

# How can transcranial magnetic stimulation be used to causally manipulate memory representations in the human brain?

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We present a focused review on the utility of transcranial magnetic stimulation (TMS) for modulating memory, with a particular focus on multimodal approaches in which TMS is paired with neuroimaging methods (electroencephalography and magnetic resonance imaging (MRI)) to manipulate and measure working memory processes. We contrast the utility of TMS for manipulating memory with other forms of noninvasive brain stimulation, as well as different forms of TMS including single-pulse, paired-pulse and repetitive TMS protocols. We discuss the potential for TMS to address fundamental cognitive neuroscience questions about the nature of memory processes and representations, while acknowledging the considerable variability of behavioral and neural outcomes in TMS studies. Also discussed are the limitations of this technology, current advancements that have helped to defray the impact of these limitations, and suggestions for future directions in research and methodology.

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## KEYWORDS

noninvasive brain stimulation, short-term memory, transcranial magnetic stimulation, working memory

## 1 | INTRODUCTION

The field of cognitive neuroscience is growing in many ways, most notably in the increasingly nuanced questions that are being explored through the use of new and powerful techniques for studying cognitive function in humans. One notable technological advancement is the combined use of noninvasive brain stimulation (NIBS)—such as transcranial magnetic stimulation (TMS)—and brain imaging methods. Researchers are using such technologies in an attempt to open up the “black box” and examine the (“invisible”) cognitive processes and representations that support functions such as attention and memory. It is argued that supplementing correlational data obtained from neuroimaging studies with causal data obtained from brain stimulation studies is critically important for closing the loop in terms of understanding structural and functional relationships between mind and brain. To that end, this article will review the use of TMS in a particular domain of cognitive neuroscience research on working memory (WM) in order to compare and contrast TMS with other forms of brain stimulation, and highlight its strengths and promise alongside the limitations that must be overcome to advance the use of this technology.

## 2 | WHAT IS TMS AND HOW DOES IT WORK?

TMS is a generally well-tolerated form of NIBS with high temporal and relatively high spatial precision. Stimulation of cortical neurons is produced when a magnetic field is induced by a strong electric current that is passed through a coil

of insulated wiring, typically in a figure-of-eight-shaped coil. The strong electrical current that is discharged generates a brief, high-intensity magnetic field maximally focused in the center of the coil. This targeted magnetic pulse instantaneously passes through the scalp, skull, and dura matter, and the induced current is able to cause neurons to fire (Hallett, 2007) and modulate cortical excitability in regions of cortex with precision at the level of tens of millimeters (Deng, Lisanby, & Peterchev, 2013). This modulation of cortical excitability also occurs in distal brain regions whose activity happens to be functionally connected with the targeted region of cortex at the time of stimulation (Casali et al., 2013; Johnson, Kundu, Casali, & Postle, 2012; Kundu, Sutterer, Emrich, & Postle, 2013; Wang et al., 2014).

Three main forms of TMS are defined as follows, and a discussion of their varying utilities is discussed later in this review. Single pulse TMS (spTMS) is just as it sounds—a single pulse delivered to the brain—and can provide a “ping and record” methodology for probing cortical excitability and effective connectivity. Though this technique is quite common, an integrative understanding of its varying effects on neuronal activity is quite complex and, although some details are briefly discussed later in the review, the reader is referred elsewhere for detailed description of the mechanism of action of TMS (e.g., Di Lazzaro, Rothwell, & Capogna, 2017). Paired-pulse TMS (ppTMS) refers to the delivery of two stimuli in succession—a conditioning pulse followed by a test pulse—which can cause inhibition or facilitation depending on the intensity of the pulses and the interval between pulses. Valero-Cabré, Amengual, Stengel, Pascual-Leone, and Coubard (2017) outline the following general types of ppTMS: when the conditioning stimulus is subthreshold and the test stimulus is suprathreshold, short interval intracortical inhibition occurs at inter-stimulus intervals (ISIs) of 1–4 ms, intracortical facilitation at ISIs of 10–15 ms, and long interval intracortical facilitation at 100 ms ISI. Short interval intracortical facilitation occurs at inter-stimulus intervals (ISIs) of 1–4 ms when a subthreshold test stimulus is preceded by a suprathreshold conditioning stimulus and long interval intracortical inhibition occurs at ISIs of 50–200 ms when both the conditioning and test stimuli are suprathreshold. Repetitive TMS (rTMS) describes stimulation protocols in which a series of individual TMS pulses are applied in trains typically  $\geq 1$  Hz, which either decreases cortical excitability with an inhibitory, suppressing effect via long-term depression-like processes (e.g., continuous theta-burst stimulation, cTBS) or increases cortical excitability and functional connectivity via long-term potentiation-like processes (e.g., intermittent theta-burst stimulation, iTBS; Huang, Edwards, Rounis, Bhatia, & Rothwell, 2005). Although TMS protocols that are within established safety guidelines are well-tolerated by most subjects, some protocols may be rather uncomfortable or even painful for some subjects and, therefore, must be administered with caution (Rossi, Hallett, Rossini, & Pascual-Leone, 2009). The combination of subthreshold conditioning stimulus followed by two suprathreshold test stimuli is termed short interval cortical facilitation (SICF) (Wagle-Shukla et al., 2009).

An aspect of rTMS protocols that needs to be carefully considered and systematically investigated concerns the dose-response effects associated with different frequencies, intensities and durations of stimulation. The effects of causally modulating cortical firing differs depending on several factors, especially regarding the level of intensity, but also the frequency with which pulses are applied, the time intervals between trains of pulses, as well as the shape and direction of the electromagnetic field, among others (for review, see Rossini et al., 2015). When low-frequency ( $< 1$  Hz) rTMS is applied, there is typically evidence for the suppression or inhibition of neuronal firing in a localized area, whereas high-frequency ( $> 1$  Hz) rTMS tends to lead to facilitation of neuronal firing in a localized area (Siebner & Rothwell, 2003). As the intensity and duration of rTMS is increased, the powerful aftereffects are stronger and are sustained for longer period of time beyond the stimulation period, for example, from ~5 to 40 min following a single session to several days following multiple sessions of high-frequency rTMS (Gersner, Kravetz, Feil, Pell, & Zangen, 2011; Siebner & Rothwell, 2003). It is important to note that high frequency rTMS may have more risks than spTMS, ppTMS, and low-frequency rTMS. Safety guidelines concerning frequency and intensity limits, as well as recommendations on train length, should be followed to minimize potential risks. For more information, see U.S. Food and Drug Administration/Center for Devices and Radiological Health (2011) and Rossi et al. (2009).

A full review of the method of activation of TMS is beyond the scope of the current review but it is quintessential for cognitive neuroscientists to understand the complex and technical details of the mechanisms by which TMS modulates brain activity in order to establish appropriate inferences about its effects on cognitive processes and representations. For comprehensive reviews of the technical aspects of magnetic stimulators, and associated methodological concerns see Groppa et al. (2012), Kammer, Beck, Thielscher, Laubis-Herrmann, and Topka (2001), and Sauvé and Crowther (2014).

### 3 | TMS AS COMPARED TO OTHER FORMS OF NONINVASIVE BRAIN STIMULATION

To fully understand the unique utility of TMS, it must be contrasted with the other mainstay of NIBS, transcranial electrical stimulation (tES). tES comes in three main variants: transcranial alternating-current stimulation, transcranial direct-current

**BOX 1****GLOSSARY**

*Transcranial magnetic stimulation:* Non-invasive brain stimulation technique in which electrical pulses discharged through an insulated coil held to the scalp produce a strong, localized magnetic field that can cause neurons to fire in a focused brain region.

