two monkeys showing the spatial specificity of the recordings. (*e*, *f*) The plots show the average cell response rate at each of the five recording sites under the center of the TMS coil (Center), 1 mm anterior/posterior (+1A, +1P), and 1 or 2 mm medial (+1M, +2M). The graphs show responses to TMS delivered at 120% MT (*green curves*), TMS delivered at 60% MT (*purple curves*), and no TMS (*gray curves*). Illustration created by Marco Davare using data from Romero et al. (2019a).

measures are at different spatial and temporal scales. The relationship between the relatively local, low-frequency oscillations at the single-unit level and the global and more varied frequencies in EEG and magneto-encephalography (MEG) is a clear direction for future research.

These physiological results are impressive, but from a psychological point of view perhaps most interesting is the finding that in some neurons the transient burst in the first phase of the recordings and the reduced activity in the second phase were paralleled by impaired performance on the grasping task. Neurons in PFG are known to be involved in action goal selection (Bonini et al. 2011, Rozzi et al. 2008) and grasping behavior (Davare et al. 2010, Nelissen & Vanduffel 2011). This is the strongest link to date directly associating TMS-induced neural activity changes with an effect on behavior.

Romero et al. (2019b) have also begun to assess the effects of continuous theta burst stimulation (cTBS) on single-unit responses. They measured neural responses after 300 pulses of cTBS and found that the large majority of neurons in area PFG showed significant reduction in activity. The responses fell into three groups: an early group in which 47% of cells were affected in the first 5 min after cTBS, a later group in which 44% of cells showed inhibitory effects between 5 and 30 min after cTBS, and a very late group of remaining cells that showed reduced excitability more than 30 min post-cTBS. These results show that theta burst stimulation, although based on animal studies and widely used in behavioral studies, does not have unitary effects, and this must now be taken into consideration in interpreting behavioral studies (Huang et al. 2005, Rahnev et al. 2013, Rounis et al. 2010).

These findings are a landmark in our understanding of the physiological effects of TMS and, at the very least, provide a more than respectable starting point in answering questions about local spread, interaction with task-relevant neurons, and duration of effects. They also help to settle the muddle of metaphors between neural noise, signal reduction, and stochastic resonance accounts of TMS effects. It seems we were all partly right, which means we were all also wrong: Nobody won and no one must claim prizes. The early and late excitatory responses (**Figure 1**) correspond with a large noise-like effect the neurons would otherwise not have produced (Miniussi et al. 2013, Walsh & Cowey 2000). The second phase of reduced responses is exactly what the signal reduction hypothesis predicted (Harris et al. 2008). The oscillatory phase, unlike the earlier burst and inhibition phases, occurred with subthreshold stimulation, and this is consistent with the stochastic resonance account (Schwarzkopf et al. 2011). But rather than prompting us to defend our own partly correct metaphors, this tri-temporal pattern of single-unit responses should force us to rethink how we interpret behavioral results.

The question of what other parts of a network are affected by TMS is the subject of the next section.

## FUNCTIONAL ANATOMICAL NETWORKS

Combining TMS with fMRI enables us to map the remote effects of targeted neural disruption across the entire brain. The value of this approach is threefold. First, it allows us to map the secondary effects of TMS. Second, any complex human behavior is computed across a network of areas distributed across the brain, and experiments that combine TMS with fMRI can causally map the extent and functionality of these networks (Bestmann et al. 2005, 2008b, 2010; Blankenburg et al. 2008; Lee & D'Esposito 2012; Pitcher et al. 2014; Ruff et al. 2006, 2009; Siebner et al. 2009a). Third, there are cortical and subcortical areas that cannot be directly stimulated by TMS; however, recent combined TMS-fMRI studies have demonstrated that stimulating lateral brain areas can modulate the neural response in remote areas including the parahippocampal gyrus (Mullin & Steeves 2013), hippocampus (Wang et al. 2014, Warren et al. 2019), and amygdala (Pitcher et al. 2017). Many compelling studies have now combined TMS and neuroimaging to exploit these advantages.

One research area in which combined TMS-fMRI studies have proven especially useful is the study of how frontal cortex exerts top-down control over visual perception and decision making. Following from stimulation studies that had shown top-down control of frontal cortex in visual discrimination tasks (Silvanto et al. 2006), Ruff and colleagues (2006) recorded fMRI data while TMS was delivered over the frontal eye field (FEF). They revealed that stimulation of the right FEF reduced activity of the retinotopic representation of the central visual field in areas V1 through V4, while also increasing the representations of the peripheral visual field. A follow-up TMS study confirmed the behavioral relevance of these results by demonstrating that TMS delivered over the FEF enhanced perceived contrast for peripheral relative to central visual stimuli. This landmark study demonstrates how combining TMS with fMRI allows us to go beyond what we could accomplish using each method alone.

Combined TMS-fMRI studies have proved invaluable in studying other cognitive networks. Many single-site studies have addressed the causal role of a particular area in various psychological functions (Dayan et al. 2013, de Graaf et al. 2014, Parkin et al. 2015, Pitcher et al. 2007), but TMS-fMRI allows us to map the remote effects of neural disruption across the brain networks. This is a move from areal causality to inter-areal causality: The previously troubling question of whether behavioral effects were due to secondary stimulation is now a tractable question of interest. A good example is the face perception network. Imaging studies show that different brain areas preferentially represent different facial aspects such as emotion, identity, attentional focus, and social cues, but they are limited in what they can say about how these areas functionally interact. TMS-fMRI can systematically disrupt these brain areas and examine the causality of connections in the network. Pitcher et al. (2014) used this approach to distinguish the cortical pathways that process dynamic and static facial features. Theta burst stimulation (TBS) was delivered over the right occipital face area (rOFA) or the right posterior superior temporal sulcus (rpSTS). Contrary to existing face-processing models (Haxby et al. 2000), static facial aspects like identity and dynamic facial aspects such as expression were found to be processed via dissociable cortical pathways that begin in the early visual cortex.