*Transcranial direct-current stimulation:* Non-invasive brain stimulation technique in which low levels of direct electrical current are passed between two or more electrodes attached directly to the scalp with the goal of modulating cortical excitability in underlying brain areas.

*Transcranial alternating-current stimulation:* Non-invasive brain stimulation technique in which low levels of alternating electrical current are passed between two or more electrodes attached directly to the scalp with the goal of modulating cortical oscillations in underlying brain areas.

*Transcranial random noise stimulation:* Non-invasive brain stimulation technique in which low levels of direct electrical current are passed between two or more electrodes attached directly to the scalp at random amplitude and frequency with the goal of modulating cortical excitability.

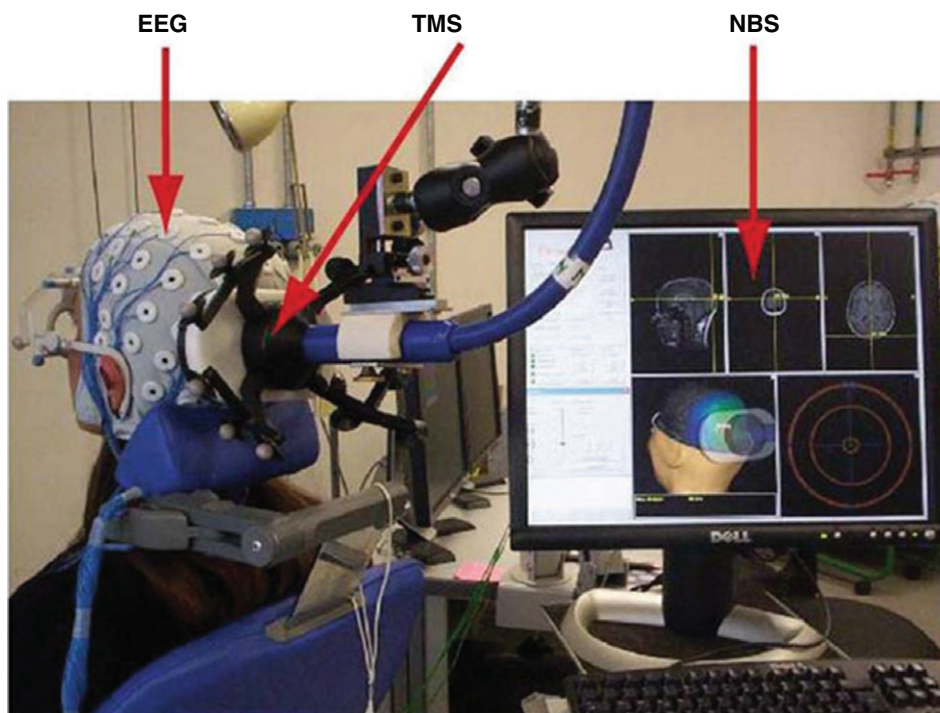
*Direct acute electrical stimulation:* Invasive brain stimulation technique that accomplishes acute/sub-acute periods of electrical stimulation using temporarily implanted electrodes - either subdural grid electrodes, which directly stimulate the surface of the cortex, or depth electrodes that penetrate the brain and directly stimulate cortical and/or subcortical structures.

*Direct chronic electrical stimulation:* Invasive brain stimulation technique that accomplishes sustained periods of electrical stimulation using chronically implanted electrode systems with internalized current generators, potentially leading to long-term potentiation and/or neurogenesis.

stimulation (tDCS), and transcranial random noise stimulation (see Box 1). These methods of stimulation use weak electrical currents conducted between two or more electrodes affixed directly to the scalp to putatively modulate the ongoing (endogenous) neural activity across a diffuse range of the underlying brain regions by altering the transmembrane potential of the neurons and, therefore, cortical excitability of the areas (Nitsche et al., 2008). The initial hope for the potential of tDCS to enhance cognition was buoyed by encouraging findings, but, like TMS, the conversation has recently included a more critical debate about the potential limitations and challenges of this method (Polania, Nitsche, & Ruff, 2018). Recent meta-analyses (Horvath, Forte, & Carter, 2015; Mancuso, Ilieva, Hamilton, & Farah, 2016) call for skepticism, which is corroborated by failed replications (Robison, McGuirk, & Unsworth, 2017), and the “file-drawer” problem (Minarik et al., 2016). Unlike TMS, tDCS does not directly cause neuronal firing, and it is unclear to which extent a sufficient signal from tDCS passes the scalp, skull, and dura matter to even potentially modulate cortical excitability (Lafon et al., 2017; Underwood, 2016). However, it is undeniable that tES methods have allowed researchers to explore previously uncharted territory in how experimentally altered neural activity casually affects behavior.

Since tES is a mainstay of NIBS along with TMS, it is worthwhile to compare the respective utilities of these two families of methods for the investigation of WM processes. It is critical to note that with all of the variants of tES, it is not possible to selectively target and modulate the activity of a precise brain region as tES methods have less anatomical specificity than can be provided by a TMS coil (Kim, Ekstrom, & Tandon, 2016). Furthermore, these forms of stimulation are temporally imprecise. It is not possible to turn the stimulation on and off to selectively modulate fast-acting, dynamic cognitive processes that occur during, for example, the encoding, maintenance, or retrieval of a stimulus. A full review of these other NIBS techniques is beyond the scope of the current review—interested readers should see Berryhill, Peterson, Jones, and Stephens (2014), Brunoni and Vanderhasselt (2014), Polania et al. (2018), and Wagner, Valero-Cabre, and Pascual-Leone (2007).

TMS can also be contrasted with invasive forms of brain stimulation such as direct acute electrical stimulation (aDES) and direct chronic electrical stimulation (cDES, e.g., deep brain stimulation). These approaches provide opportunities to directly stimulate deep cortical and subcortical structures, which may not be directly stimulated with TMS. Moreover, they do so at a level of spatial precision that is far greater than noninvasive techniques (Suthana & Fried, 2014). An obvious drawback of these approaches, however, is that they require a craniotomy and neurosurgery to implant the electrodes. Therefore, such drastic measures are only suitable for patients with severe conditions. For reviews comparing forms of both invasive (aDES and cDES) and noninvasive (TMS and tDCS) brain stimulation, see Kim et al. (2016) and Rossini et al. (2015).



**FIGURE 1** Simultaneous electroencephalography (EEG) and transcranial magnetic stimulation (TMS) setup with navigated brain stimulation (NBS, Reprinted with permission from Rosanova et al. (2012). Copyright 2012 Springer Nature)

#### 4 | BENEFITS OF USING TMS FOR INFERRING CAUSAL BRAIN-BEHAVIOR RELATIONSHIPS

In contrast to the different forms of tES, TMS can be used to causally stimulate precise brain regions at specific points in time, for example, at the exact moment when a specific brain region is hypothesized to be involved with a particular cognitive process. Critically, this can all be done noninvasively in humans while they are awake and performing just about any cognitive task. Therefore, if a researcher hypothesizes that a specific region of the cerebral cortex underlies the performance of a particular cognitive task, TMS may be used to causally perturb parts of that network at different time points—either during the task (online) or before the task (offline)—thus probing the necessity of those neural processes to the task. The differences between online and offline stimulation is elaborated below.