While face areas like the occipital face area OFA and the pSTS can be directly stimulated (Pitcher et al. 2007, 2014), other parts of the face network, such as the amygdala, cannot be directly targeted by TMS but can be accessed by network analysis of secondary stimulation. Neuroanatomical studies in nonhuman primates identified a cortical pathway from the STS into the amygdala (Aggleton et al. 1980). Pitcher et al. (2017) combined offline TBS with fMRI to test whether they could identify causal evidence for this cortical pathway in the human brain. Participants were scanned while viewing face and object videos. TBS delivered over the rpSTS

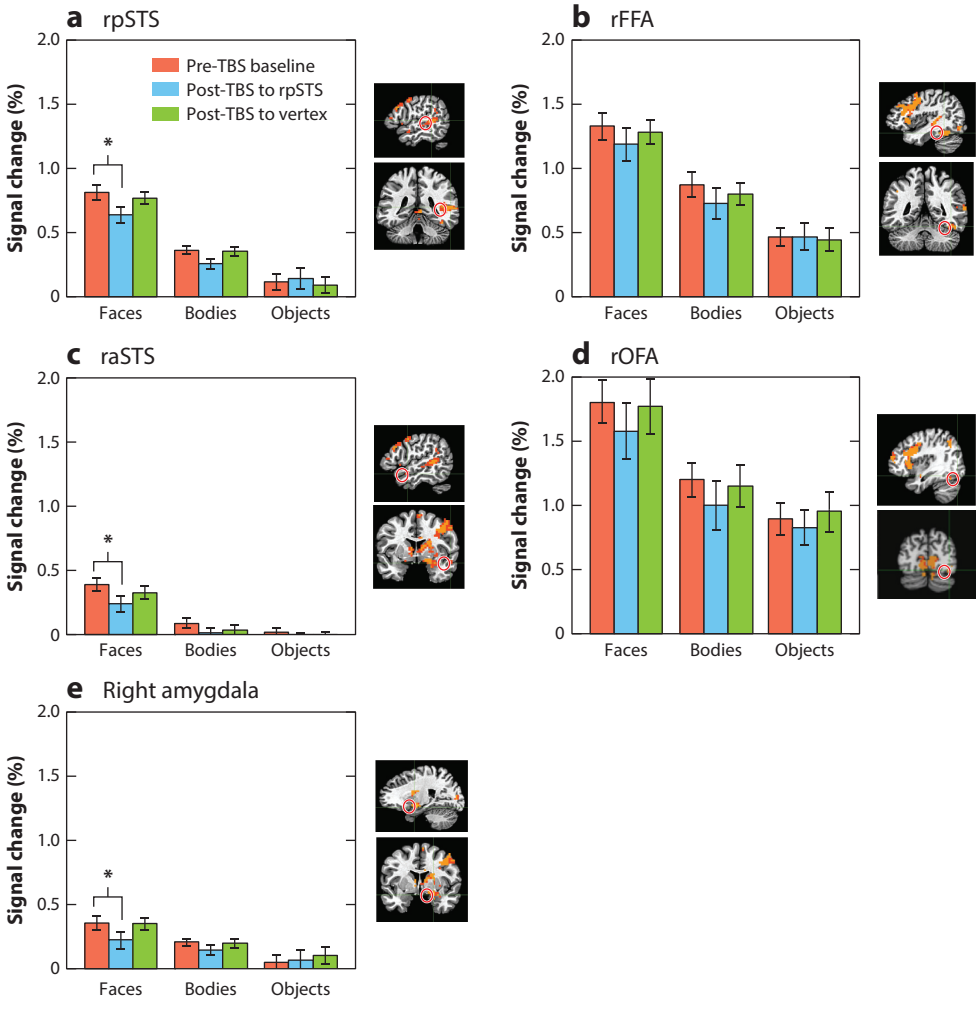



**Figure 2**

Results of Pitcher et al.'s (2017) study. The panels show signal change data for the dynamic face, body, and object stimuli before and after theta burst stimulation (TBS) in the five core regions of interest (ROIs): (*a*) right posterior superior temporal sulcus (rpSTS), (*b*) right fusiform face area (rFFA), (*c*) right anterior superior temporal sulcus (raSTS), (*d*) right occipital face area (rOFA), and (*e*) right amygdala. Brain slices show examples of the face-selective (dynamic faces > dynamic objects) ROIs in a typical participant. TBS delivered over the rpSTS selectively and significantly reduced the blood-oxygen-level-dependent (BOLD) response to dynamic faces only in the rpSTS, raSTS, and right amygdala. Error bars denote standard errors; asterisks denote significant effects.

reduced the neural response to face videos in the right amygdala, a result consistent with the nonhuman primate data (**Figure 2**). These studies show how TMS-fMRI can map in humans the functional connectivity of brain areas anatomically defined in nonhuman primates and extend the cognitive inferences based on TMS effects beyond the site of stimulation.

A further advance is using TMS-fMRI to observe cognitive networks in the absence of task demands. Handwerker et al. (2020) combined TMS and resting-state fMRI (rsfMRI) to map the remote effects of transient cortical disruption in the face network across the entire brain. TBS

delivered over the rpSTS reduced resting-state connectivity across the extended face-processing network compared to TBS delivered over a control site. This connectivity reduction was observed not only between the rpSTS and other face-selective areas, but also between nonstimulated face-selective areas across the ventral, medial, and lateral brain surfaces (e.g., right amygdala and bilateral fusiform face areas and occipital face areas). This result suggests that the typical functional connectivity of a network is dependent on the normal operation of all the nodes in that network. The ability to observe network integrity in the absence of task demands makes TMS-rsfMRI of interest for use with clinical populations who may find scanner-based testing difficult. For example, TBS combined with rsfMRI has been used to study connectivity in aging (Abellaneda-Perez et al. 2019), visuospatial neglect (Fu et al. 2017), cerebellar functions (Rastogi et al. 2017), and depression (Baeken et al. 2017).

Combining rsfMRI with TMS can also be used to measure how stimulation can improve functional connectivity in an anatomical network. An impressive example of this approach is provided by Wang et al. (2014), who investigated the cortical-hippocampal brain networks that underpin associative memory. They used rsfMRI to identify functional connectivity between the left hippocampus and the left parietal lobe. High-frequency TMS (20 Hz for 2 sec every 30 sec) was then delivered over this left parietal site for 20 min over 5 consecutive days. TMS increased functional connectivity between the stimulation site and the left hippocampus relative to a sham TMS condition. This increase in functional connectivity was accompanied by improved behavioral performance on an associative memory task in which words were paired with faces. The results of this study are compelling from both a scientific and a clinical perspective. From a scientific perspective, the anatomical specificity of the enhanced functional connectivity (replicated in Warren et al. 2019) demonstrates that TMS can induce spatially distinct effects in anatomical networks. From a clinical perspective, the enhancement of memory has clear implications for potential treatments of patients with memory disorders.

Taking the TMS-fMRI advances together with the single-unit physiology findings, we are clearly progressing toward an integrated understanding of the local, aerial, network, and functional effects of TMS on behavior.

## SPIKE TIMING–DEPENDENT PLASTICITY

From the basic physiology of TMS effects and the network responses revealed by combinations of TMS and fMRI, we learned that the inferences made about TMS in psychological experiments were vindicated in important ways. Great strides have also been made at the interface of physiology and behavior in studies using two coils to stimulate the cortex. This genuine advance, not even referenced in what is considered to be the "TMS Bible" (Wasserman et al. 2008), is STDP and refers to time-dependent changes in pre- and postsynaptic activity. This Hebbian mechanism has been studied in vitro and in vivo in small animals, and neuropharmacological studies have revealed the role of N-methyl-D-aspartate (NMDA) and glutamate in the induction of long-term potentiation and the role of GABAeregic synapses in inhibition (Caporale & Dan 2008) with remarkable temporal specificity. The model for Hebbian learning is that repeated paired stimulation of one area (conditioning pulse) followed by a second area (test pulse) a few milliseconds later increases synaptic efficiency between the two sites, resulting in the second area being more receptive to input from the first. Using TMS in humans, studies of the motor system have established that PAS in which a peripheral nerve stimulus is paired with a cortical TMS pulse can induce changes in MEPs if the two stimuli fall within a narrow time window of a few milliseconds. TMS over M1 delivered 10 ms after peripheral stimulation of the median nerve (MN) reduced the subsequent MEP, and an MN–M1 interval of 25 ms increased it (Müller-Dahlhaus et al. 2010; Stefan et al. 2000, 2002;

Wolters et al. 2003). These PAS studies were brought into the psychological domain by Rizzo et al. (2009), who showed that Hebbian plasticity could be induced by two coils placed over the cortex and measured both physiologically (via MEP) and behaviorally. Rizzo and colleagues called this ccPAS, and we will use the term ccPAS to refer to all double cortex stimulation studies of plasticity.[1] Rizzo et al.'s (2009) is a breakthrough study and contains all the components required to understand all other psychological ccPAS studies. Pairs of TMS pulses were delivered at 0.05 Hz for 30 min over M1 of the right hand (left hemisphere) and then over M1 of the left hand (right hemisphere), with an 8 msec delay between the hemispheres (left hemisphere M1 TMS is the conditioning stimulus here, and the right hemisphere M1 is the conditioned target). The intensity was set for each subject to produce a 1 mV peak-to-peak electromyography, which was between 115% and 125% of the resting motor threshold. The physiological effect was to increase the MEP in the conditioned hand representation and to decrease interhemispheric inhibition (IHI). IHI was measured by delivering single pulses over left and right M1 with long delays of 35–45 msec that are known to produce inhibition of the MEP response (Daskalakis et al. 2002). Behaviorally, the ccPAS speeded simple reaction time responses with the left index finger (the conditioned finger representation) for up to 30 min post-ccPAS. This experiment is a watershed for ccPAS in TMS studies of behavior and plasticity. After 70 years of knowing the Hebb rule, 100 years of learning research, and 35 years of TMS, psychologists now have a method for studying Hebbian plasticity in learning with human brain stimulation.

The M1 effects in ccPAS seem to be robust and replicable, but since Rizzo et al.'s (2009) work, behavioral change has been more elusive. Buch et al. (2011) conditioned M1 with ventral premotor (PMv) TMS while subjects performed a reach-and-grasp task. The STDP effect, which lasted for at least an hour, was state dependent (see the section titled State Dependency) in that when the subject was performing the task the PMv TMS induced excitation over M1, but when at rest the PMv TMS increased the inhibitory effects of PMv on M1. There was no effect on the performance of the task itself, however. Chao et al. (2015) also obtained a ccPAS change in M1 excitability by conditioning with TMS over the posterior parietal cortex (PPC) 8 msec prior to M1. Like Buch et al. (2011), they found that the STDP effects on the MEP lasted over an hour but had no impact on a peg board task. Johnen et al. (2015) used ccPAS to examine whether inducing a stronger connection between PMv and M1 [90 pulse pairs at 0.1 Hz with a PMv-M1 interstimulus interval (ISI) of 8 ms] would translate into an increase in functional connectivity measured by fMRI while subjects performed a reach-and-grasp task. Here, ccPAS increased the strength of connectivity between the two areas during the performance of the task, but not at rest. Subsequent analysis showed that the PMv-M1 ccPAS had specific effects on interactions between other nodes in the sensorimotor network. Functional connectivity was increased between PMv and AIP and was decreased between the dorsal premotor cortex (PMd) and M1 and between PMd and the posterior superior parietal lobule (pSPL). There were no effects on behavior measures.

Santarnecchi et al. (2018) also examined how ccPAS changes cortical network activity (**Figure 3**). They applied ccPAS over a parietal region of the default mode network (DMN) and a region of the prefrontal cortex in the task-positive network (TPN) (Raichle 2015). The two regions they stimulated were negatively correlated nodes of their respective networks, identified

[1] The terminology in the literature is not friendly to the newcomer. Experiments using the same method are variously referred to as PAS, cPAS (meaning cortical PAS), ccPAS (meaning cortico-cortical PAS), or simply as paired stimulation. Here we use PAS to refer only to studies in which peripheral nerve stimulation is paired with M1 stimulation. For studies in which two cortical sites are stimulated we use the term ccPAS after Rizzo et al. (2009).