The observable effects of the stimulation are seen not only through behavioral performance, but, when coupled with simultaneous neuroimaging methods (e.g., functional magnetic resonance imaging [fMRI], electroencephalography [EEG]), through modulation of the underlying neural signals that result in the observed behavior modification as well. Sophisticated data analytic techniques (such as machine learning algorithms) allow decoding of patterns of brain activity that reflect cognitive representations and processes, thus providing additional, novel insights into the mind (Figure 1).

While the utility of TMS is far-reaching, the current review focuses on recent work in the specific field of short-term memory and WM research in order to illustrate how these methodological advancements are providing novel insights about core neurocognitive processes that support the ability to retain information “in mind” in the service of ongoing processing and goal-directed actions.

#### 5 | REVIEW AND COMPARISON OF TMS PROTOCOLS INVESTIGATING WORKING MEMORY

To highlight the importance of subtle methodological details in the search for effective protocols for modulating memory functioning, the current review attempts to compare and contrast the extant literature that has applied single-pulse, paired-pulse, and rTMS protocols within a focused domain regarding the cognitive neuroscience of WM. Although this field is still rapidly growing, an emerging picture is revealed about where we are and where the field is going, particularly with regards to the identification of dose–response relationships and an understanding of some of the seemingly counterintuitive effects of TMS. Table 1 contains a wide sample of recent, innovative spTMS and rTMS studies that explore questions of short-term/WM in healthy, young adults, and can be used to compare and contrast the differing methodologies and outcomes.



TABLE 1 Sample of studies utilizing transcranial magnetic stimulation (TMS) to investigate working memory in healthy adults

Reference	Task design	Stimuli type	Stimulation location	Navigated brain stimulation	Control condition	Stimulation protocol	Stimulation timing	Effect of TMS
Rose et al. (2016)	Two-item delayed recognition task (two retro-cues, two recognition probes)	Words, faces, motion	MVPA-defined, non-overlapping, participant-specific, category-sensitive areas during WM delay for "words", "faces", or "motion"	MVPA of fMRI	Control condition: absent memory item; Control site: non-targeted category sites; Control timing: when item is no longer relevant	spTMS, 90–115 V/m, paired with online EEG	2–3 s after cue	TMS re-activated neural decoding of the unattended memory item and increased false alarms to recognition probes of the unattended memory item, but only when the item was still potentially relevant on the trial
Kundu et al. (2013)	<i>Training</i> : adaptive, visuospatial, dual n-back task; <i>Assessment</i> : location change detection task with distractors	<i>Training</i> : color and location; <i>Assessment</i> : location	Left SPL	sMRI	Control task: adaptive, speeded visuospatial task with no explicit WM; component (Tetris)	spTMS, 110–140 V/m; paired with online EEG	First pulse: $750 \pm 250$ ms poststimulus offset; Second pulse: $2000 \pm 250$ ms later	TMS-ER detected training-related transfer to location change detection task with distractors—that is, strengthened task-related effective connectivity across frontoparietal and parieto-occipital networks
Johnson et al. (2012)	Visuospatial STM task	Location of abstract shapes	Left SPL	sMRI	Control task: fixation	spTMS; 0.5 Hz; 110–140 V/m; paired with online EEG	(STM task) first pulse $750 \pm 250$ ms poststimulus offset; second pulse $2000 \pm 250$ ms later. (fixation) groups of four pulses with each pulse separated by $2000 \pm 250$ ms	Task performance increased overall strength of electrical currents induced by TMS, increased the spatial spread of TMS-evoked activity to distal brain regions, and increased ability of TMS to reset the phase of ongoing broadband cortical oscillations.
Zanto, Rubens, Thangavel, and Gazzaley (2011)	Two-item delayed-recognition task (pre-cue to attend color or motion)	Color or motion	Right IFJ	fMRI and sMRI	Sham stimulation with coil angled 90° away from the participant's head	rTMS 1 Hz; 120% RMT; paired with offline EEG	10-Minute train in between sessions	TMS modulated activity in posterior cortex during early encoding, which predicted a subsequent decrement in WM accuracy (especially for those with stronger fronto-posterior functional connectivity)
Higo, Mars, Boorman, Buch, and Rushworth (2011)	Two-item match/nonmatch task	Houses, bodies and faces	Left fO	fMRI and sMRI	No TMS	rTMS 1 Hz; 90% RMT; paired with offline fMRI	15-Minute train in between sessions	TMS-mediated interference of fO activity diminished the selective attentional modulation in the occipitotemporal regions
Feredoes, Heinen, Weiskopf, Ruff, and Driver (2011)	Visual delayed recognition task with distractors	Houses and faces	Right DLPFC	fMRI and sMRI	"Low intensity" (40% RMT) stimulation	rTMS 11 Hz with online fMRI	Middle of delay period (when distractors might appear)	TMS to the DLPFC (as a "physiological probe") increased activity in regions representing the current memory targets, but only when distractors were present

(Continues)

TABLE 1 (Continued)

Reference	Task design	Stimuli type	Stimulation location	Navigated brain stimulation	Control condition	Stimulation protocol	Stimulation timing	Effect of TMS
Mottaghy et al. (2000)	Two-back verbal working memory task	Letters	Right and left DLPFC	10–20 system, validated with sMRI	Control task: zero-back (X and Y) task; control site: Fz	rTMS 4 Hz; 110% RMT; paired with online PET	30 s train during two-back task	TMS significantly worsened performance in the WM task while inducing significant reductions in rCBF at the stimulation site and in distant brain regions
Van Lamsweerde and Johnson (2017)	Six-item continuous adjustment recall task (one retro-cue) with visual mask or TMS during delay period	Colored blocks	Retinotopic early visual cortex	sMRI	Control site: attended to the hemifield ipsilateral to stimulation	spTMS; 110% PT	At 0, 100, or 200 ms poststimulus offset	TMS at 0 ms poststimulus offset decreased quantity of VWM representations in the affected hemifield, with disruption entirely disappearing later into the delay. TMS also produced an unexpected reduction in swap rate across all time intervals
Oliveri et al. (2001)	Visual-object and visual-spatial two-back tasks	Spatial locations and abstract patterns	(Exps. 1, 2, 3) posterior (parietal and temporal); (Exps. 4, 5) frontal (SFG and DLPFC) cortical regions	10–20 system	No TMS	spTMS; 130% RMT	(Exps. 1, 2, 4) 300 ms; (Exp. 4) 600 ms; (Exps. 3, 5) 0 ms and 3300 ms poststimulus offset	At 300 ms, temporal TMS increased RTs in the visual-object, whereas parietal TMS increased RTs in the visual-spatial WM task. At 600 ms, TMS of the SFG selectively increased RTs in the visual-spatial WM task, whereas TMS of the DLPFC interfered with both WM tasks, in terms of both accuracy and RTs
Mull and Seyal (2001)	Verbal working memory three-back task	Letters A–J	Right and left DLPFC	10–20 system	No TMS	spTMS; 115% RMT	400 ms poststimulus offset	TMS to the left DLPFC caused increased errors in the WM task, while TMS over the right DLPFC did not alter WM performance
Desmond, Chen, and Shieh (2005)	Six-item Sternberg verbal WM task	Upper-case, consonant letters	Right superior cerebellum	fMRI and sMRI	Sham stimulation (with click sound) and no TMS; Control task: motor control task	spTMS; 120% RMT	0 ms poststimulus offset	TMS increased RTs on correct trials of the verbal WM and motor control tasks (significantly greater for WM than motor control) and had no effect on WM accuracy
Cattaneo, Vecchi, Pascual-Leone, and Silvanto (2009)	Visual-spatial working memory task	Clock hands	Retinotopic early visual cortex	Functional localization: phosphene induction	Control site: vertex	spTMS 65% stimulator max	0 ms poststimulus offset or 2 s poststimulus offset	TMS to early visual cortex immediately after stimulus offset impaired memory performance while TMS at the end of the retention period facilitated memory performance