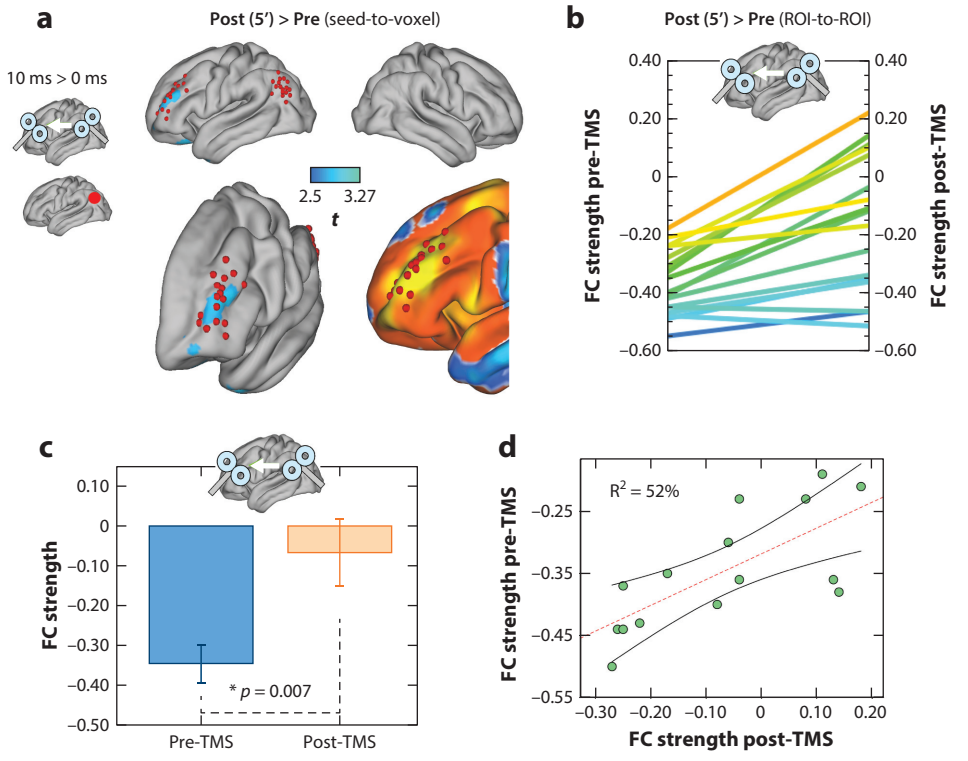



**Figure 3**

Spike timing–dependent effects of cortico-cortical paired associative stimulation (ccPAS) between the left angular gyrus (a node in the default mode network) and the left frontal lobe (a node in the task positive network) on functional connectivity (FC) (Santarnecchi et al. 2018). (*a*) At the group level, the ccPAS induced an increase in the coupling of the two regions. (*b*) The figure illustrates the increase in FC for the individual subjects in panel *a*, showing that the gain in FC was correlated with pre-ccPAS FC. In all subjects the FC was negative before ccPAS. In approximately one-third of these subjects, the FC was positive following ccPAS. (*c*) The graph shows the group data from panel *b*. (*d*) The graph shows the correlation of FC strength before and after transcranial magnetic stimulation (TMS). Illustration by Emiliano Santarnecchi.

by individual fMRI. Following a previous STDP study of the fronto-parietal network (Casula et al. 2016), they adopted three temporal conditions: DMN/TPN ISI + 10 ms, DMN/TPN ISI − 10 ms, and DMN/TPN ISI = 0 ms. Pairs of pulses were delivered at 0.2 Hz over 15 min. Rather than measuring STDP in the motor cortex, they asked how different parts of cognitive networks respond to TMS test pulses when the dependent variable is the BOLD signal.

Two findings of major interest here are that (*a*) when the DMN pulse preceded the TPN pulse by 10 ms there was a clear change in the negative correlation of the two sites, and (*b*) in a third of subjects the correlation became positive (**Figure 3**). The effects, like those found by Buch et al. (2011), were state dependent. If the correlated activity between the two sites was weaker prior to ccPAS, the effects consistent with STDP were increased in size. Again, however, there was no report of any behavioral effects.

Part of the interest in ccPAS is the hope that STDP may prove clinically useful, but most of the studies conducted after the one by Rizzo et al. (2009) either do not measure or do not see a behavioral change consequent on the STDP, despite significant physiological changes. Another

attempt to match the physiology of ccPAS-induced STDP to behavior was made by Kohl et al. (2019), who bi-directionally stimulated the inferior frontal cortex (IFC) and pre-SMA. Based on Weise et al.'s (2013) PAS model, they hypothesized that stimulating the pre-SMA 4 or 10 ms prior to IFC would inhibit the subthalamic nucleus (STN) and interfere with a behavioral task, and that stimulating IFC 4 or 10 ms prior to pre-SMA would facilitate the STN and task performance (see Weise et al. 2013, figure 2). They delivered 100 pairs of ccPAS pulses at 0.2 Hz. The two tasks they gave to their subjects were the stop signal reaction time (SSRT) task and a temporal discounting task. While they reported some effects on a SSRT, they found no effects on a delay discounting task.

The clear challenge in this area is to bridge the gap between the physiologically robust STDP effects (measured by MEPs or fMRI) and behavior. Two studies in particular may help to direct the next steps, by Veniero et al. (2013) and Momi et al. (2020). They each raise different issues to be pursued from physiological, EEG, imaging, and behavioral perspectives.

Veniero et al. (2013) induced long-term potentiation (LTP)- and long-term depression (LTD)-like STDP and measured the effects on evoked potentials. They induced bidirectional STDP by stimulating PPC and M1 with 100 pulse pairs over 8 min with an ISI of 5 msec (see also Koch et al. 2013). When ccPAS had an inhibitory effect on the MEP, there was an increase in beta coherence between PPC and M1. When ccPAS induced an excitatory effect as measured by the MEP, there was an increase in alpha coherence between the two regions. Given the detailed work on TMS-EEG in vision, attention, and awareness in particular (Herring et al. 2015, Romei et al. 2008, Taylor 2018), it is clear that the paradigm of Veniero and colleagues is consistent with prior work and worthy of extension. The combination of ccPAS with EEG may help to understand why the physiological effects do not have behavioral consequences as often as one might hope.