(Continues)

TABLE 1 (Continued)

Reference	Task design	Stimuli type	Stimulation location	Navigated brain stimulation	Control condition	Stimulation protocol	Stimulation timing	Effect of TMS
Jolij and Lamme (2010)	Induced phosphenes via TMS following target grating presentation on a tilted background with concurrent background tilt shift	Orientation	Retinotopic early visual cortex	Measured from inion	Control task: a second grating was flashed 300 ms after the target grating, immediately followed by a TMS pulse	spTMS; 90% stimulator max	300 ms poststimulus offset	TMS re-activated weak visual representations in early visual areas and produced “visual echoes,” that is, reactivation of orientation
Silvanto and Cattaneo (2010)	2-Item change detection task (single retro-cue) preceded by phosphene induction	Motion	V5/MT+	Functional localization: phosphene induction	No TMS; Control tasks: motion stimuli and TMS but no response, TMS but no motion stimuli or response	spTMS; 120% PT	3 s poststimulus offset	TMS caused the reported phosphenes to contain motion features of the memory item when the phosphene spatially overlapped with the memory item, that is, the stimulation produced reactivation of motion
Van De Ven, Jacobs, and Sack (2012)	1- or 3-item change detection task (one pre-cue that signalled hemifield of stimulus presentation)	“BORTs,” that is, gray surfaces of nonnatural shapes	Retinotopic lateralized occipital cortex	fMRI and sMRI; functional localization: phosphene induction	No TMS	spTMS; 110% PT	100, 200 and 400 ms poststimulus offset	TMS at 200 ms in the 5-item condition caused decreased memory performance in the affected hemifield. TMS-induced interference decreased the strength (amplitude) of the memory representation, which most strongly affected the high memory load trials
Rademaker, Van De Ven, Tong, and Sack (2017)	4-Item continuous adjustment recall task (one retro-cue)	Orientation	Retinotopic early visual cortex	fMRI and sMRI	Sham stimulation; Control site: diagonal quadrant	rTMS 10 Hz (3 pulses); 80% PT	At cue onset or midway through 2 s delay	Early TMS impaired performance as compared to late TMS. TMS improved performance (smaller recall error) when overlapping with cued item location
Silvanto and Soto (2012)	1-Item change detection task with subliminal distractor at incongruent or congruent orientation	Orientation	Retinotopic early visual cortex	Functional localization: phosphene induction	Sham stimulation with coil held perpendicular to scalp; Control task: no distractor	rTMS 10 Hz; 90% PT	Pulse train (3 pulses) applied concurrently with onset of distractor	TMS impaired the fidelity of VSTM content in the absence of the distractor, and facilitated VSTM performance in the presence of the incongruent distractor

(Continues)

TABLE 1 (Continued)

Reference	Task design	Stimuli type	Stimulation location	Navigated brain stimulation	Control condition	Stimulation protocol	Stimulation timing	Effect of TMS
Silvanto, Muggleton, Covey, and Walsh (2007)	(1) induced phosphenes via TMS following adaptation to single-color or dual-color displays; (2) one-item delayed response task with adaptation mask	(1) color; (2) colored stripes	Retinotopic early visual cortex	Functional localization: Phosphene induction	No TMS	rTMS 20 Hz; (1) 110% PT; (2) 80% PT	(1) 30 s of adaptation followed by three TMS pulses applied every 2 s; (2) three TMS pulses at stimulus onset	(1) TMS induced a phosphene with the color of the adapting stimulus (reactivates color) and (2) TMS facilitated detection of the congruent stimuli and impaired detection of the incongruent stimuli, that is, TMS perceptually facilitated the attributes encoded by the least active neural populations
Motiagh, Gangitano, Sparing, Krause, and Pascual-Leone (2002)	Spatial or face-recognition delayed-response task (three items in succession)	Faces, location	Dorsomedial, dorsolateral or ventral prefrontal cortex	10–20 system with post hoc sMRI validation	No TMS	rTMS 1 Hz; 90% RMT	10 min train in between two sets of three blocks each	TMS to the DMPFC impaired performance in the spatial task, while TMS to the VPCF impaired performance on the face-recognition task. TMS to the DLPFC affected performance in both tasks
Zokaei, Manohar, Husain, and Feredoes (2014)	2-Item, delayed-recall continuous adjustment task with an incidental cue that brought one target into a privileged state	Location and color	Left MT+	fMRI	Low, “ineffective” intensity stimulation of 24% stimulator maximum	rTMS 20 Hz; 60% stimulator max	250 ms TMS train (four pulses) 2600 ms poststimulus offset	TMS caused privileged items to be recalled with less precision, whereas nonprivileged items were recalled with higher precision. Thus, only the privileged item was susceptible to disruptive TMS over MT+
Feredoes, Tononi, and Postle (2006)	4-Item delayed recognition task with proactive interference	Consonant letters	Left IFG	sMRI	No TMS; Control sites: left SMA/right MI and left PCG	rTMS 8 Hz; 110% RMT	1250-ms period at onset of the memory probe	TMS only to the left IFG caused a disruption of WM accuracy (restricted to high-proactive interference probes)
Mackey and Curtis (2017)	Memory-guided delayed saccade task	Location	Right DLPFC; left sPCS and IPS2	fMRI and nonlinear pRF mapping	No TMS	rTMS 50 Hz; 53% stimulator max	One train of 3 pulses halfway through delay period	TMS to sPCS caused an increase in memory-guided saccade (MGS) errors especially in the contralateral visual field, but not FEP errors. TMS to IPS2 impaired FEP errors in the contralateral visual field. TMS to the right DLPFC caused no observable impairments

(Continues)



TABLE 1 (Continued)

Reference	Task design	Stimuli type	Stimulation location	Navigated brain stimulation	Control condition	Stimulation protocol	Stimulation timing	Effect of TMS
Postle et al. (2006)	5-Item delayed recognition of item position task	Consonant letters	MFG of the DLPFC, SPL	fMRI and sMRI	Control site: PCG; No TMS	rTMS 5 Hz; 100% RMT	6 s train at 2 s postinstruction offset	While TMS of the DLPFC selectively disrupted WM manipulation, TMS of the SPL disrupted both WM manipulation and WM retention
Feredoes and Postle (2009)	4-Item response deadline, delayed item-recognition task	Consonant letters	Left IFG	sMRI	Control site: left MFG; Control tasks: nonrecent positive, recent positive, and nonrecent negative probe types	rTMS; 110% RMT	Three conditions: early (3 pulses, 0–250 ms from probe onset), late (3 pulses, 500–750 ms from probe onset), and full (10 pulses, 0–1250 ms from probe onset)	Only early TMS to left IFG caused reduced WM accuracy specifically for high proactive-interference probes. Additionally, the magnitude of this effect was predicted by individual differences in susceptibility to proactive interference

*Note.* DLPFC, dorsolateral prefrontal cortex; DMPPFC, dorsomedial prefrontal cortex; FEP, final eye position; Fz, frontal midline in EEG system; IFG, inferior frontal gyrus; IFJ, inferior frontal junction; IPS2, third intra-parietal sulcus area in parietal cortex; M1, primary motor cortex; MFG, middle frontal gyrus; MGS, memory-guided saccade; MVPA, multivariate pattern analysis; PCG, postcentral gyrus; pRF, population receptive field; PT, phosphene threshold; rCBF, regional cerebral blood flow; RMT, resting motor threshold; SFG, superior frontal gyrus; SMA, supplementary motor area; sMRI, structural MRI; sPCS, superior precentral sulcus; SPL, superior parietal lobule; TMS-ER, TMS-evoked response; V5/MT+, middle temporal visual area; VPFC, ventral prefrontal cortex; VSTM, visual short-term memory.