Another issue for replication and development is that of producing behavioral effects. Momi et al. (2020) used ccPAS to try to synchronize two positively correlated nodes of the left fronto-parietal network. They tested ccPAS bi-directionally with pairs of pulses delivered for 15 min at 2 Hz with an ISI of 10 ms. Over 5 weeks of repeated stimulation and behavioral testing, they observed STDP and indications of directional-specific behavioral changes. Fronto-parietal ccPAS was associated with a small improvement in relational reasoning, and parieto-frontal ccPAS with an improvement on a logical reasoning task (see Momi et al. 2020, figure 3). This is a rare example of ccPAS producing a complex behavioral change. We return to this issue in the next section (see also Chiappini et al. 2018, Nord et al. 2019, Romei et al. 2016a).

## STATE DEPENDENCY

In one sense, all TMS research is based on state dependency. Comparison of a resting and an active MT is a measure of state-dependent motor thresholds. There have been many examples of behavioral context affecting TMS in the motor system, all demonstrated by measuring an effect on the MEP (Bestmann & Krakauer 2015, Bestmann et al. 2008a). However, for state dependency to be useful in studying psychological concepts not accessible to the MEP, we needed a new approach. The state-dependent approach in perception and cognition experiments is owed mostly to the efforts of Juha Silvanto (see Silvanto et al. 2006, 2007, 2008). The effects of TMS are dependent on the current state of excitation of the brain tissue being stimulated. In cognitive experiments, however, we do not have a direct measure such as the MEP of the current state of, say, the dorsolateral prefrontal cortex (DLPC), PPC, FEF, OFA, etc. Silvanto's major contribution was to leverage state dependency in psychological experiments to enhance the functional resolution of TMS to selectively target specific, even overlapping, neural representations.

Silvanto used adaptation to influence the initial state of the region being stimulated. His first study (Silvanto et al. 2007) is simple, elegant, and serves as a model for thinking about state-dependent TMS in cognition. Subjects adapted to color/orientation stimuli for 30 sec and were required to report the color of a test stimulus. TMS was delivered at different times after presentation of the test stimuli. On non-TMS trials, the subjects experienced the complementary color of the adapting stimulus, but TMS over the visual cortex induced a bias toward the original, adapted stimulus color.

The method has now been used widely in studies of mental imagery (Cattaneo et al. 2012), short-term memory (Soto et al. 2012), letter selection, abstraction, action observation, and semantic processing (Cattaneo et al. 2008, 2009, 2010). The study by Cattaneo et al. (2010) is of particular interest because it observed a naming effect with TMS delivered outside visual or language areas. They tested the effects of TMS on category-specific neuronal representations in the encoding of tool words in the left PMv. Subjects were primed with a category name (i.e., "tool" or "animal") to adapt the PMv to one or the other category of objects. TMS was then applied at the onset of a target word that was either congruent or incongruent with the primed category. The outcome was the removal of the priming effect.

Another example of nonsensory effects of state-dependent TMS came from a study of action recognition. Mazzoni et al. (2017) adapted subjects to point-light displays of affective movements. They applied repetitive TMS (rTMS) at the onset of the point-light displays over the anterior intraparietal sulcus (aIPS), pSTS, or occipital pole. Only TMS over aIPS had any effect on the subjects' identification of the happy or fearful motion displayed, and it served to reverse the effects of adaptation.

We can now bring the two recent advances of STDP and state-dependent TMS together. As we noted in the introduction, and we shall see again in the section titled Behavioral Findings, there is increasing integration of TMS with other methodologies. Three studies serve as useful examples of how state dependency and ccPAS may be used in conjunction. The first of these studies (Arai et al. 2011) used three coils to stimulate M1 bilaterally and SMA using ccPAS. They induced bidirectional and spatio-temporal-specific STDP, enhancing the MEP if the SMA–M1 delay was 6 ms and decreasing it if the M1–SMA delay was 15 ms. The new factor here was the requirement that for these associations to occur, both left and right M1 had to be stimulated peri-simultaneously. It is a complex experiment, but the pattern of advances in TMS and cognition to date has followed the path of finding the most interesting advances in motor physiology and adapting them to study psychological functions. It may be that the next phase of state-dependent, Hebbian plasticity in psychological studies will require three coils.

The second study, by Romei et al. (2016a), is an important example of ccPAS outside the motor system. Using V5 and V1 TMS delivered at 0.1 Hz for 90 pairs of stimuli with an ISI of 20 ms, Romei and colleagues improved the subjects' performance on a motion coherence task. In a follow-up study, Chiappini et al. (2018) showed that this strengthening of re-entrant V5–V1 projections was state dependent (**Figure 4**). The subjects were adapted to a direction of motion during which ccPAS was delivered. In other words, this is a state-dependent ccPAS protocol. Based on previous experiments, V5 was stimulated at 80% of phosphene threshold and V1 at phosphene threshold. Controls were administered for time (a V5–V1 delay of 100 ms) and direction (with V1 preceding V5). The outcome was that when tested on a direction of motion threshold detection task, sensitivity was increased in the direction congruent with the ccPAS stimulation. As the authors put it, this "allows targeting of cortico-cortical pathways associated with specific functions" (Chiappini et al. 2018, p. 735).

One particular class of experiments uses dual-coil stimulation to probe interactions between brain areas. They constitute an application of the functional anatomical paradigm (without the