Traditionally, TMS was viewed as a “virtual lesion” approach, where applying TMS was expected to lead to impairment. This view was supported by the large number of studies that found impairments following a variety of spTMS and rTMS protocols when applied to lateral prefrontal cortex (Feredoes et al., 2006; Feredoes & Postle, 2009; Mackey & Curtis, 2017; Mottaghy et al., 2000, 2002; Mull & Seyal, 2001; Oliveri et al., 2001; Postle et al., 2006; Zanto et al., 2011), parietal cortex (Mottaghy et al., 2002; Oliveri et al., 2001; Postle et al., 2006), sensory cortex (Van De Ven et al., 2012; Van Lamsweerde & Johnson, 2017), and the cerebellum (Desmond et al., 2005). However, other studies applying TMS to the visual cortex show both WM disruption and facilitation with the same TMS protocol, depending on the task parameters. Repetitive TMS to sensory cortex was found to improve WM precision of nonprivileged (motion) items while impairing precision of privileged (motion) items (Zokaei et al., 2014), and visual short-term memory (VSTM) was facilitated for items with an incongruent, subliminal memory mask but impaired for the same items with no memory mask (Silvanto & Soto, 2012). Rademaker et al. (2017) hypothesized, based on their similarly variable findings, that while TMS at 0 ms poststimulus presentation might disrupt early-phase consolidation in a nontopographic manner, TMS also increases precision of the item at the targeted retinotopic location.

These highly varied and seemingly inconsistent results can be viewed more coherently if one views the effects of TMS as the result of nonlinear interactions between TMS protocol (e.g., intensity, frequency, duration) and neural excitability (state-dependency). After finding that TMS facilitated performance at the end of a retention period but impaired performance at the beginning of a retention period, Cattaneo et al. (2009) hypothesized that TMS preferentially activates neurons in a low initial activation state (low firing rate). This hypothesis is additionally supported by studies showing that spTMS to sensory cortex can reactivate WM for weak representations of color (Silvanto et al., 2007), gratings (Jolij & Lamme, 2010), and motion (Rose et al., 2016; Silvanto & Cattaneo, 2010) and modeling work demonstrating that a neuron in a high initial activation state (i.e., firing strongly in response to a visual stimulus) can be less excitable in response to strong external stimulation (such as a TMS pulse) than a neuron in a lower initial activation state (Matthews, 1999; see also Siebner, Hartwigsen, Kassuba, & Rothwell, 2009).

Silvanto and Cattaneo (2017) recently codified a common theoretical framework for the effects of TMS wherein distinct intensity ranges induce different effects. They posit that low intensities facilitate neural activity and behavior whereas high intensities induce suppression, but what classifies as “low” or “high” intensity depends on the underlying brain state—changes in neural excitability can shift the range for facilitation versus suppression and thus lead to the seemingly inconsistent results detailed above. According to this model, facilitation will happen at high intensities if the neurons have reduced excitability due to adaptation or inhibition. For example, neurons not involved in task-related processes are inhibited by the ongoing task and will thus be facilitated by TMS. Neurons involved in task-related processes will be suppressed by TMS with a reduction of the signal-to-noise ratio and behavioral impairment. This framework is also in line with the phenomenon of stochastic resonance, where low levels of noise can push the intensity of weak signals above threshold, thereby enhancing detection (Schwarzkopf, Silvanto, & Rees, 2011).

As it relates to our review of TMS effects on WM, it is worth highlighting the unique utility of ppTMS to selectively activate and measure specific neural mechanisms at the cellular and synaptic level and, therefore, the unique insights that may be revealed by this form of stimulation. Rogasch, Daskalakis, and Fitzgerald (2015) utilized a ppTMS paradigm with an interval of 100 ms (similar to the LICI paradigm used in motor cortex) in combination with EEG to assess the role of cortical inhibition in the dorsolateral prefrontal cortex (DLPFC). They found that greater suppression of the N100, a TMS-evoked potential linked with inhibitory activity, was related to individual differences in WM ability, suggesting presynaptic inhibitory mechanisms in the DLPFC may play an important role in cognitive performance. Thus, ppTMS uniquely allowed for investigation of inhibitory states in the brain, and the role that intracortical inhibition has on WM ability.

## 5.1 | Online protocols

Online TMS-EEG protocols have shown further utility to investigate the neural bases of WM through various analysis techniques that utilize various aspects or consequences of the TMS-evoked response (TMS-ER). Source localization analyses of the TMS-ER on simultaneously recorded EEG allows the assessment of the cortical excitability of the stimulated brain region(s) and effective connectivity between brain regions, that is, connectivity between the site of TMS to other distal regions that are functionally coupled with the site of TMS at that point in time (Massimini et al., 2005). Additionally, a measure of phase locking conveys the extent to which TMS induces a resetting of the phase of an ongoing cortical oscillation (Casali, Casarotto, Rosanova, Mariotti, & Massimini, 2010). Together, these measures provide inferences that are analogous to functional connectivity, cross-channel coherence, or phase–amplitude coupling analyses of neural data from different channels, but the causal nature of the induced signal spread also reflects the source or directionality of neural communication between distal sites. Double-coil stimulation methods provide further direct, causal evidence for the direction and timing of neuronal transmission from one site to another in functionally coupled circuits (Wilhelm, Quoilin, Petitjean, & Duque, 2016).

Importantly, because the TMS-ER is dependent on the endogenous neural activity in the targeted region at the time of stimulation, the evoked response is sensitive to endogenous influences such as global brain state (Johnson et al., 2012). Performing a WM task (as opposed to passive fixation) increased the overall strength of electrical currents induced by TMS, increased the spatial spread of TMS-evoked activity to distal brain regions, and increased the ability of TMS to reset the phase of ongoing broadband cortical oscillations. By contrast, task performance had little effect on the dominant frequency of the TMS-ER, both locally and at distal brain areas (Johnson et al., 2012). This method, therefore, provides a potent way to assess changes in cortical excitability and connectivity influenced by task-dependent changes in a participant's cognitive state.

Kundu et al. (2013) provide an excellent example of the aforementioned techniques in their online TMS-EEG protocol investigating load-specific and WM training-related changes in *cortical excitability* and *effective connectivity*. Participants were trained on an adaptive, visuospatial, dual n-back task for 40–60 min per day, 5 days a week, for 5 weeks. Following this extensive WM training program, TMS-EEG was administered while the participants performed a VSTM “transfer” task that required retaining varying set sizes of locations. TMS was delivered during the retention interval (delay period) to the superior parietal lobule to test the hypothesis that training-related improvements in VSTM is supported by strengthened effective connectivity between frontoparietal and occipitoparietal networks that were common to both the training and transfer tasks. The findings revealed load-specific changes as well as transfer of training-related gains from the WM training program in the amount of significant current density and scatter from SPL TMS to the DLPFC (Kundu et al., 2013). Thus, the pairing of TMS-EEG with a WM training protocol helped to clarify the conditions under which the training program provided lasting benefits to cognitive performance in certain individuals more than others—namely, differing levels of structural and functional reorganization of these brain networks following the training.

Studies employing TMS alongside fMRI are able to uniquely probe the causal connections between different brain regions involved in WM processes, especially with regards to connectivity between cortical and deeper cortical/subcortical (hippocampal, thalamic) regions as well as between frontal and parietal cortical regions. In addition, fMRI as a simultaneous neuroimaging method provides a higher spatial resolution than EEG, which is useful when studies are especially concerned with localization. To adjudicate between two hypothesized influences of DLPFC on posterior areas during WM maintenance—maintenance of memory targets or suppression of distractors—event-related TMS was used as a “physiological probe” to modulate the BOLD response without affecting task performance (Feredoes et al., 2011). The results show unique evidence for the “target protection” account: it was shown that TMS to the DLPFC increased activity in category-specific visual regions representing the current memory targets, but only when distractors were present (Feredoes et al., 2011). This target protection role of the DLPFC in the presence of distractors would not have been elucidated without the dual methods of TMS-fMRI allowing visualization of cortical activity along with causal intervention.

## 5.2 | Offline protocols

Another option for investigators is the *offline* protocol, where TMS is applied and then brain activity is measured following TMS to assess persisting effects of stimulation. This type of protocol was utilized to investigate the role of the prefrontal cortex, specifically the right inferior frontal gyrus, in biasing selective attention and visual WM processes through top-down modulation of neural activity in posterior, visual cortex (Zanto et al., 2011). In the experiment, rTMS was used to perturb PFC function before participants performed a selective-attention, delayed-recognition task that required top-down attentional selection processes. This rTMS perturbation of PFC resulted in diminished perceptual processing and activity in posterior cortex during early encoding stages. The diminished top-down modulation predicted a decrease in WM accuracy, with a greater WM decrease in participants with stronger functional connectivity between frontal and posterior regions. In contrast to earlier, converging findings from the neuropsychological literature (Stuss & Knight, 2002), these findings provide causal evidence in the *healthy* human brain for the role of the right IFJ in top-down modulation of posterior brain activity and perceptual/encoding processes in the service of selective attention.

Offline TMS-fMRI studies have also provided the unique ability to address research questions where purely correlational data are unable to disentangle the specific contributions of frontal cortical regions, especially concerning their co-activation with and potential control of other cortical regions. For example, the frontal operculum (fO) had been repeatedly shown to be active during complex tasks requiring cognitive control, yet its mechanism of action had remained elusive until researchers used a TMS-fMRI protocol involving causal stimulation. Researchers first showed that the fO regulated increases and decreases of activity in multiple occipitotemporal cortical areas on a selective versus nonselective attention task where task performance depended on directing attention to different classes of stimuli held in memory (Higo et al., 2011). The causal dependency of these activity changes were then demonstrated: reducing the excitability of fO with TMS selectively diminished top-down modulation of the occipitotemporal regions during selective attention trials, while having no effect on the bottom-up, stimulus-driven modulation occurring when a single stimulus was presented in isolation (Higo et al., 2011).

### 5.3 | Summary

The above examples demonstrate the implications that the use of neuronavigated TMS with simultaneous neuroimaging has had on elucidating the neural bases of WM. These studies provide a generalizable model of how TMS and concurrent EEG or fMRI protocols can be used to probe difficult research questions in a way that provides strong, causal evidence that minimizes or is free from many confounds present in other methodologies (see Thut & Miniussi, 2009 for an excellent discussion on these issues). With multimodal combinations of neurostimulation and neuroimaging such as these, researchers can observe effects of TMS not just on behavior, but also on neural activity with a high degree of temporal precision (when combined with EEG) or spatial precision (when combined with fMRI). The benefits from the specificity that this exogenous brain stimulation provides will allow cognitive neuroscience researchers to rule out other confounding explanations of the behavioral and/or neural findings and move toward the development of stronger, causal models of network architecture in brain circuitry and functioning.

To demonstrate the theoretical and empirical utility of this multimodal approach, we end this section of the review by presenting a case study that highlights how TMS and concurrent neuroimaging can be creatively applied to controversial and fundamental questions in the field of WM. This recent work provides evidence for a hypothesis that calls for considerable revision to the theoretical understanding of the way WM operates (Rose et al., 2016).

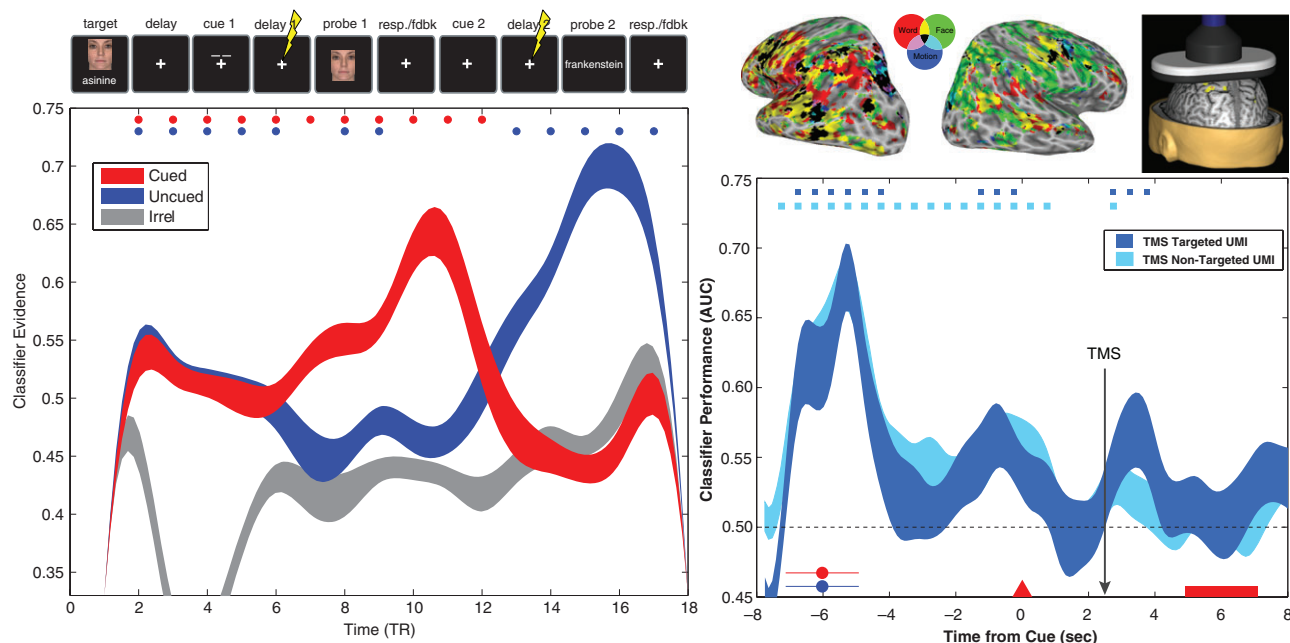
## 6 | A CASE STUDY: ONLINE ADMINISTRATION OF FMRI-GUIDED TMS WITH SIMULTANEOUSLY RECORDED EEG DURING WORKING MEMORY PERFORMANCE

The long-held, canonical view states that WM maintenance is reliant upon sustained, elevated neural activity across a delay period. However, increasing amounts of evidence are accumulating that suggest persistent neural activity is not necessary for continuous representation of memoranda in WM. Rather, alternative, “activity-silent” short-term retention mechanisms may be sufficient to maintain information in WM (for reviews, see Serences, 2016; Stokes, 2015).