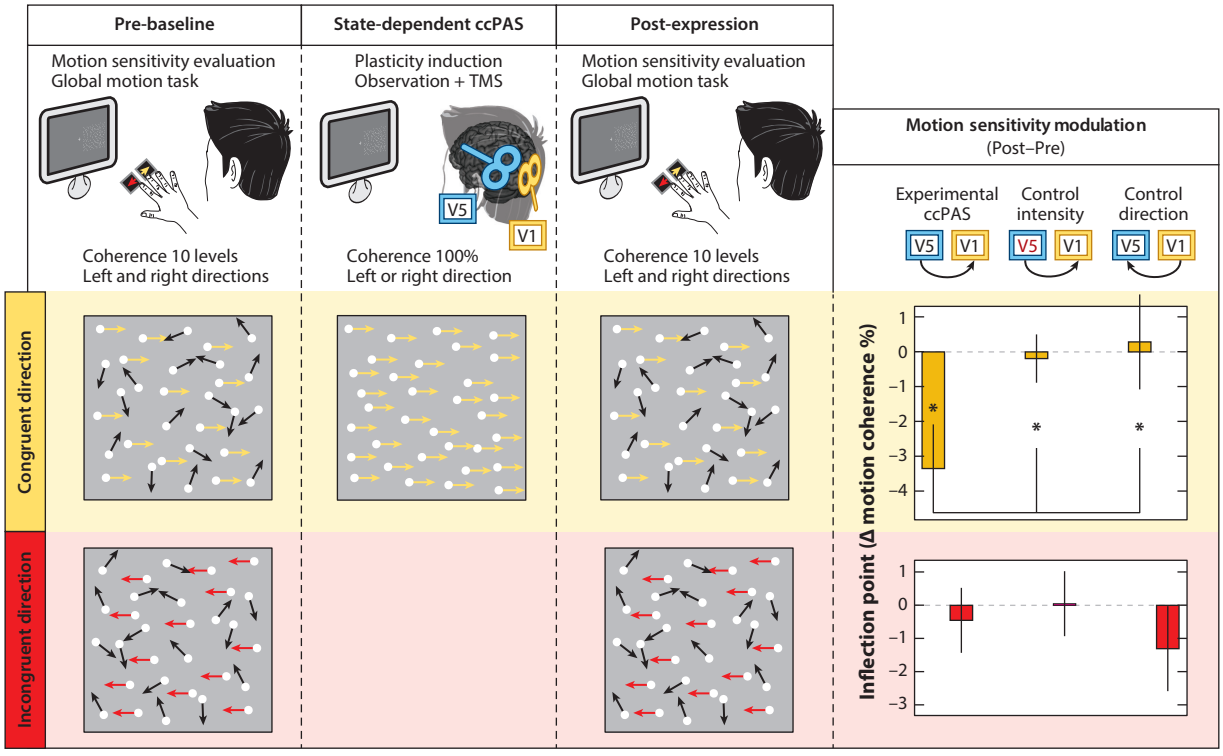



**Figure 4**

State-dependent cortico-cortical paired associative stimulation (ccPAS) (Chiappini et al. 2018). Subjects were tested on a global motion coherence task to set a baseline. They were then adapted to one direction of motion while stimulated with V5–V1 ccPAS. The subjects were then retested 30 min post-ccPAS/adaptation on the motion coherence task. The data panels at the far right show that motion coherence thresholds were significantly reduced when V5 TMS (at 80% phosphene threshold) preceded V1 TMS (at 100% phosphene threshold). Control conditions for intensity (V5 and V1 both at 100% phosphene threshold) and direction (V1 TMS 20 ms prior to V5 TMS) did not yield any change in phosphene threshold. Illustration by Vincenzo Romei.

need for fMRI) and also a type of state-dependent experiment (using TMS to influence state). Researchers at Hartwigsen's lab have dubbed them condition-and-perturb experiments and have shown their utility in action programming and semantic decision making (see also O'Shea et al. 2007, experiment 4). Hartwigsen et al. (2012) used two coils to apply 1 Hz offline TMS over the PMd before the subjects performed a spatially pre-cued reaction time task. During the task they then used 10 Hz online rTMS over the supramarginal gyrus (SMG) (see Hartwigsen et al. 2012, figure 1). The joint stimulation of the two areas produced a deficit in reaction times on invalidly cued trials that was not seen with SMG stimulation alone. The same group extended the condition-and-perturb principle to a different form of offline stimulation and in a different behavioral domain. Hartwigsen et al. (2016) used cTBS over SMG or angular gyrus as the offline conditioning stimulation, and 10 Hz over the anterior or posterior inferior frontal gyrus (IFG) in the condition online while subjects performed phonological or semantic decision tasks (see Hartwigsen et al. 2016, figure 2). Dual stimulation of angular gyrus offline and aIFG online produced specific RT deficits on the semantic decision task (see Hartwigsen et al. 2016, figures 5, 6). The functional specificity of these three experiments provides a proof of principle that we hope will be exploited widely in future experiments.

## BEHAVIORAL FINDINGS

Many inventive and impressive behavioral experiments have exploited advances in our understanding of psychological processes and combinations of TMS with other methods. Some of the studies discussed in the previous sections were chosen because they provided the first and/or good illustrations of TMS-imaging, STDP, or state dependency. This section surveys the breadth of TMS behavioral effects.

Visual awareness has been the subject of many TMS studies. Allen et al. (2014) used offline cTBS to reproduce blindsight-like effects. As discussed above, theta stimulation may not have a single effect at a single site. By combining cTBS with magnetic resonance spectography (MRS) and MEG, Allen et al. (2014) were able to show that although cTBS reduced cortical activity and increased GABA concentrations, awareness thresholds were decreased rather than increased as predicted. The behavioral and MRS effects of cTBS were stable between 0 and 48 min post-cTBS, so it is not possible to assess the results with Romero et al.'s (2019a) work in mind, but they provide a good example of how physiologically inhibitory TMS can result in behavioral enhancements. The same group also used MEG as a chronometric guide to use TMS to test the roles of pre-SMA and IFC in response inhibition (see Allen et al. 2018).

A related example of improvement following offline stimulation shows how using psychophysical tasks can help to parse the possible physiological mechanisms. Tadin et al. (2011) used 1 Hz TMS for 15 min over V5 or posterior occipital cortex while the subjects performed a motion discrimination task with stimuli of different sizes. TMS over V5 is usually employed to disrupt motion perception, but the area is also involved in spatial suppression because of its large receptive fields. Tadin and colleagues therefore used the psychophysical manipulation to show that disruption of the suppression caused by V5 TMS led to an improvement on movement discrimination tasks using large visual stimuli. So we see a pattern emerging in TMS and enhancements: TMS, which is still largely thought of as a neuro-disruptive method, can elicit functional improvements due to state dependency (e.g., Silvanto et al. 2008), psychophysical parameters (e.g., Tadin et al. 2011), different phases of physiological effects (e.g., Romero et al. 2017, 2019a,b), or inhibition of connected areas (e.g., Allen et al. 2014).