The synaptic theory of WM, initially proposed by Mongillo, Barak, and Tsodyks (2008), and recently revised by Trübetschek et al. (2017), provides compelling arguments largely based on computational modeling of plausible biophysical mechanisms that could support such activity-silent short-term retention. Briefly, this theory posits that stimulus-specific representations can be retained in WM in the pattern of synaptic weights in the network that represents the information, even in the absence of sustained neural spiking activity. For example, poststimulus modulation of the level of presynaptic calcium concentration persists for a short period of time such that the output of a subsequent, nonspecific sweep of activity applied to the network should appear structured (i.e., specific to the just-seen stimulus) given the potentiated synapses in the network (see also, Barak & Tsodyks, 2014; Sreenivasan, Curtis, & D'Esposito, 2014). However, empirical evidence for many tenets of the theory in the awake, behaving human brain had been limited by the substantial technological challenges precluding observation of such phenomena. How does one measure something that is activity silent?

### 6.1 | Study design

Rose et al.'s solution was an online spTMS-EEG protocol that allowed the recording of neural activity during the application of TMS while healthy young adults performed a WM task that controlled which of two items was actively held in the focus of attention while the other was held in a more passive state outside of focal attention. In this task, which built on theoretical frameworks that information can be held in WM in one of several states of activation (Lewis-Peacock, Drysdale, Oberauer, & Postle, 2012; Oberauer, 2009), participants were initially presented with two items (e.g., a face and a word) that needed to be remembered. See Figure 2 for a depiction of the task design. An initial retro-cue (C1) indicated which item would be tested by an impending memory probe (P1), which was then followed by a second retro-cue (C2) and a second memory probe (P2). Critical to the task design is the equal likelihood that the initially uncued “unattended memory item” (UMI) was equally likely to be cued at C2. Therefore, even though it was not in the focus of attention following C1, the UMI nevertheless needed to be maintained in WM for a potential memory judgment later in the task. In Experiment 1, multivariate pattern analysis (MVPA) showed that the initially active representation of the UMI dropped to baseline following C1 but reappeared if C2 indicated that the UMI would be tested on P2 (see also Lewis-Peacock et al., 2012). This suggested that information in WM that is held outside of focal attention can be sustained via mechanisms other than elevated neural activity. This “return-to-baseline” pattern has since been replicated with a variety of methods (for reviews, see LaRocque, Lewis-Peacock, & Postle, 2014; Serences, 2016; Stokes, 2015). The need to probe for these activity-silent representations led to the hypothesis that was tested in the following three experiments. That is, if an UMI is encoded in a distributed pattern of synaptic weights and held in an acquiescent state that is nonetheless more accessible than trial-irrelevant information, the readout from a nonspecific burst of energy (like a single pulse of TMS) that is filtered through this network should reveal this latent representation.



**FIGURE 2** In this task, two visual stimuli are presented (left and right of central fixation) and retained. Retro-cues indicate which item will be tested first (red ribbon), and then which item will be tested second (blue ribbon) with 100% validity. The first retro-cue causes the cued item to be in an attended state while the other item transitions to an unattended state. This unattended item must be retained, however, because there is 50% chance that it will be cued and tested on the second half of the trial. Data depict average MVPA classifier evidence from wholebrain fMRI for the cued, uncued, and irrelevant (absent, gray ribbon) category (face, word, and motion, respectively, in the example trial) as a function of time from stimuli presentation (in MRI TR #, with 1 TR = 2 s). Ribbon width reflects  $\pm 1$ SEM. TMS was applied to category selective nodes in a distributed network, identified by wholebrain searchlight MVPA of fMRI data. Light blue ribbons depict the TMS-induced reactivation of latent WM. Classifier performance decoded the unattended memory item (UMI) category from EEG oscillations on targeted and nontargeted trials relative to absent trials from the time of presentation of the UMI (blue circle) and attended memory item (AMI, red circle) 5–7 s before cueing the AMI (red triangle), at which point classifier evidence of the UMI category dropped to baseline (note that the AMI decoding time series is not shown for simplicity). Administering TMS caused a return of neural evidence of the UMI category, especially when TMS targeted the category of the UMI on that trial; then the evidence for the UMI returned to baseline while the AMI category was tested (red rectangle) (for details, see Rose et al., 2016)

## 6.2 | Results

MVPA of EEG data recorded while participants were performing the WM task provided compelling evidence to support this idea. When spTMS was applied to category-preferring regions of the brain in the delay following C1, there was a “reactivation” of the UMI as reflected by MVPA evidence in the EEG for the UMI category relative to the absent category on that trial. This “reactivation effect” occurred even when the single pulse of TMS was applied to a brain region corresponding to a category different to that of the UMI category. This would suggest that the TMS-induced reactivation may occur through a spreading of the stimulation through trial-relevant cortical networks.

While TMS following C1 was able to reactivate the UMI, TMS following C2 was unable to reactivate the UMI *when it was no longer relevant to the trial*. If uncued, the UMI was no longer any different than trial-irrelevant information, and was thus dropped from WM. TMS could reactivate neural patterns of an activity silent UMI when it was still potentially relevant later on in the trial—and this evidence is relative to the (lack of) reactivation of information about the absent category on that trial (which was relevant on preceding trials seconds earlier) (see Rose et al., 2016, figure 4). However, as soon as subjects received C2 that indicated which item could be dropped for good on that trial, TMS could not reactivate stimulus-specific representations in the EEG for the uncued, now irrelevant information. In summary, these results support the idea of at least two levels of WM: one that is consistent with the canonical notion of sustained elevated neural activity supporting active retention in WM and a newer, alternative, “activity-silent” storage mechanism that appears to be quite dynamic and modifiable via cognitive control.

## 6.3 | Replication sans TMS-EEG

These results were recently replicated by Wolff, Jochim, Akyürek, and Stokes (2017), but instead of using TMS to “ping” the brain to reveal the activity silent states of representation, these researchers applied a nonspecific visual bullseye-shaped stimulus to recover neural patterns from EEG/ERP associated with activity silent representations of orientations from Gabor patches held in WM. However, because the “ping” was applied with a visual stimulus, it cannot be ruled out that this reactivation



effect was the result of an exogenous, cue-directed orientation of attention to the representations in memory. In contrast, TMS is often considered to be analogous to injecting neural noise into the system. Critically, applying TMS did not present new visual information; rather, it causally manipulated activity in areas of the brain that were identified to have information about one of the three categories during a WM delay period. Relative to a nonspecific perceptual stimulus, the TMS-induced reactivation of neural evidence for the targeted category of the latent WM representation versus evidence for the stimulus category that was absent on that trial provides strong inference that exogenous stimulation can selectively activate a specific brain region representing activity-silent information at that point of time. Nonetheless, taken together, the results of both studies provide strong, converging evidence for the existence of such dynamic, activity-silent, short-term retention mechanisms.

## 7 | LIMITATIONS AND FUTURE DIRECTIONS

### 7.1 | Difficulties of a huge parameter space and gaps in the literature

It should be noted that there are several nontrivial issues associated with the use of TMS for investigating higher-order cognitive phenomena, especially when combined with concurrent neuroimaging. As can be seen in Table 1, the potential variability in important parameters for TMS studies is sizeable. Obviously, it is important to consider contrasts between the stimulated brain region as a way to reveal a causal role of the targeted brain regions in processing cognitive representations. Adequately considering the context of the individual's mind and brain at the time of stimulation, and how it might change over the course of an experimental session, is also of paramount importance. For example, whereas TMS-induced modulation of memory functioning may be observable early on in an experimental session, the effects may disappear or change later on in a session (e.g., Zanto et al., 2011) as practice effects or strategies for task performance develop or as the deleterious effects of proactive interference and/or fatigue set in.

Each individual manipulation in a protocol (i.e., in stimulation intensity, train frequency, timing between trains) is likely to contribute to the substantial variation in the effect on outcome measures, with additional moderation likely resulting from parameters such as the coil design, polarity, directionality, and pulse shape as well (Deng et al., 2013). Because of this variability in TMS protocols, systematically investigating the effects of TMS by contrasting temporal, spatial, and contextual variables of protocols is desperately needed. Although Table 1 is far from an exhaustive list of TMS studies of WM, it can and should be used to guide future research in novel directions that help to rectify gaps in the literature. Future studies need to manipulate parameters systematically to nail down the most effective protocols for revealing information about WM processes in the brain. As indicated by the BRAIN Initiative (Insel, Landis, & Collins, 2013), an important next step is the establishment of reliable dose–response relationships with behavioral outcomes.

### 7.2 | Need for better control conditions

As seen in Table 1, different TMS studies utilize a variety of control methods that range in their validity as a control condition. Many use a “sham” stimulation condition as their baseline to control for the placebo effects associated with the subjective belief that one is undergoing stimulation. Popular sham conditions include angling the coil 45–90° away from the participant's head or using a specific sham coil that produces no stimulation. Even when such sham conditions attempt to include clicking sounds and/or some kind of somatosensory stimulation to simulate or induce the peripheral behavioral and physiological changes associated with the administration of TMS, such passive stimulation represents inferior control conditions as compared to active stimulation controls. Duecker and Sack (2015) recently argued that sham TMS approaches are insufficient control conditions, and point out that in order to make claims about behavioral and/or physiological consequences of stimulation of a *particular brain region* at a *particular point of time* during task execution, it must necessarily be shown that the same effects do not occur when stimulating another brain region and/or time point. With this in mind, TMS studies should strive to have an active TMS control condition in order to make causal claims. Additional support for active TMS control conditions comes from the fact that one cannot be certain beforehand of the anatomically nonspecific effect of rTMS for a given behavior (Feredoes & Postle, 2009).

However, the choice of active control site needs to be carefully considered and driven by solid theoretical justification. For example (and as a cautionary warning), the vertex has commonly been used as a control site under the assumption that it has relatively little influence over the ongoing processes that would be involved in most tasks. However, it was recently shown that TMS stimulation of the vertex evoked widespread BOLD deactivations across the brain—especially in areas associated with the default mode network, which is known to be important for attention and memory functioning (Jung, Bungert, Bowtell, & Jackson, 2016).

### 7.3 | Technological and computational challenges

A factor that must not be neglected concerns the technological and computational challenges of performing TMS research with simultaneous neuroimaging. The most obvious problem with TMS and simultaneously recorded EEG is the very large TMS pulse artifact that results from the large but brief time-varying magnetic field following TMS discharge. However, researchers must also deal with the electrical charge artifact, TMS-evoked muscle artifacts, movement artifacts, TMS-evoked sensory artifacts, artifacts due to eye-blinks and/or persistent muscle activity, capacitor recharge artifact, and artifacts created during the analysis stage (e.g., from filtering). Though it is difficult to properly remove all of these sources of artifact while retaining sources of true neural activity in the evoked signal, researchers have developed methods of dealing with these artifacts in a systematic, well-validated manner. Hoping to improve and standardize analysis across the field of TMS-EEG research, Rogasch et al. (2017) released the TMS-EEG signal analyzer (TESA), an open-source extension for EEGLAB that includes functions that are specific for TMS-EEG analysis. Other open source toolboxes include TMSEEG (Atluri et al., 2016) and code within the FieldTrip toolbox (see Herring, Thut, Jensen, & Bergmann, 2015).

### 7.4 | Benefits of neuronavigated TMS

The lack of neuronavigated TMS is likely to be an insidious, pernicious contributor to the considerable heterogeneity of results from TMS studies (as is evident in Table 1), especially when considering the small sample sizes of most studies. Sack et al. (2009) investigated this problem by systematically comparing four TMS coil positioning approaches by using them to induce behavioral change in a single cognitive study: a number comparison task. After comparing individual fMRI-guided TMS neuronavigation, individual MRI-guided TMS neuronavigation, group functional Talairach coordinates, or 10–20 EEG position, individual fMRI-guided TMS neuronavigation was found to produce the largest behavioral effect sizes and required the smallest number of subjects to reveal a statistically reliable behavioral effect. In contrast, the 10–20 EEG position approach yielded the smallest behavioral effect size due to variability between subjects and required  $\sim 10\times$  the number of subjects (as compared to individual fMRI-guided TMS) to reveal a statistically significant behavioral effect (Sack et al., 2009).

As such, future TMS research should also aim to include the most effective coil positioning approach available to the researchers. Note that coordinates from a standard template space (MNI or Talairach & Tournoux) that are obtained from previous studies or meta-analyses, for example, should be converted and applied to coordinates in each individual subject's native MRI space (i.e., unwarped sMRI); however, published manuscripts should report all TMS target coordinates converted to a standardized template in order to facilitate replication and reproducibility.

### 7.5 | Strive for personalized TMS

As illustrated in Table 1, the current most common way to determine stimulation intensity is to test individual motor or phosphene threshold and titrate based on those results. However, researchers should acknowledge and address the fact that motor cortex excitability is not necessarily the same as cortical excitability everywhere else in the brain (Deblieck, Thompson, Iacoboni, & Wu, 2008). Use of individually specified targets and demonstrating effects on behavior at a given stimulation intensity help to establish efficacy of stimulation. Additionally, one potentially fruitful way forward may be to “personalize” TMS parameters for each individual based on physiological indices of the targeted cortical regions. For example, one way to implement personalized rTMS would be to measure the peak frequency of behaviorally relevant oscillations in the targeted brain region and titrating the stimulation frequency based on these individual results (see Thut et al., 2011 for an excellent example). While implementing this approach is nontrivially difficult, we highlight this possibility for future directions because adjusting stimulation frequency based on individual brain oscillations in the region of interest would hopefully establish even more effective stimulation protocols for a given individual.

## 8 | CONCLUSION

TMS with simultaneous neuroimaging are technologies with much promise for causally manipulating memory representations in a noninvasive manner in the human brain. TMS must be understood as distinct from other forms of noninvasive brain stimulation for its utility to be appropriately evaluated. Its unique benefit arises from causing neurons to fire in specific areas of the cortex in awake, healthy humans. It allows for high temporal precision, and the combination of TMS with various neuroimaging techniques can be used to uncover the neural activity that is time-locked to behavioral outcomes. However, the limitations of TMS must be known and overcome to move research forward. Researchers should strive toward the use of fMRI-guided neuronavigation and personalized TMS stimulation protocols, as well as an informed choice of active control conditions. Such efforts should help to improve the establishment of replicable and meaningful manipulation of memory

representations. A systematic exploration of the parameters of TMS studies of WM—specifically comparing TMS at different stimulation frequencies and intensities in specific sites throughout, for example, the frontal, parietal and sensory cortices, would propel the field forward in understanding of the various outcomes of TMS stimulation. The current review highlights several promising approaches, but also reveals a strong need for the extension and refinement of existing protocols for elucidating and enhancing the neural bases of memory encoding, maintenance, and retrieval.

## CONFLICT OF INTEREST

The authors have declared no conflicts of interest for this article.

## FURTHER READING

NIH Multimodal Brain Stimulation Speaker Series (6 videos). Retrieved from <https://www.youtube.com/playlist?list=PLV9WJDAawyhZyRFXGMdfu5JN7a0srPz45>

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