Attentional functions in the parietal cortex have long been a focus of TMS research (e.g., Herring et al. 2015, Mahayana et al. 2014, Olk et al. 2015) but behavioral studies within the last 10 years have revealed attentional effects in other areas (Rangelov et al. 2015), anatomical specificities for other functions in the human parietal cortex (Crawford et al. 2011; Vesia & Crawford 2012; Vesia et al. 2010, 2018), and interactions between attention and TMS physiological effects (Bergmann et al. 2016, Herring et al. 2015, Romei et al. 2016b, Taylor 2018, Thut et al. 2017). Rangelov et al. (2015) asked whether feedforward retinotectal input is necessary for attentional capture to occur. They bypassed retinotectal input by inducing phosphenes with TMS as valid and invalid cues. The phosphenes produced similar, though slightly weaker, cueing effects than real visual stimuli, but the paradigm of bypassing anatomical pathways by use of phosphenes is one that can be generalized and used in TMS-fMRI, TMS-EEG, and state-dependent experiments. Still in the domain of attentional functions, Herring et al. (2015) showed that single-pulse TMS-induced oscillatory activity in the visual system has the same neural origins and character as endogenous oscillations (thanks to Romero and colleagues we can now begin to look at those origins with physiological specificity). They measured transcranial evoked potentials (TEP) and EEG alpha responses while subjects attended to either a visual or an auditory stimulus in a cross-modal attention task. An early component of the TEP (N40) was enhanced by TMS while TMS-locked alpha power was reduced during visual attention conditions. It is tempting to note the similarity of timing between the TEP and the single units in Romero et al.'s (2017, 2019a,b) work, but we

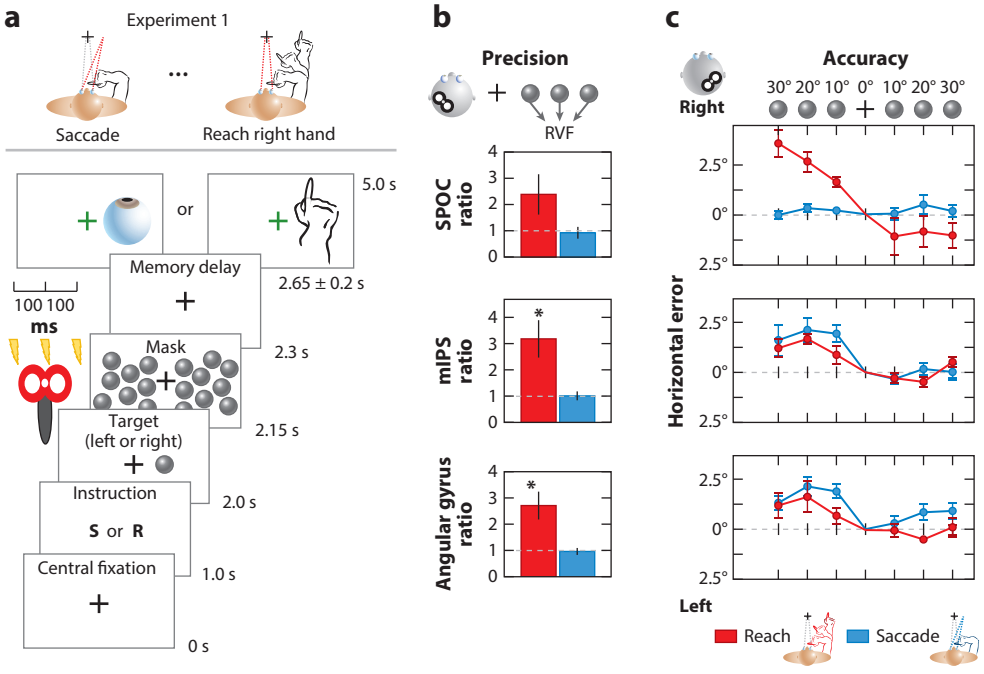



**Figure 5**

Anatomical and functional specificity of transcranial magnetic stimulation (TMS) over regions of the parietal cortex specific to reaching or saccades (Vesia et al. 2010). (*a*) Subjects were given a delayed spatial response task in which they planned either a reach or a saccade. Repetitive TMS (rTMS) was delivered during a brief, variable delay period between 300 and 700 ms. (*b*) Relative to baseline precision, rTMS over left but not right medial intraparietal sulcus (mIPS) or angular gyrus decreased precision of reaching into the right visual field (RVF). rTMS over the superior parietal occipital cortex (SPOC) had no effect. Red bars indicate left-hemisphere TMS; blue bars indicate right-hemisphere TMS. (*c*) rTMS of the right SPOC, but not left mIPS or angular gyrus, impaired the accuracy of saccades. Illustration by Michael Vesia.

would caution against expecting single units, EEG, and behavioral chronometries to show the same temporal patterns because they access different neuronal populations and events (see Walsh & Cowey 2000, figure 5).

The parietal cortex is perhaps over-dominated by attention research in psychology, so it is important to remind ourselves that it has other functions. Work by Vesia et al. (2010) and subsequent studies from the same group have elegantly parsed the functional specificity of human parietal areas based on single-unit evidence from nonhuman primate studies (see **Figure 5**). They delivered triple pulses of 10 Hz TMS over the superior parietal occipital cortex (SPOC) and two sites in the intraparietal sulcus (the medial intraparietal sulcus and, more caudally, the angular gyrus). Subjects were cued to perform a delayed spatial saccade or reach task, and the rTMS was delivered during the delay period. TMS over both the medial intraparietal sulcus and the angular gyrus increased the variability of reaching responses and impaired reach and saccade accuracy for contralateral targets. TMS of SPOC impaired reach accuracy but did not affect saccades.

We will end with an area of investigation that exemplifies everything we have highlighted in this review: memory. TMS studies under the banner of memory range from priming to working, episodic, meta, and declarative memory. Traditionally one might begin at the end, so to speak, in the hippocampus or the frontal lobes, but there have been remarkable memory-related findings

from TMS studies of occipital lobe function. Hilbert et al. (2019), for example, in studying working memory measured by digit span, described what one might call trait-dependent TMS effects. By administering digit span tasks to subjects and taking subjective reports of their mnemonic strategies, Hilbert and colleagues discovered that 1 Hz TMS close to the occipital pole given offline for 10 min before the task impaired memory performance in subjects who were categorized as visualizers. This shows that TMS is useful in identifying inter-individual differences in working memory processes. Several TMS studies have indicated a role for the sensory cortex in working memory (Campana et al. 2006, D'Esposito & Postle 2015, van de Ven & Sack 2013). Zokaei et al. (2014), for example, using online rTMS over V5, established that the probability of remembering the direction of motion of an object was a function of task relevance and serial position—not parameters one habitually associates with the sensory cortex. Their result may appear counterintuitive in that more recent stimuli were disrupted while more temporally distant items were facilitated by TMS over V5. A related effect was obtained with single-pulse TMS over the occipital cortex by van Lamsweerde & Johnson (2017), which disrupted the number of items subjects could remember. Van Lamsweerde & Johnson interpreted these effects as interfering with working memory consolidation. The timing of the TMS effects of Zokaei et al.'s (2014) and van Lamsweerde & Johnson's (2017) experiments falls within the first two phases of the single-unit responses discussed in the section titled Physiology and Behavior. They also affirm the importance of considering stimulus representations in the sensory cortex when studying some aspects of memory. These investigations into sensory working memory and representational states have been extended in a combined TMS-fMRI-EEG in a retro-cued recall paradigm. Rose et al. (2016) reported that the representations of items in working memory that are cued for upcoming relevance can be reactivated and decoded from simultaneous EEG recordings. The reactivation by TMS also enhanced memory performance (see also Manohar et al. 2019).

In the realm of episodic memory, an incremental series of studies has used rTMS, rsfMRI, fMRI, and EEG to distinguish between different memory pathways and enhance episodic memory performance over a period of 24 hr. The first experiment, which yielded an improvement in a face-word association memory task (Wang et al. 2014), is reviewed above in the section titled Functional Anatomical Networks. A follow-up study combining TMS and EEG (Nilakantan et al. 2017) conceptually replicated the finding using an object-location memory task and measuring it as a function of memory performance and stimulation. TMS improved spatial precision but not overall accuracy of performance, and it also caused two changes in electrophysiological measures. Oscillatory power in the theta–alpha range was reduced on successful recall trials, and the amplitude of recall-associated event-related activity was reduced post-TMS. The third study in this series (Kim et al. 2018) used a third memory paradigm and measured the effects of TMS on memory formation with fMRI. The authors were able to show, across three functional measures and three different memory tasks, that rTMS of an accessible part of the posterior cortico-hippocampal network selectively improved memory and changed network-wide patterns of activity.

## A COMMON MECHANISTIC EFFECT OF TMS ON BEHAVIOR?

Sometimes the best one can hope for as a scientist is to be intelligently and testably incorrect. Our early suppositions about TMS mechanisms fall into this category. From the work reviewed here, an important conceptual and mechanistic link presents itself. In the state-dependent experiments we see TMS activating adapted neuronal populations (Silvanto et al. 2007); in the working memory experiments we see TMS preferentially activating temporally less privileged representations (Zokaei et al. 2014); in phosphene awareness experiments we see TMS reactivating weak echoes (Jolij & Lamme 2010); and in the working memory reactivation experiments (Rose et al. 2016) we

see TMS preferentially activating latent representations. So, across physical parameter space (Silvanto), time (Zokaei), relevance (Rose), and state of awareness (Jolij & Lamme), there is a common picture of TMS preferentially stimulating weakly activated populations. We began this review by emphasizing the need to understand the physiology of TMS better, but intellectual traffic is never one-way, and these behavioral experiments set new questions for future physiological recordings. If, as in the past, we were now asked how we know what TMS is doing, we could return the question to the electrophysiologists with psychological dividends and ask, what do psychological states do to the physiological responses? Embracing the bidirectional interactions between the physiological effects of TMS and the physiological state of the brain being stimulated is a prerequisite for the next stage of progress.

## CONCLUSION

So where are we now? We may be accused of being overoptimistic about the advances in the last 10–12 years, but we'd enter a plea of not guilty. Foundations such as single-unit recordings, STDP, state dependency, anatomical reliability, MEPs, phosphenes, and network effects have depth in a literature that is almost unrecognizable from the point-and-shoot era predating our review. It is true that sample sizes are often small or appear so compared with those of pure behavioral experiments—combining TMS with a variety of methods and measures (fMRI, EEG, MEG, MRS, eye movements, MEPs, etc.) and using two coils isn't easy—and effect sizes go unreported (or selectively so). There have been few preregistered studies, and even some of those few have based much of their interpretation on unplanned analyses. All of these are weaknesses and are fixable: It is important to report null results (de Graaf & Sack 2011), to consider preregistration of experiments (Nosek et al. 2018), adequately report the stimulation methods and dosage (Peterchev et al. 2012), and adopt and adapt open data practices from other areas of research (Nichols et al. 2017). However, these issues are neither unique nor even particularly specific to our field compared to others, and slow and clumsy though the progress may seem to some, slow and clumsy are not entirely bad ways of making scientific progress (Frith 2020, Lewandowsky & Oberauer 2020). We encourage all authors and reviewers to partake in improving the overall quality of the field. However, we do not want to diminish the significance of the efforts, results, and knowledge that have accrued: The overall message from the literature we have surveyed is overwhelmingly positive. The field has moved on technically (e.g., Allen et al. 2014, 2018; Polanía et al. 2018; Thut et al. 2017), conceptually (Romero et al. 2017, 2019a,b; Chiappini et al. 2018), and empirically (e.g., Amemiya et al. 2017; Brown et al. 2019a,b; Ruzzoli & Soto-Faraco 2014; Willacker et al. 2019). If, as Medawar (1967, p. 87) states, "research is surely the art of the soluble," the last decade or so of research in TMS and cognition has, at the very least, brought many new questions into that realm of the soluble.

## DISCLOSURE STATEMENT

The authors are not aware of any affiliations, memberships, funding, or financial holdings that might be perceived as affecting the objectivity of this review.

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